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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Executive Summary for 1980 Propazine Carcinogenicity Study in Mice (MRID 00044335).

DP Barcode: D228305 f.s.
PC Code: 080808
Tox Chem No: 184

TO: Rick Whiting
Science Analysis Branch
Health Effects Division (7509C)

FROM: Kit Farwell Kit Farwell 7.26-96
Section 3, Toxicology Branch I
Health Effects Division (7509C)

THRU: Edwin Budd, Acting Section Head
Section 3, Toxicology Branch I
Health Effects Division (7509C) Budd 7/29/96

Attached is the Executive Summary for the 1980 Carcinogenicity Study in Mice (MRID 00044335) using propazine as the test material. Also attached are a copy of the original DER (Document #00575), a table of selected microscopic lesions, and the 1987 Registration Standard (pages 5 and 9).

Technical grade propazine was administered to groups of 60/sex/dose CD-1 mice in the diet for 2 years at dose levels of 0, 3, 1000, or 3000 ppm, corresponding to 0, 0.45, 150, or 450 mg/kg/day. There were no compound-related effects on mortality, clinical signs, body weight, food consumption or gross pathology. Hematology, urinalysis, clinical chemistry and organ weights were not determined. At 3000 ppm, an increased incidence of myocardial degeneration was observed in the female mice (17/59 vs 4/60 in controls) and an increased incidence of hemosiderin-laden macrophages was observed in the livers of male mice (15/59 vs 3/60 in controls). At the doses tested, there was not a treatment-related increase in tumor incidence. **The LOEL is 3000 ppm (450 mg/kg/day)** based upon myocardial degeneration in females and hemosiderin-laden macrophages in the livers of males. **The NOEL is 1000 ppm (150 mg/kg/day).**

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This carcinogenicity study is classified **ACCEPTABLE** and **SATISFIES** the requirement for a carcinogenicity study in mice (Guideline 83-2).

ATTACHMENT

cc: Bill Dykstra

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SUPPLEMENT TO DATA EVALUATION RECORD
Original DER in HED Document # 00575,
attached with supporting table.

STUDY TYPE: Carcinogenicity study, mice, 83-2 (b)

DP BARCODE: D228305 f.s. SUBMISSION CODE: none
P.C. CODE: 080808 TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine technical

CITATION: Jessup, D.C. (1980) 2-Year Carcinogenicity Study in Mice. International Research and Development Corporation (Mattawan, MI). Study No. 382-004. 4/24/80. MRID 00044335. Unpublished.

SPONSOR: Ciba-Geigy Corporation

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 00044335), technical grade propazine was administered to groups of 60/sex/dose CD-1 mice in the diet for 2 years at dose levels of 0, 3, 1000, or 3000 ppm, corresponding to 0, 0.45, 150, or 450 mg/kg/day.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption or gross pathology. Hematology, urinalysis, clinical chemistry and organ weights were not determined. At 3000 ppm, an increased incidence of myocardial degeneration was observed in the female mice (17/59 vs 4/60 in controls) and an increased incidence of hemosiderin-laden macrophages was observed in the livers of male mice (15/59 vs 3/60 in controls). At the doses tested, there was not a treatment-related increase in tumor incidence. **The LOEL is 3000 ppm (450 mg/kg/day)** based upon myocardial degeneration in females and hemosiderin-laden macrophages in the livers of males. **The NOEL is 1000 ppm (150 mg/kg/day).**

This carcinogenicity study is classified **ACCEPTABLE** and **SATISFIES** the requirement for a carcinogenicity study in mice (Guideline 83-2).

COMPLIANCE: A Quality Assurance statement was provided. GLP, Data Confidentiality, and Flagging statements were not provided; this was not the practice when this study was conducted.

COMMENT: A copy of the original DER (Document #00575) and a table of selected microscopic lesions are attached. The 1987 Registration Standard (attached, pages 5 and 9) assigned to this study a systemic LOEL of 3000 ppm based on focal myocardial degeneration in high-dose females and increased hemosiderin-laden macrophages in the livers of high-dose males.

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It is this reviewers opinion that focal myocardial degeneration in high-dose females and hemosiderin-laden macrophages in the livers of high-dose males are both equivocal effects. No other microscopic changes in myocardium other than focal myocardial degeneration in high-dose females were noted. Hemosiderin-laden macrophages in the livers of high-dose males appeared increased because of an apparent decrease in male controls. See the attached table of microscopic lesions.

It is noted that several other microscopic changes (centrilobular focal hepatocellular hypertrophy in high-dose males, focal glandular hyperplasia of the stomach in high-dose males and increased diffuse extramedullary hematopoiesis in high-dose females) also appeared increased in high-dose animals compared to controls. However, these all appear to be random findings and unlikely to be treatment-related since no other microscopic findings in the same organs showed signs of treatment-related effects.

MICROSCOPIC LESIONS

CONDITION	SEX	0 ppm	3 ppm	1000 ppm	3000 ppm
HEART					
Myocardial degeneration, focal	M	8/60	0/0	0/0	11/59
	F	4/60	0/0	0/1	17/59
Myocarditis, acute, focal	M[2]	---	---	---	---
	F	2/60	0/0	0/1	0/59
Myocarditis, chronic, focal	M	0/60	0/0	0/0	1/59
	F	1/60	0/0	0/1	0/59
Myocardial fibrosis, focal[1]	M	5/60	0/0	0/0	11/59
	F	6/60	0/0	1/1	8/59
Amyloidosis, focal	M	14/60	0/0	0/0	11/59
	F	15/60	0/0	0/1	11/59
LIVER					
Hemosiderin-laden macrophages, focal	M	3/60	1/28	3/33	15/59
	F	13/61	6/22	6/25	11/59
Hepatocellular hypertrophy centrilobular, focal	M	14/60	9/28	7/33	26/59
	F	6/61	2/22	0/25	8/59
STOMACH					
Glandular hyperplasia, focal	M	4/58	5/13	0/11	10/58
	F	5/60	3/7	1/13	4/58
SPLEEN					
Hematopoiesis, increased extramedullary, diffuse	M	8/60	3/12	2/7	8/59
	F	10/60	3/7	5/15	19/58
Amyloidosis, focal	M	10/60	1/12	0/7	2/59
	F	7/60	1/7	2/15	6/58
Hemosiderin, increased diffuse[3]	M	2/60	0/12	0/7	4/59
	F	7/60	0/7	0/15	5/58

[1]Combined "myocardial fibrosis, focal" and "fibrosis, myocardial, focal" entries for males from Table 8 in study report.

[2]Acute focal myocarditis was not reported for males.

[3]Combined "increased hemosiderin pigment, diffuse" and "increased hemosiderin, diffuse" entries from Table 8 in study report.

NOTE: This table is abstracted from Table 8 in study report.

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Attachment

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

doc. 00575

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 8, 1981

SUBJECT: EPA Reg.#100-543, Technical Propazine; 6(a)(2) Data
CASWELL#184 Accession#243350-58

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769) WWD for LOC 6/10/81

TO: Robert Taylor (25)
Registration Division (TS-767)

Recommendations:

1. Technical propazine was not oncogenic in the 2-year mouse feeding study. The study is acceptable as Core-Minimum Data.

2. Technical propazine was considered weakly oncogenic to the mammary gland of female rats at 1000 ppm in diet. This finding triggers an oncogenic RPAR criterion. The study is acceptable as Core-Minimum Data.

3. The NOEL for reproductive parameters in the three-generation rat reproduction study was 100 ppm of technical propazine in the diet. The study is acceptable as Core-Minimum Data.

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Review:

1. 2-Year Carcinogenicity Study in Mice (IRDC Report No. 382-004; April 24, 1980)

Test Material: Propazine technical; ARS No. 2046/76; Batch No. FL-76 1357; 35 lbs; white powder

Two hundred forty male (weighing from 21 to 28 grams) and 240 female (weighing from 20 to 25 grams) weanling Charles River CD-1 mice were initiated in this 2-year carcinogenicity study. The mice were housed individually in hanging wire-mesh cages and maintained in a temperature-, -humidity-, and light- (12-hr light/12-hr dark) controlled room. Water and the appropriate diets were available ad libitum throughout the study.

The mice were ear punched to identify treatment group. Beginning on December 17, 1976, ear punch verifications were recorded at each cage change.

The study was initiated on November 3, 1976. During the 5 weeks following initiation, three replacement mice were substituted for the following animals; a control female (#24827 replaced by #2503) that died (11/9/76), a mid-dose male (#24999 replaced by #25204) reported missing (11/9/76), and a mid-dose female (#25079 replaced by #25205) found dead (11/30/76). The rest of the replacement mice were appropriately sacrificed and discarded at the end of the 5-week period (December 8, 1976). The study was terminated on November 2 and 3, 1978.

In accordance with a computer-generated table of random numbers, the mice were selected and assigned to groups as follows:

Dose Level ppm	No. of Mice Initiated	
	Male	Female
0 (control)	60	60
3	60	60
1000	60	60
3000	60	60

The mice were observed three times daily (twice daily on weekends and holidays) for signs of overt toxicity, moribundity, and mortality. Detailed observations were recorded weekly as were the incidence, size and location of palpable masses.

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Individual body weights were recorded monthly. Group mean food consumption was measured weekly. This was accomplished by weighing the food to be used for each group and then distributing it among the food jars in that group. At the end of the week, the food remaining in the jars was collected by groups and weighed. From this mean, individual food with compound and compound consumption values were calculated monthly.

At the completion of the experimental period, surviving mice from all groups were sacrificed by carbon dioxide asphyxiation and necropsied. At necropsy, an examination was made of the external body surfaces and orifices. Each mouse was then opened and contents of cranial, thoracic and abdominal cavities examined for any gross abnormalities. Tissues from each mouse, including the eviscerated carcass was collected for fixation in buffered 10% formalin.

Mice that died during the course of study were also necropsied and tissues collected as above.

Microscopic examination of formalin fixed, hematoxylin and eosin stained paraffin sections was performed for all mice in the control and high-dose groups. The following tissues were examined:

pituitary
peripheral nerve
thyroids/parathyroids
adrenal
trachea
esophagus
aorta
testes/ovaries
prostate/uterus
stomach
duodenum
small intestines (3 levels)
large intestines (2 levels)
urinary bladder
brain
spinal cord (3 levels)
eye and optic nerve
skeletal muscle
skin/mammary gland
lymph nodes (cervical mesenteric)
salivary gland
pancreas
liver
kidneys
spleen
heart
lung
sternum (bone marrow)
and any other tissues with lesions

Lymph nodes, thymus, spleen, and bone marrow were processed and examined in the mid- and low-dose female groups; additional sections were also prepared from tissues in these groups which were previously examined because gross lesions were noted at necropsy.

Statistical analyses of the data were performed.

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Results:

No signs of overt toxicity were observed for any of the treated mice. Some incidental and intermittent signs seen in several control and treated mice were: corneal opacity, hair loss, tonic convulsions upon handling, soft stools, white internal eyes, extended and/or ulcerated penis, dilated pupils (unresponsive to light), tremors, functional and structural impairment of limbs, red material in vaginal opening, altered posture, labored breathing, and yellow material on ventral abdomen. A few palpable masses were observed in both control and treated mice, but the incidence was no greater for the treated animals than for the controls.

There were no compound-related effects observed on the rate of survival of the treated mice when compared with controls. Survival at week 104 was as follows:

Dosage Level ppm	No. Survivors/No. Initiated	
	Male	Female
0 (control)	27/60	33/60
3	35/60	34/60
1000	37/60	27/60
3000	37/60	23/59*

*Mouse found missing, week 20.

Statistical analysis of the body weights through week 104 indicated that while there were occasional statistically significant values among the body weights of the treated mice when compared with controls, there were no compound-related effects observed with respect to body weight. Group mean body weights at week 104 were as follows:

Dosage Level ppm	Group mean body weight gms	
	Male	Female
0 (control)	37	34
3	38	35
1000	37	35
3000	37	33

There were no compound-related effects apparent when the food consumption of treated mice was compared with that of the controls.

An increase in certain morphological changes were seen in the high-dose male and female mice in comparison to the control. In high-dose males, there was an increase above controls in focal myocardial fibrosis, centrilobular focal hepatocellular hypertrophy and focal glandular hyperplasia of the stomach. In high-dose females, there was an increase above controls in focal myocardial degeneration, focal sinusiodal lymphoid infiltrations of the liver, and diffuse hematopoiesis of the spleen. Amyloidosis was a degenerative lesion of common occurrence in almost all mice.

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The prevalence was generally similar for control and treatment groups and the occurrence of amyloidosis was not considered compound-related.

Neoplasms were found with low prevalence in both control and treatment groups. The lung was the most common site of neoplasia with pulmonary (alveologenic) adenoma. The prevalence, however, of this spontaneous pulmonary neoplasm was not increased by compound administration. The initial evaluation showed an increase in the incidence of lymphoreticular cell tumors in females in the 3000 ppm group. Reevaluation of this data and examination of affected tissues in the 3 and 1000 ppm groups eliminated the apparent effect as shown in Table 1 below:

TABLE I

Incidence of Malignant Lymphoma/Reticulum cell Sacroma
*animal number

0		3 ppm		1000 ppm		3000 ppm	
Male	Female	Male	Female	Male	Female	Male	Female
24735*	24783	24858	24903	24971	25027	25108	25149
24756	24788	24863	24908	24982	25032	25119	25152
24767	24791	24876	24922	24986	25048	25139	25172
24772	24806	24881	24923		25056		25174
	24831		24942		25059		25177
	24842		24951		25062		25183
	25203		24952		25064		
			24960		25065		
					25072		
					25078		
4	7	4	8	3	10	3	6

Conclusion:

Technical propazine was not oncogenic in the 2-year mouse feeding study.

Classification: Core-Minimum Data

2. 2-Year Chronic Oral Toxicity Study in Rats with Technical Propazine (IRDC Report No. 382-007; April 28, 1980)

Test Material: Propazine technical; ARS No. 2046/76; Batch No. FL-761357; 35 lbs; white powder

Two hundred sixty male (weighing from 102 to 209 gm) and 260 female (weighing from 94 to 179 gm) weanling Charles River CD rats were selected randomly and initiated in this study.

The rats were housed individually in hanging wire-mesh cages and maintained in a temperature-, humidity-, and light- (12-hr light/12-hr dark) controlled room. Test and control diets as well as water were available ad libitum throughout the study.

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Attachment

005823

83-2 Oncogenicity

There are sufficient data available to satisfy the data requirements for oncogenicity studies in two species (rat, mouse).

Sixty male or 60 female CD rats/dose were selected randomly and given 0, 3, 100 and 1000 ppm of Propazine in their diets for 2 years (MRID 41408). Gross necropsy showed an increase in subcutaneous masses and nodules in females of the 1000 ppm dose group, which correlated with an increase in mammary neoplasms. These neoplasms included adenomas, adenocarcinomas, fibroadenomas, and papillary adenomas. The increase in tumor bearing animals was statistically-significant and considered compound-related. The number of tumor-bearing animals/number examined is as follows [control: 27/56; 3 ppm: 33/57; 100 ppm: 32/60; 1000 ppm: 39/55 (*$p<0.05$)].

Sixty male or 60 female CD-1 mice/dose were selected randomly and given 0, 3, 1000 and 3000 ppm of Propazine in their diets for 2 years (MRID 44335). Propazine was not found to be oncogenic. There were significant incidences of non-neoplastic lesions in high-dose males of hemosiderin-laden macrophages (control: 3/60; high dose: 15/60) and myocardial degeneration in high dose females (control:4/60; high dose: 17/59). The oncogenic NOEL is > 3000 ppm and the systemic NOEL is 1000 ppm*. *[Note: technically a systemic NOEL was not established since the low and mid dose animals were not examined. See discussion in ADI Reassessment (Section D)].

No additional oncogenicity studies are required.

83-3 Teratogenicity in Two Species

There are sufficient data available to evaluate the teratogenicity of technical Propazine in one species (rat).

Propazine (25 female Sprague Dawley rats/dose; 0, 10, 100, 500 mg/kg/day) was not teratogenic in the rat at dosages up to 500 mg/kg (HDT). (MRID 150242). Maternal toxicity was observed in the mid- and high-dose females as decreased food consumption and decreased body weight gain. Additionally, high-dose females exhibited periods of salivation (clear) during gavage. The NOEL for maternal toxicity is 10 mg/kg (low-dose).

Developmental toxicity was observed at the high-dose as increased 14th ribs and incomplete ossification of skeletal structures and decreased fetal body weight. At the mid-dose, delayed ossification of the interparietals was observed. The NOEL for developmental toxicity is 10 mg/kg (low-dose).

A developmental toxicity study in rabbit is required.

83-4 Reproduction

There are sufficient data available to satisfy the data requirements for a reproductive toxicity study for technical Propazine.

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Ten male and 20 female CD rats/dose were continuously administered diet at dosage levels of 0, 3, 100 and 1000 ppm throughout the period of study, until removed for sacrifice, during a three generation reproduction study (F0, F1, F2: a

Tot Chapter of 1987 Registration Standard 7

005823

D. ADI REASSESSMENT

The Toxicology Branch ADI Committee has recently reviewed the data base (Toxicology Branch ADI Committee Rfd asssessment for Propazine; verification date of 3/87). The ADI was established at 0.02 mg/kg/day using a 2-year rat feeding/oncogenicity study in which the systemic NOEL was set at 100 ppm (5 mg/kg)* based on significant depression in body weight of both males and females at the high dosage level of 1000 ppm (MRID 41408). The final safety factor was 300 based on an uncertainty factor of 100 to account for inter- and intra-species differences and an additional factor of 3 to account for the incompleteness of the chronic data base since the one-year dog feeding study may yield a more sensitive toxicological endpoint. This ADI value has been approved by Toxicology Branch pending verification by the Agency Rfd Committee.

The ADI Committee noted that there were data gaps for 1) a chronic dog study, 2) a rat teratology study and 3) a rabbit teratology study. Since the completion of the ADI Committee's deliberation, an acceptable rat teratology study has been submitted (MRID 150242). Propazine produced maternal toxicity in the midand high-dose females as well as decreased food consumption and decreased body weight gain. The NOEL for maternal toxicity is 10 mg/kg (low-dose). Developmental toxicity was observed at the high-dose as increased 14th ribs and incomplete ossification of skeletal structures and decreased fetal body weight. At the mid-dose, delayed ossification of the interparietals was observed. The NOEL for developmental toxicity is 10 mg/kg (low-dose). Both the maternal and developmental toxicity NOELs are greater than the NOEL found in the 2-year rat study and therefore would not normally supersede the ADI established previously from the chronic data due to the short-term nature of the dosing period and the specific endpoints being studied in the developmental tests. Therefore, no change in the ADI is recommended.

*Note: The 2-year mouse study (MRID 44335) reported an elevation in myocardial degeneration at the high dose (3000 ppm/150 mg/kg/day) in 17/59 (28%) animals as compared to 4/60 (6%) in controls. . Histopathology was not performed on cardiac tissue from the low (3 ppm/0.15 mg/kg/day) and intermediate (1000 ppm/50 mg/kg/day) dose animals. Therefore, a NOEL for this toxic effect cannot be determined. It is theoretically possible, but unlikely, that cardiac effects might be observed at the low dose of 3 ppm, i.e., the LEL = 0.15 mg/kg/day, which would require that its use be considered in the determination of the ADI. First of all, the mouse is not generally considered acceptable for the determination of systemic toxicity NOELs. Further, the low dose of 3 ppm is 1000 fold lower than the high dose at which the increased incidence of myocardial degeneration was noted and the incidence of the effect is not extremely higher than the control values. Thus, the use of the 100 ppm dose level from the rat study appears to be a reasonable, scientific decision.

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Tox Chapter of 1987 Registration Standard

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Attachment 1

IRDC's Historical Control Incidence of Mammary Tumors in Sprague Dawley Rats

Study Identification

STUDY	START DATE	END DATE
A	7/21/76	7/21/78
B	4/15/76	4/13/78
C	8/7/74	8/6/76
D	4/28/76	4/28/78
E	3/17/77	3/20/79
F	5/12/76	5/16/78
G	7/14/76	7/14/78
H	1/2/76	5/10/78
I	9/29/75	9/26/77
J	2/18/75	5/27/77
K	9/2/75	9/2/77
L	7/23/75	7/19/77
M	8/9/76	8/10/78
N	11/3/76	11/3/78
O	7/27/76	7/28/78
P	7/30/76	8/2/78
Q	11/9/76	11/10/78
R	10/1/76	10/3/78
S	8/30/76	8/30/78
T	6/23/77	6/26/79
U	4/15/77	4/19/79
V	3/30/76	4/5/78

Attachment 2

IRDC's Historical Control Incidence of Mammary Tumors
in Sprague Dawley Rats

Individual Study Incidence Data

STUDY*	ADENOMA	FIBROADENOMA	ADENOCARCINOMA	ANIMALS WITH ONE OR MORE TUMORS
C	1/47 (.02)	18/47 (.38)	5/47 (.11)	21/147 (.45)
J	7/107 (.07)	75/156 (.48)	20/156 (.13)	95/156 (.61)
L	***	25/42 (.60)	3/42 (.07)	29/42 (.69)
K	***	22/64 (.34)	1/64 (.02)	22/64 (.34)
I	9/74 (.12)	22/74 (.30)	2/74 (.03)	32/74 (.43)
V	21/98 (.21)	42/98 (.43)	6/98 (.06)	67/98 (.68)
B	***	23/60 (.38)	4/60 (.07)	23/60 (.38)
D	12/100 (.12)	47/100 (.47)	1/100 (.01)	52/100 (.52)
H**	5/41 (.12)	19/41 (.46)	12/41 (.29)	28/41 (.68)
F	2/60 (.03)	22/60 (.37)	1/60 (.02)	23/60 (.38)
G	11/97 (.11)	37/97 (.38)	13/97 (.13)	49/97 (.51)
A	6/48 (.13)	20/48 (.42)	10/48 (.21)	25/48 (.52)
O	1/65 (.02)	22/65 (.34)	6/65 (.09)	28/65 (.43)
P	6/64 (.09)	12/64 (.19)	14/64 (.22)	21/64 (.33)
M	***	15/29 (.52)	5/29 (.17)	18/29 (.62)
S	7/50 (.14)	19/50 (.38)	6/50 (.12)	27/50 (.54)
R	4/57 (.07)	21/57 (.37)	8/57 (.14)	24/57 (.42)
N	13/60 (.22)	22/60 (.37)	4/60 (.07)	32/60 (.53)
Q	3/64 (.05)	21/64 (.33)	2/64 (.03)	27/64 (.42)
E	3/55 (.05)	14/55 (.25)	8/55 (.15)	23/55 (.42)
U	9/150 (.06)	53/150 (.35)	41/150 (.27)	82/150 (.55)
T	2/47 (.04)	18/47 (.38)	8/47 (.17)	21/47 (.45)
TOTAL	122/1284(.10)	589/1528(.39)	180/1528(.12)	769/1528 (.50)

* arranged in chronological order
** study ran for 28 months instead of 24
*** no data available

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

JUL 31 1996

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Propazine Qualitative Risk Assessment Based On 1995 Re-Read of Female Mammary Gland Slides From 1981 Sprague-Dawley Rat Dietary Study

P.C. Code 80808

TO: William Dykstra, Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (7509C)

FROM: Lori L. Brunsman, Statistician
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: Hugh M. Pettigrew, Section Head
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Background

A chronic oral toxicity study with Propazine in Sprague-Dawley rats was conducted by International Research and Development Corporation, Mattawan, Michigan, for Ciba-Geigy Corporation, Agricultural Division, Greensboro, North Carolina, and issued April 18, 1981 (IRDC Study No. 382-007; MRID No. 000414-08).

The study design allocated groups of 60 rats per sex to dose levels of 0, 3, 100, or 1000 ppm of Propazine for 105 weeks. An additional 5 rats per sex in the control and high dose groups were designated for interim sacrifice at week 53.

At the request of the Environmental Protection Agency, the Griffin Corporation completed an independent re-review of all mammary gland slides of female rats in the aforementioned study, draft report dated August 12, 1994. Griffin Corporation then requested a Pathology Working Group (PWG) Peer Review of the proliferative lesions of the mammary glands of female rats be conducted by Experimental Pathology Laboratories, Inc. (EPL) to resolve differences in diagnosis between the original study

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pathologist and the reviewing pathologist. The PWG was conducted November 30, 1994, and the final report dated January 20, 1995. The results of the PWG are presented in this memo.

Survival Analyses

The statistical evaluation of mortality indicated a significant increasing trend with increasing doses of Propazine in female rats. See Table 1 for mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls, for mammary gland adenomas and adenomas, fibroadenomas and/or adenocarcinomas combined, all at $p < 0.01$. There was also a significant increasing trend, and significant differences in the pair-wise comparisons of the 3 and 1000 ppm dose groups with the controls, for mammary gland adenocarcinomas, all at $p < 0.05$.

The statistical analyses of the female rats were based upon Peto's Prevalence Test since there was a statistically significant positive trend for mortality with increasing doses of Propazine in female rats. See Table 2 for tumor analysis results.

Table 1. Propazine - Sprague-Dawley Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	1/64[a]	2/62[b]	4/60	8/58	12/50	23/59 (39)**
3	0/60	2/60	0/58	3/58	18/55	23/60 (38)
100	1/60	0/59	0/59	1/59	14/58	16/60 (27)
1000	3/63[c]	0/60	5/60	6/55	24/49	33/58 (57)

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

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

[a]One accidental death at week 13, dose 0 ppm.

[b]One accidental death at week 52, dose 0 ppm.

[c]Two accidental deaths at week 13, dose 1000 ppm.

( )Percent.

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.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 2. Propazine - Sprague-Dawley Rat Study

Female Mammary Gland Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	3	100	1000
Adenomas (%)	1/52 (2)	4/55 (7)	4/58 (7)	9[a]/52 (17)
p =	0.001**	0.127	0.124	0.004**
Fibro-adenomas (%)	20/53 (38)	24/55 (44)	26[b]/59 (44)	24/54 (44)
p =	0.218	0.391	0.347	0.106
Adeno-carcinomas (%)	5/57 (9)	13[c]/58 (22)	8/59 (14)	13/55 (24)
p =	0.047*	0.025*	0.222	0.014*
Combined (%)	23[d]/57 (40)	31[e]/58 (53)	31[f]/59 (53)	37[g]/55 (67)
p =	0.005**	0.124	0.213	0.001**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at week 77, dose 1000 ppm.
[b]First fibroadenoma observed at week 71, dose 100 ppm.
[c]First adenocarcinoma observed at week 50, dose 3 ppm.

[d]Three animals in the 0 ppm dose group had multiple tumors.
[e]Ten animals in the 3 ppm dose group had multiple tumors.
[f]Seven animals in the 100 ppm dose group had multiple tumors.
[g]Nine animals in the 1000 ppm dose group had multiple tumors.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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PROPAZINE 2-YEAR RAT STUDY: MAMMARY TUMOR OCCURRENCE AT DOSES ABOVE THE MTD

A 2 year rat study was performed on propazine technical at International Research and Development Company (IRDC), Mattawan MI. The study was initiated on July 27, 1976 and the final sacrifice occurred on July 26-28, 1978. The final report (Study Number 382-007) is dated April 28, 1980. This report has been submitted to EPA by Ciba Crop Protection (MRID # 00041408).

The purpose of this paper is to present the case that the increase in mammary tumors observed in this study in females at the top dose of 1000 ppm is the result of exceeding the maximum tolerated dose (MTD). This argument is based on the following:

1) A decreased body weight gain versus controls from 18 to 53% was evident in the the high dose females at various time points in the study. This resulted in a body weight depression of 11.4% in these animals at study termination. The body weight changes were observed in the absence of any significant effect on food consumption and the presence of a large decrease in food efficiency.

2) The top dose of 1000 ppm for the top dose females was theoretically expected to achieve approximately 50 mg/kg/day. Due to the large decrease in food efficiency, the dose actually delivered to the animals was approximately 68 mg/kg/day.

3) There was decreased survival in females dosed at 1000 ppm versus the concurrent controls (42% versus 60% in controls). This increased mortality was consistent with the decreased body weight gain and was not due to mammary tumor-burden.

4) The incidence of female mammary adenomas and carcinomas at all dose levels was within both the scientifically appropriate historical control data at IRDC and

the Charles River historical control data base.

Body Weight Gain Effects

A review of the body weight data indicates that there was an excessive depression of body weight in females at the 1000 ppm level. Individual body weight gain data for the control and high dose females for weeks 0-13, 0-52, 0-78, and 0-104 are presented in Tables 1 and 2, respectively. Group body weight gain averages as percent of control and as body weight gain decrement versus controls is summarized in Table 3. At 24 months, the high dose females were 11.4% lower than the control females in body weight, which translates to an 18% body weight gain depression. At 90 days, the females at the high dose showed a severe body weight gain decrease of 27%, well above acceptable MTD levels. This body weight gain decrement was even more dramatic at 12 and 18 months with a 53% and 26% body weight gain depression, respectively. These body weight changes were seen in the face of minor decreases in food consumption and large decreases in food efficiency.

In Tables 4 and 5, the mammary tumor weights of both the control and high dose females were subtracted from the respective total body weights, resulting in a marginal increase in the high dose body weight gain depression from 18% to 21.4% at 24 months. The dramatic decrease in body weight gains whether calculated with or without tumors clearly indicates that the MTD had been exceeded in the high dose females.

Higher Than Expected Dosing

As a result of the decrease in food efficiency, calculations of the compound consumption (based on dietary analysis of propazine and the animals' food consumption) indicated that the high dose females actually were exposed to an increase of 36% (68 mg/kg/day) over the theoretical dietary concentration of 50 mg/kg/day expected to be achieved at a dietary concentration of 1000 ppm (IRDC

Report). The data in this Table (possibly Appendix??) indicates that the high dose males received approximately the anticipated theoretical dosage level of 50 mg/kg/day throughout the study, whereas the females received a much higher dosage on an mg/kg/day basis. This may explain in part why the females in the top dose showed such excessive toxicity. However, based on the body weight gain and survival results excessive toxicity would probably have been noted even at a lower dose closer to the theoretical dose of 50 mg/kg/day.

Effect on Survival

It is apparent from the two EPA cancer peer review documents on propazine (dated August 10, 1987 and January 10, 1989) that the EPA reviewers considered survival of the female rats at the high dose of 1000 ppm to be adversely affected. To quote the cancer peer review document on propazine (page 3, August 10, 1987): "significant survival disparities were found between female dose groups; survival in the mid-dose group was better than in controls; high dose group survival was statistically significantly lower than in the mid-dose group, and had the lowest survival of all."

The IRDC report indeed shows that survival of the high dose females is severely compromised and consistent with the excessive depression in body weight gain in these animals. Table 6 gives the number of surviving animals at weekly intervals for the first 13 weeks and monthly thereafter. The data clearly indicate a dramatic decrease in survival versus the concurrent controls beginning between weeks 95 and 100. Tables 7 and 8 present the fate, weeks on study, and whether the animal was diagnosed with a mammary tumor for individual animals in the control and high dose groups, respectively. These data indicate that 10 (17%) high dose females died during weeks 96 through 100 versus 1 (2%) in the controls. An evaluation of whether these late-study deaths were in the absence or presence of mammary tumors is presented in the table below:

FEMALE DEATHS IN WEEKS 96-104				
CONTROLS			HIGH DOSE	
Animal No.	Mammary Tumor		Animal No.	Mammary Tumor
39426	No		39796	No
			39801	No
			39808	No
			39811	No
			39819	No
			39822	No
			39826	No
			39827	No
			39836	No
			39840	No

It is apparent from this table that mammary tumor burden was not a factor in the poor survival of these high dose females and that death was associated with some other toxicity. The fact that the MTD had been exceeded in this study is clearly supported by the survival data.

Tumor Incidence Within Concurrent Historical Controls

A set of historical control data from IRDC, the performing laboratory, was submitted to the Agency in 1981 (MRID #246140), but was not considered as part of the first or second cancer peer reviews. This historical control data, including the concurrent studies from IRDC two years prior and two years after the propazine study onset, are tabulated by study in Tables 9 and 10. These historical controls clearly show that the tumors seen in the propazine study at all dose levels for adenomas as well as adenocarcinomas were within the performing laboratory's own historical control data.

Mammary gland tumors in the Sprague-Dawley rat can be numerous and variable. The percentage incidence of mammary gland adenocarcinomas at 3 ppm (30.5%) and 1000 ppm (27.7%) in the propazine study is also within the reported range for this tumor type (7.1-31.4%) (Lang, P.L., "Spontaneous Neoplastic Lesions and Selected Non-neoplastic Lesions in the Crl:CD BR Rat." Charles River Laboratories. February, 1992). Likewise the incidence of mammary gland adenomas (12.3%) in the propazine study at 1000 ppm (only dose with a statistically significant increase) is within the reported range for this tumor type (1.4-12.9%) (*ibid*).

Conclusions

In summary, the body weight gain and survival data clearly indicate that the high dose female rats were given a dose of propazine that exceeded the MTD, and therefore the high dose female group should be excluded from any risk assessment or weight-of-evidence arguments concerning this study. Additionally, the incidence of mammary gland tumors in all doses in this study were within the range of current laboratory historical control incidences and those reported by the breeder, Charles River.

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BODY WEIGHT GAIN - CONTROL FEMALES

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 13 B.W.	0-13 WEEKS B.W.G.	WEEK 52 B.W.	0-52 WEEKS B.W.G.	WEEK 78 B.W.	0-78 WEEKS B.W.G.	WEEK 104 B.W.	0-104 WEEKS B.W.G.
39404		114	241	127	357	243	442	328	--	--
39405		128	230	102	275	147	--	--	--	--
39406	X	111	220	109	280	169	341	230	399	288
39407		125	216	91	270	145	332	207	458	333
39408	X	144	255	111	337	193	395	251	450	306
39409		115	227	112	328	213	--	--	--	--
39410		148	306	158	392	244	470	322	482	334
39411		125	256	131	321	196	--	--	--	--
39412		146	279	133	327	181	372	226	435	289
39413		131	239	108	324	193	--	--	--	--
39414		113	223	110	275	162	286	173	230	117
39415	X	117	246	129	363	246	448	331	513	396
39416		122	254	132	311	189	327	205	--	--
39417	X	128	276	148	394	266	506	378	422	294
39418	X	127	260	133	372	245	466	339	342	215
39419		122	234	112	341	219	415	293	400	278
39420		114	220	106	302	188	365	251	383	269
39421	X	119	248	129	388	269	--	--	--	--
39422	X	118	234	116	296	178	317	199	368	250
39423	X	126	243	117	332	206	472	346	603	477
39424	X	134	258	124	361	227	--	--	--	--
39425		128	259	131	--	--	--	--	--	--
39426		127	260	133	356	229	493	366	--	--
39427		123	240	117	331	208	395	272	--	--
39428	X	128	243	115	289	161	384	256	400	272
39429	X	132	271	139	340	208	448	316	--	--
39430	X	121	259	138	404	283	555	434	677	556
39431	X	129	258	129	392	263	483	354	544	415
39432		123	265	142	407	284	--	--	--	--
39433	X	118	223	105	289	171	331	213	411	293
39434	X	123	233	110	251	128	285	162	305	182
39435		121	235	114	301	180	366	245	476	355
39436		116	266	150	388	272	332	216	--	--

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BODY WEIGHT GAIN - CONTROL FEMALES (con't)

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 13 B.W.	0-13 WEEKS B.W.G.	WEEK 52 B.W.	0-52 WEEKS B.W.G.	WEEK 78 B.W.	0-78 WEEKS B.W.G.	WEEK 104 B.W.	0-104 WEEKS B.W.G.
39437		132	256	124	372	240	595	463	--	--
39438		141	289	148	377	236	407	266	452	311
39439		132	237	105	271	139	297	165	333	201
39440	X	130	279	149	429	299	506	376	568	438
39441		138	258	120	313	175	338	200	379	241
39442		131	272	141	506	375	631	500	650	519
39443	X	142	268	126	345	203	421	279	421	279
39444	X	149	286	137	375	226	437	288	448	299
39445		157	313	156	505	348	--	--	--	--
39446		128	230	102	307	179	366	238	400	272
39447		127	266	139	330	203	297	170	--	--
39448		123	259	136	360	237	444	321	527	404
39449	X	121	276	155	366	245	415	294	291	170
39450	X	108	283	175	478	370	563	455	499	391
39451		127	256	129	435	308	520	393	578	451
39452		94	203	109	--	--	--	--	--	--
39453	X	118	256	138	357	239	431	313	492	374
39454	X	146	297	151	448	302	497	351	568	422
39455	X	112	218	106	280	168	355	243	421	309
39456	X	126	270	144	310	184	341	215	--	--
39457		130	264	134	332	202	354	224	--	--
39458	X	127	321	194	561	434	655	528	786	659
39459	X	128	245	117	374	246	442	314	--	--
39460	X	142	291	149	404	262	507	365	622	480
39561		134	311	177	516	382	716	582	--	--
AVERAGE B.W.G. -				129.7		353.6		301.2		337.2

BODY WEIGHT GAIN - HIGH DOSE FEMALES

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 13 B.W.	0-13 WEEKS B.W.G.	WEEK 52 B.W.	0-52 WEEKS B.W.G.	WEEK 78 B.W.	0-78 WEEKS B.W.G.	WEEK 104 B.W.	0-104 WEEKS B.W.G.
39786	X	111	207	96	265	154	333	222	--	--
39787	X	148	260	112	319	171	377	229	--	--
39788		114	223	109	289	175	338	224	382	268
39789	X	115	216	101	276	161	--	--	--	--
39790	X	136	196	60	253	117	290	154	353	217
39791		163	260	97	298	135	--	--	--	--
39792	X	152	246	94	315	163	360	208	452	300
39793		133	220	87	269	136	305	172	--	--
39794	X	146	236	90	314	168	366	220	432	286
39795	X	127	224	97	277	150	338	211	374	247
39796	X	108	199	91	269	161	332	224	--	--
39797	X	117	212	95	267	150	324	207	--	--
39798	X	138	217	79	277	139	306	168	--	--
39799	X	131	250	119	325	194	376	245	313	182
39800	X	135	215	80	241	106	284	149	310	175
39801		137	244	107	328	191	401	264	--	--
39802		118	199	81	265	147	295	177	321	203
39803	X	158	255	97	353	195	328	170	--	--
39804	X	123	216	93	286	163	358	235	--	--
39805	X	112	208	96	297	185	364	252	631	519
39806		120	239	119	301	181	332	212	--	--
39807	X	131	250	119	311	180	376	245	400	269
39808		133	262	129	359	226	430	297	--	--
39809	X	137	211	74	306	169	334	197	381	244
39810	X	136	216	80	258	122	288	152	--	--
39811	X	168	287	119	450	282	469	301	--	--
39812		124	214	90	272	148	--	--	--	--
39813	X	138	216	78	340	202	397	259	--	--
39814	X	141	209	68	333	192	417	276	508	367
39815		178	285	107	341	163	408	230	497	319
39816	X	132	224	92	280	148	348	216	410	278
39817	X	143	238	95	305	162	337	194	371	228

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BODY WEIGHT GAIN - HIGH DOSE FEMALES (con't)

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 13 B.W.	0-13 WEEKS B.W.G.	WEEK 52 B.W.	0-52 WEEKS B.W.G.	WEEK 78 B.W.	0-78 WEEKS B.W.G.	WEEK 104 B.W.	0-104 WEEKS B.W.G.
39818	X	131	229	98	306	175	344	213	393	262
39819	X	161	250	89	350	189	402	241	--	--
39820	X	111	190	79	264	153	312	201	330	219
39821		146	248	102	384	238	386	240	--	--
39822	X	138	225	87	288	150	326	188	--	--
39823	X	136	232	96	310	174	373	237	419	283
39824	X	125	226	101	281	156	348	223	429	304
39825		124	--	--	--	--	--	--	--	--
39826		141	227	86	285	144	314	173	--	--
39827	X	99	186	87	263	164	284	185	--	--
39828		108	211	103	300	192	349	241	--	--
39829	X	154	290	136	350	196	--	--	--	--
39830		103	208	105	215	112	233	130	--	--
39831	X	115	209	94	281	166	--	--	--	--
39832	X	103	209	106	287	184	357	254	385	282
39833		123	235	112	337	214	--	--	--	--
39834	X	132	228	96	350	218	417	285	490	358
39835	X	141	251	110	358	217	461	320	495	354
39836	X	123	240	117	295	172	358	235	--	--
39837		114	191	77	266	152	328	214	411	297
39838	X	123	233	110	292	169	326	203	353	230
39839	X	148	236	88	321	173	349	201	400	252
39840	X	172	235	63	316	144	392	220	--	--
39841	X	134	230	96	283	149	313	179	--	--
AVERAGE B.W.G. -				94.4		167.1		222.8		277.7

TABLE 3

EFFECT OF TREATMENT ON BODY WEIGHT GAIN

GROUP	INTERVAL	AVERAGE B.W.G. (gms.)	B.W.G. AS PERCENT OF CONTROLS	B.W.G. DECREMENT VERSUS CONTROLS
Control	0-13 weeks	129.7	--	--
	0-52 weeks	~~353.6~~ 213	--	--
	0-78 weeks	301.2	--	--
	0-104 weeks	337.2	--	--
High Dose	0-13 weeks	94.4	73%	27%
	0-52 weeks	167.1	47%	~~53%~~ 21.5%
	0-78 weeks	222.8	74%	26%
	0-104 weeks	277.7	82%	18%

w/o terminal weights

16%
23%
27%
17%

Bill's calculations using 0-12 wks

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TABLE 4

CONTROL FEMALES - B.W.G. WITHOUT MAMMARY TUMOR WEIGHT

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 104 B.W.	MAMMARY TUMOR WEIGHT	0-104 WEEKS B.W.G.
39404		114	--	--	--
39405		128	--	--	--
39406	X	111	399	1.43	286.6
39407		125	458	0	333
39408	X	144	450	41	265
39409		115	--	--	--
39410		148	482	0	334
39411		125	--	--	--
39412		146	435	0	289
39413		131	--	--	--
39414		113	230	0	117
39415	X	117	513	1.57	394.4
39416		122	--	--	--
39417	X	128	422	2.16	291.8
39418	X	127	342	5.71	209.3
39419		122	400	0	278
39420		114	383	0	269
39421	X	119	--	--	--
39422	X	118	368	1.294	248.7
39423	X	126	603	0.32	476.7
39424	X	134	--	--	--
39425		128	--	--	--
39426		127	--	--	--
39427		123	--	--	--
39428	X	128	400	0	272
39429	X	132	--	--	--
39430	X	121	677	0	556
39431	X	129	544	0	415
39432		123	--	--	--
39433	X	118	411	74.82	218.2
39434	X	123	305	0	182
39435		121	476	0	355
39436		116	--	--	--

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CONTROL FEMALES (con't)- B.W.G. WITHOUT MAMMARY TUMOR WEIGHT

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 104 B.W.	MAMMARY TUMOR WEIGHT	0-104 WEEKS B.W.G.
39437		132	--	--	--
39438		141	452	0	311
39439		132	333	0	201
39440	X	130	568	0	438
39441		136	379	0	241
39442		131	650	0	519
39443	X	142	421	13.96	265.0
39444	X	149	448	80.51	218.5
39445		157	--	--	--
39446		128	400	0	272
39447		127	--	--	--
39448		123	527	0	404
39449	X	121	291	0	170
39450	X	108	499	138.14	252.9
39451		127	578	0	451
39452		94	--	--	--
39453	X	118	492	0	374
39454	X	146	568	0	422
39455	X	112	421	0	309
39456	X	126	--	--	--
39457		130	--	--	--
39458	X	127	786	272.48	386.5
39459	X	128	--	--	--
39460	X	142	622	0	480
39561		134	--	--	--

AVERAGE B.W.G. WITHOUT MAMMARY TUMOR WEIGHT- 319.6

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TABLE 5

HIGH DOSE FEMALES - B.W.G. WITHOUT MAMMARY TUMOR WEIGHT

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 104 B.W.	MAMMARY TUMOR WEIGHT	0-104 WEEKS B.W.G.
39786	X	111	--	--	--
39787	X	148	--	--	--
39788		114	382	0	268.0
39789	X	115	--	--	--
39790	X	136	353	0	217
39791		163	--	--	--
39792	X	152	452	0	300
39793		133	--	--	--
39794	X	146	432	0	286
39795	X	127	374	6.85	240.2
39796	X	108	--	--	--
39797	X	117	--	--	--
39798	X	138	--	--	--
39799	X	131	313	32.92	149.1
39800	X	135	310	0	175.0
39801		137	--	--	--
39802		118	321	0	203
39803	X	158	--	--	--
39804	X	123	--	--	--
39805	X	112	631	381	138.0
39806		120	--	--	--
39807	X	131	400	66.7	202.3
39808		133	--	--	--
39809	X	137	381	0	244.0
39810	X	136	--	--	--
39811	X	168	--	--	--
39812		124	--	--	--
39813	X	138	--	--	--
39814	X	141	508	0	367.0
39815		178	497	0	319.0
39816	X	132	410	0	278
39817	X	143	371	0	228.0

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HIGH DOSE FEMALES - B.W.G. WITHOUT MAMMARY TUMOR WEIGHT

ANIMAL NO.	MAMMARY TUMOR	PRETEST B.W.	WEEK 104 B.W.	MAMMARY TUMOR WEIGHT	0-104 WEEKS B.W.G.
39818	X	131	393	0	262
39819	X	161	--	--	--
39820	X	111	330	0	219
39821		146	--	--	--
39822	X	138	--	--	--
39823	X	136	419	0	283
39824	X	125	429	70.69	233.3
39825		124	--	--	--
39826		141	--	--	--
39827	X	99	--	--	--
39828		108	--	--	--
39829	X	154	--	--	--
39830		103	--	--	--
39831	X	115	--	--	--
39832	X	103	385	47.86	234.14
39833		123	--	--	--
39834	X	132	490	0	358
39835	X	141	495	0	354
39836	X	123	--	--	--
39837		114	411	0	297.0
39838	X	123	353	0	230.0
39839	X	148	400	54.46	197.5
39840	X	172	--	--	--
39841	X	134	--	--	--

AVERAGE B.W.G. WITHOUT MAMMARY TUMOR WEIGHT- 251.3

B.W.G. AS PERCENT OF CONTROLS- 78.6%

B.W.G. DECREMENT VERSUS CONTROLS- 21.4%

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TABLE 6

FEMALE SURVIVAL DATA

WEEK OF STUDY	CONTROLS			HIGH DOSE		
	ANIMALS ON TEST	NUMBER OF SURVIVORS	PERCENT SURVIVAL	ANIMALS ON TEST	NUMBER OF SURVIVORS	PERCENT SURVIVAL
1	70	70	100%	70	70	100%
2	70	70	100%	70	70	100%
3	70	70	100%	70	70	100%
4	70	70	100%	70	70	100%
5	70	70	100%	70	70	100%
6	70	70	100%	70	70	100%
7	70	70	100%	70	69	99%
8	70	70	100%	70	69	99%
9	70	70	100%	70	69	99%
10	70	70	100%	70	69	99%
11	70	70	100%	70	69	99%
12	70	70	100%	70	69	99%
13	70	69	99%	70	67	96%
17	70	69	99%	70	67	96%
22	70	69	99%	70	66	94%
26	70	68	97%	70	65	93%
30	70	68	97%	70	65	93%
34	70	68	97%	70	65	93%
39	70	68	97%	70	65	93%
43	70	68	97%	70	65	93%
48	70	68	97%	70	65	93%
52	70	65	93%	70	65	93%
56	60	56	93%	60	54	90%
61	60	55	92%	60	54	90%
65	60	55	92%	60	54	90%
69	60	55	92%	60	54	90%
74	60	53	88%	60	51	85%
78	60	48	80%	60	49	82%
83	60	45	75%	60	47	78%
87	60	42	70%	60	41	68%
91	60	41	68%	60	39	65%
95	60	40	67%	60	37	62%
100	60	39	65%	60	27	45%
104	60	36	60%	60	25	42%

TABLE 7

SURVIVAL IN THE PRESENCE OR ABSENCE OF MAMMARY TUMOR

CONTROL GROUP

ANIMAL NO.	MAMMARY TUMOR	FATE	WEEKS ON STUDY	SURVIVAL TO END OF STUDY	
				WITH TUMOR	WITHOUT TUMOR
39404		ND	104		
39405		ND	78		
39406	X	SS	105	*	
39407		SS	105		*
39408	X	SS	105	*	
39409		ND	78		
39410		SS	105		*
39411		ND	61		
39412		SS	105		*
39413		ND	78		
39414		SS	105		*
39415	X	SS	105	*	
39416		MS	85		
39417	X	SS	105	*	
39418	X	SS	105	*	
39419		SS	105		*
39420		SS	105		*
39421	X	ND	77		
39422	X	SS	105	*	
39423	X	SS	105	*	
39424	X	MS	75		
39425		ND	51		
39426		ND	97		
39427		ND	87		
39428	X	SS	105	*	
39429	X	ND	101		
39430	X	SS	105	*	
39431	X	SS	105	*	
39432		MS	70		
39433	X	SS	105	*	
39434	X	SS	105	*	
39435		SS	105		*
39436		ND	79		

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TABLE 7

SURVIVAL IN THE PRESENCE OR ABSENCE OF MAMMARY TUMOR

CONTROL GROUP (CON'T)

ANIMAL NO.	MAMMARY TUMOR	FATE	WEEKS ON STUDY	SURVIVAL TO END OF STUDY	
				WITH TUMOR	WITHOUT TUMOR
39437		MS	80		
39438		SS	105		*
39439		SS	105		*
39440	X	SS	105	*	
39441		SS	105		*
39442		SS	105		*
39443	X	SS	105	*	
39444	X	SS	105	*	
39445		ND	70		
39446		SS	105		*
39447		MS	85		
39448		SS	105		*
39449	X	SS	105	*	
39450	X	SS	105	*	
39451		SS	105		*
39452		ND	50		
39453	X	SS	105	*	
39454	X	SS	105	*	
39455	X	SS	105	*	
39456	X	MS	88		
39457		MS	83		
39458	X	SS	105	*	
39459	X	ND	102		
39460	X	SS	105	*	
39561		MS	93		

SS- Scheduled sacrifice
MS- Moribund sacrifice
ND- Natural death

TABLE 8

SURVIVAL IN THE PRESENCE OR ABSENCE OF MAMMARY TUMOR

HIGH DOSE GROUP

ANIMAL NO.	MAMMARY TUMOR	FATE	WEEKS ON STUDY	SURVIVAL TO END OF STUDY	
				WITH TUMOR	WITHOUT TUMOR
39786	X	ND	88		
39787	X	ND	94		
39788		SS	105		•
39789	X	ND	75		
39790	X	SS	105	•	
39791		ND	78		
39792	X	SS	105	•	
39793		ND	90		
39794	X	SS	105	•	
39795	X	SS	105	•	
39796	X	ND	97		
39797	X	MS	87		
39798	X	MS	84		
39799	X	SS	105	•	
39800	X	SS	105	•	
39801		MS	96		
39802		SS	105		•
39803	X	MS	84		
39804	X	MS	104		
39805	X	SS	105	•	
39806		ND	85		
39807	X	SS	105	•	
39808		ND	100		
39809	X	SS	105	•	
39810	X	ND	104		
39811	X	ND	98		
39812		ND	53		
39813	X	MS	93		
39814	X	SS	105	•	
39815		SS	105		•
39816	X	SS	105	•	
39817	X	SS	105	•	

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TABLE 8

SURVIVAL IN THE PRESENCE OR ABSENCE OF MAMMARY TUMOR

HIGH DOSE GROUP (CON'T)

ANIMAL NO.	MAMMARY TUMOR	FATE	WEEKS ON STUDY	SURVIVAL TO END OF STUDY	
				WITH TUMOR	WITHOUT TUMOR
39818	X	SS	105	•	
39819	X	MS	97		
39820	X	SS	105	•	
39821		MS	85		
39822	X	ND	96		
39823	X	SS	105	•	
39824	X	SS	105	•	
39825		ND	7		
39826		ND	99		
39827	X	ND	98		
39828		MS	81		
39829	X	MS	72		
39830		ND	83		
39831	X	MS	77		
39832	X	SS	105	•	
39833		MS	78		
39834	X	SS	105	•	
39835	X	SS	105	•	
39836	X	ND	98		
39837		SS	105		•
39838	X	SS	105	•	
39839	X	SS	105	•	
39840	X	MS	99		
39841	X	MS	86		

SS- Scheduled sacrifice
MS- Moribund sacrifice
ND- Natural death

TABLE 9

Historical Mammary Gland Tumor Incidence* in Female Control Rats

Study.	No. Rats with Mammary Exam	No. Rats with 1 or More Mammary Tumors	Fibroadenoma	Adenoma	Adenoma, Papillary	Cystadenoma	Adenocarcinoma	Papillary Adenocarcinoma/ Carcinoma	Carcinoma	Ductal Papilloma	Mixed Malignant Tumor	Fibroma	Osteogenic Sarcoma
A	48	25	20/29 (1-3)	6/11 (1-4)			10/12 (1-2)						
B	60	23	23/31 (1-3)				4/5 (1-2)						
C	47	21	18/21 (1-2)	1/1 (1)			5/5 (1)						
D	100	52	47/71 (1-7)	12/17 (1-5)			1/1 (1)						
E	55	23	14/16 (1-3)	3/4 (1-2)			8/12 (1-3)						1/1 (1)
F	60	23	22/33 (1-4)	2/2 (1)			1/1 (1)		1/2 (2)				
G(C1)	47	21	15/25 (1-3)	7/16 (1-3)			3/8 (1-2)						
G(C2)	50	28	22/37 (1-6)	4/4 (1)			8/11 (1-3)						
H	41	28	19/33 (1-4)	3/9 (1-3)		3/3 (1)	12/19 (1-4)						
I	74	32	22/31 (1-4)	9/9 (1)			2/2 (1)					1/1 (1)	
J(C1)	55	34	29/50 (1-5)	4/4 (1)			5/6 (1-2)		1/1 (1)				
J(C2)	52	33	23/35 (1-6)	3/3 (1)			8/9 (1-2)		2/2 (1)				
J(C3)	49	28	23/32 (1-3)				7/10 (1-3)	6/6 (1)					
K	64	22	22/29 (1-4)			1/1 (1)	1/1 (1)						
L	42	29	25/49 (1-4)			3/5 (1-3)	3/3 (1)			2/2 (1)			
M	29	18	15/17 (1-2)				5/5 (1)						
N	60	32	22/35 (1-3)	13/19 (1-2)			4/4 (1)					1/1 (1)	
O	65	28	22/33 (1-4)	1/1 (1)	1/1 (1)	2/2 (1)	6/9 (1-3)	3/3 (1)					
P	64	21	12/20 (1-4)	6/6 (1)			14/22 (1-5)						
Q	64	27	21/27 (1-4)	3/3 (1)			2/4 (1-3)				1/1 (1)	1/1 (1)	
R	57	24	21/30 (1-4)	4/7 (1-3)			8/10 (1-2)						

*No. of animals with tumors/No. of tumors found
(range of No. of tumors per animal)
(C) = Control

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TABLE 9

Historical Mammary Gland Tumor Incidence* in Female Control Rats

Study.	No. Rats with Mammary Exam	No. Rats with 1 or More Mammary Tumors	Fibroadenoma	Adenoma	Adenoma, Papillary	Cystadenoma	Adenocarcinoma	Papillary Adenocarcinoma/ Carcinoma	Carcinoma	Ductal Papilloma	Mixed Malignant Tumor	Fibroma	Osteogenic Sarcoma
S	50	27	19/23 (1-2)	7/15 (1-5)			6/7 (1-2)						
T	47	21	18/23 (1-3)	2/2 (1)			8/13 (1-3)					1/1 (1)	
TOTAL	1280	620	494/730 (1-7)	92/121 (1-5)	1/1 (1)	9/11 (1-3)	133/178 (1-5)	9/9 (1)	4/5 (1-2)	2/2 (1)	1/1 (1)	4/6 (1)	1/1 (1)

Combining essentially synonymous diagnoses:

120/143 (1-7)	143/192 (1-5)

Multiple occurrences of the same tumor in the same rat were not recorded in the following studies:

U(C1)	88	45	30/-	4/-		23/-
(C2)	61	37	23/-	5/-		18/-
V(C1)	48	30	18/-	11/-		3/-
(C2)	50	37	24/-	10/-		3/-
TOTAL	1528	769	589/-	138/-		190/-

*No. of animals with tumors/No. of tumors found
(range of No. of tumors per animal)
(C) - Control

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TABLE 10

HISTORICAL MAMMARY TUMOR INCIDENCE TABLE

STUDY	START DATE	END DATE
A	7/21/76	7/21/78
B	4/15/76	4/13/78
C	8/7/74	8/6/76
D	4/28/76	4/28/78
E	3/17/77	3/20/79
F	5/12/76	5/16/78
G	7/14/76	7/14/78
H	1/2/76	5/10/78
I	9/29/75	9/26/77
J	2/18/75	5/27/77
K	9/2/75	9/2/77
L	7/23/75	7/19/77
M	8/9/76	8/10/78
N	11/3/76	11/3/78
O	7/27/76	7/28/78
P	7/30/76	8/2/78
Q	11/9/76	11/10/78
R	10/1/76	10/3/78
S	8/30/76	8/30/78
T	6/23/77	6/26/79
U	4/15/77	4/19/79
V	3/30/76	4/5/78

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Reviewed by: William Dykstra, Ph.D., Toxicologist William Dykstra 7/14/96
Section I, Tox. Branch I
Secondary Reviewer: Roger Gardner, Section Head, Toxicologist
Section I, Tox. Branch I Roger Gardner 8/8/96

DATA EVALUATION REPORT

STUDY TYPE: 83-2; Carcinogenicity - Rat TOX. CHEM NO: 194

ACCESSION NUMBER: N/A MRID NO.: 00041408

TEST MATERIAL: Propazine

SYNONYMS: Milopro 4L

STUDY NUMBER: IRDC #382-007

SPONSOR: Griffin

TESTING FACILITY: IRDC, Mattawan, MI

TITLE OF REPORT: Two Year Oral Chronic Toxicity Study in Rats

AUTHOR(S): D. Clifford Jessup

REPORT ISSUED: April 18, 1981

EXECUTIVE SUMMARY: Randomized groups of 60/sex/dose Sprague-Dawley rats were fed dietary levels of 0, 3, 100, and 1000 ppm (**0.15, 5.0, or 50 mg/kg/day**) for 2 years. An additional 10/sex were added to the control and high dose groups for interim sacrifice at 12 months (5/sex) and a 4 week "recovery period" for 5/sex control and high dose animals. Hematology, clinical chemistry and urinalyses were conducted on 10/sex from control and high dose groups at 3, 6, 12, 18, and 24 months. All animals were necropsied, organ weights were taken at 12 and 24 months and 65/sex from control and high dose were examined microscopically. Mammary gland tissue from all male and female rats in all dose levels was examined microscopically.

The NOEL is 100 ppm (5 mg/kg/day). The LEL is 1000 ppm (50 mg/kg/day) and the effect is decreased body weight.

Mammary gland tumors (adenocarcinomas and adenomas) were increased above controls in 3 and 1000 ppm females and were considered compound related. Other tumor types were comparable between control and treated high dose rats of both sexes.

Classification: core-minimum

A. MATERIALS:

1. Test compound: . Description - white powder, Batch # - FL476357, 35 lbs.; Purity - not specified, assumed 100 %.

2. Test animals: Species: rat, Strain: Sprague-Dawley, Age: weanling (4 weeks), Weight: 94-179 grams, Source: Charles River, Wilmington, MA.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months male	Main Study 24 months female	Interim Sac. 12 months male	Interim Sac. 12 months female
1 Cont	0	60	60	10	10
2 Low (LDT)	3	60	60	0	0
3 Mid (MDT)	100	60	60	0	0
4 High (HDT)	1000	60	60	10	10

2. Diet preparation

Diet was prepared weekly and stored at room temperature. Samples of treated food were analyzed for stability and concentration at 0, 3, 6, 9, 12, 15, 18, 21, and 24 months of study by the sponsor.

Results - The results of these analyses were not in the report.

3. Animals received food (Purina Laboratory Chow) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: Body weight, hematological, biochemical, and urinalyses data, and absolute and relative organ weights were compared by analysis of variance (one way classification), Bartlett's test for homogeneity of variance and appropriate t-test (for equal or unequal variances) using Dunnett's multiple comparison tables to judge the significance of differences. The tumor incidence for individual tumor types were compared using the Chi-square criterion with the Yates correction for 2 x 2 contingency tables as described by Siegel to judge significance of differences. Statistical significance was

judged to be present at the $p < 0.05$ level.

5. A signed quality assurance statement (study director's statement) by the Study Director, D. Clifford Jessup, Ph.D., was present.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality.

The report states that a significant compound related increase in palpable masses was observed in high dose female rats in comparison to controls. Other frequently seen clinical signs were comparable between control and treated rats of both sexes. There was a statistically significant increasing trend in mortality in the treated female groups due to the higher number of deaths in high dose female rats. However, the mortality in the high dose female group was not statistically significantly increased by pair-wise comparison to control females according to the report. Additionally, the cause of death in animals dying on study was not reported.

SURVIVAL AT 104 WEEKS

	MALES	**FEMALES**
CONTROLS	31/60	36/60 (significant trend)
LOW	42/60	37/60
MID	46/60	46/60
HIGH	38/60	25/60

2. Body weight

Animals were weighed weekly for the first 3 months and monthly, thereafter. Due to the poor reading quality of the paper copy available for review, only body weight and food consumption data corresponding to weeks 0, 12, and 104 was reported in the DER to reduce possible reading errors. The decreased body weight and weight gain in both sexes (> 10%) at the high dose is considered toxicologically

significant and evidence that adequate dose levels were used to assess carcinogenicity. A pairwise comparison of mortality between controls and high dose female rats, together with a Peto analysis, will be performed by SAB statisticians.

MALES

BODY WEIGHT (g)

	Weeks		
	0	12	104
Control	169	475	712
Low	170	459 -3.3%	667 -6.3%
Mid	168	453 -4.6%	679 -4.6%
High	167	424 -10.7%	619 -13.1%

DECREASED BODY WEIGHT GAIN

	Weeks	
	0 - 12	0 - 104
High	-16.0%	-16.7%

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FEMALES

BODY WEIGHT (g)

	Weeks 0	12	104
Control	128	259	463
Low	132	254 -1.9%	445 -3.9%
Mid	138	254 -1.9%	437 -5.6%
High	131	241 -6.9%	417 -11.4%

DECREASED BODY WEIGHT GAIN

	Weeks 0 - 12	0 - 104
High	-15.2%	-14.6%

3. Food consumption and compound intake

Consumption was determined weekly for 10/sex/dose) for first 3 months and monthly thereafter. Mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data for the first 30 weeks. There were few differences between control and treated rats of both sexes in the quantity of food consumed. The slight decreases in food consumption in the male and female high dose rats were not sufficient to account for the significant body weight decreases in these high dose groups. Therefore, food efficiency was significantly lower in the high dose male and female groups in comparison to controls during the measured intervals. Additionally, compound intake in high dose females was higher (68 mg/kg/day) than is usually expected from comparison to females in other chronic studies (50 mg/kg/day).

MALES

FOOD CONSUMPTION (g/rat/day)

	Weeks		
	1	13	104
Control	20.4	24.2	24.8
Low	-	22.4	24.2
Mid	21.7	24.9	24.5
High	20.5	23.4	23.4

FEMALES

FOOD CONSUMPTION (g/rat/day)

	Weeks		
	1	13	104
Control	16.4	15.8	18.3
Low	16.6	14.3	18.3
Mid	16.8	14.1	18.2
High	16.9	14.4	18.0

COMPOUND INTAKE

	MALES	FEMALES
LOW	0.1	0.2
MID	5.2	6.4
HIGH	51	68

4. Ophthalmological examination

This parameter was not performed.

5. Blood was collected before treatment and at 3, 6, 12, 18, 24 months for hematology and clinical analysis from 10/sex high dose and control animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
x	Platelet count*		Reticulocyte count
	Blood clotting measurements		
x	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - Decreases of up to 9.7% was seen at 6 and 12 months in high dose males for RBC, hematocrit, and hemoglobin in comparison to controls. However, 3 and 18 month values in these same parameters were not statistically different from controls and 24 month values were significantly elevated by 16%. High dose females had decreases in erythrocytes at 18 and 24 months, but hematocrit and hemoglobin were comparable to controls at these times. The changes in hematological findings were not consistent over time and did not display any treatment related pattern. For these reasons, the findings at the high dose in both sexes were considered unrelated to treatment.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
	Calcium*		Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorous*	x	Cholesterol*
	Potassium*		Globulins
	Sodium*	x	Glucose*
	Enzymes		Total bilirubin

x	Alkaline phosphatase (ALK)	x	Total serum Protein (TP)*
	Cholinesterase (ChE)#		Triglycerides
	Creatinine phosphokinase*^		Serum protein electrophores
	Lactic acid dehydrogenase (LAD)		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies
# Should be required for OP
^ Not required for subchronic studies

Results - There were no consistent decreases or increases in biochemical measurements at the high dose in both sexes in comparison to controls. The observed statistically significant differences between high dose and control values were small in magnitude and the high dose values were within the normal range over time for biochemical control findings.

6. Urinalysis

Urine was collected from 10/sex control and high dose fasted animals at 3, 6, 12, 18, 24 months. The CHECKED (X) parameters were examined.

X		X	
x	Appearance*	x	Glucose*
x	Volume*	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH		Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*		Urobilinogen

^Not required for subchronic studies
* Required for chronic studies

Results - There were no consistent urinalysis findings in high dose rats of both sexes which were consistently different over time in comparison to controls. Differences between the high dose and control values of both sexes were small in magnitude.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed. Additionally, 5/sex control and high dose rats were sacrificed at 12 months and 5/sex from control and high dose which were placed in compound withdrawal for 4 weeks were also sacrificed at 12 months. A complete set of tissues as listed was examined from all rats from the control and high dose group (65/sex) except those which were in the "recovery group" (5/sex) after 12 months of study. In addition mammary tissue was examined from all rats on study.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue	x	Aorta*	x	Brain*+
x	Salivary glands*	xx	Heart*	x	Periph. nerve*#
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*#
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen	x	Eyes (optic n.)*#
x	Jejunum*		Thymus*	Glandular	
x	Ileum*	Urogenital		xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+	x	Lacrimal gland#
x	Colon*	x	Urinary bladder*	x	Mammary gland*#
	Rectum*	xx	Testes*+	x	Parathyroids*++
xx	Liver *+		Epididymides	xx	Thyroids*++
	Gall bladder*	x	Prostate	Other	
x	Pancreas*		Seminal vesicle	x	Bone*#
Respiratory		xx	Ovaries*+	x	Skeletal muscle*#
x	Trachea*	x	Uterus*	x	Skin*#
x	Lung*			x	All gross lesions and masses*
	Nose^				
	Pharynx^				
	Larynx^				

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. Organ weight - There were no statistically significant differences in absolute and relative organ weights in both sexes at 12 and 24 months, except for the significant increase in relative brain weight in high

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dose males. This finding is not considered a toxic effect, but is rather due to the decrease in body weight of high dose males and the unchanged brain weight at both sacrifice periods.

b. Gross pathology - The report states that a significant compound related increase in palpable masses was observed in high dose female rats in comparison to controls. There were no other compound related gross necropsy findings in sacrificed animals or animals dying on study.

c. Microscopic pathology -

1) Non-neoplastic - There were no compound related findings in microscopic results at 12 months in examined high dose rats in comparison to controls.

2) Neoplastic - Mammary gland tumors (adenocarcinomas and adenomas) were increased above controls in 3 and 1000 ppm females and were considered compound related. The diagnoses in the table below were based on the Pathology Work Group, brought together to reexamine the mammary gland slides in females as required by the previous CPRC, by the Griffin Corporation. Other tumor types were comparable between control and treated high dose rats of both sexes. An analysis of the tumor results will be conducted by the HED pathologist and statistician

INCIDENCE OF FEMALE RATS WITH MAMMARY GLAND NEOPLASMS

	CONTROL	LOW-DOSE	MID-DOSE	HIGH-DOSE
12-Month Sacrifice Including Unscheduled Deaths From Weeks 0-52				
No. Examined	9	2	1	10
Fibroadenoma		1		
Terminal Sacrifice and Unscheduled Deaths from Weeks 53-105				
No. Examined	55	57	59	55
Adenocarcinoma	8	16	10	18
Adenoma	2	5	6	8
Fibroadenoma	22	26	25	24
All Animals From Weeks 0-105				
No. Animals with Benign Tumors	24	29	28	28
No. Animals with Malignant Tumors	8	16	10	18
No. Animals with Both Benign and Malignant Tumors	5	8	5	6
No. Animals with Mammary Gland Tumors	27	37	33	40

D. DISCUSSION:

The study was conducted in the 1970s and the report issued in 1981. Adequate number of rats were placed on study for each dose level. The 4 week high dose "recovery group" (5/sex in control and high dose) did not show any unusual difference in comparison to controls. Body weight decreases in excess of 10% showed that both sexes were adequately dosed to evaluate carcinogenicity. Based on decreased body weight, the NOEL is 100 ppm (5 mg/kg/day) for systemic toxicity.

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

CASWELL#: 184
CAS-REG#: 139-40-2

P.C. CODE 080808- 2-Chloro-4,6-bis(isopropylamino)-s-triazine FILE LAST PRINTED: 03/26/96

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-1(a) and 83-2(b) Feeding/carcinogenic-2 year Species: mice Interntl. Res. and Develop. Co 382-004; 4/24/80	Propazine Tech batch #FL-	243350 00044335	Systemic NOEL = 100 ppm, Systemic LEL = 3000 ppm (HDT); (increased focal myocardial fibrosis, focal myocardial degeneration.) Oncogenic NOEL > 3000 ppm (HDT) Levels tested = 0, 3, 100 and 3000 ppm in CD-1 strain.		Minimum 000575 Minimum 004542 005823
83-1(a) and 83-2(a) Feeding/carcinogenic-2 year Species: rat Interntl. Res. and Develop. Co 382-007; 4/28/80	Propazine Tech Batch #FL-	243353 00041408	Systemic NOEL = 100 ppm, Systemic LEL = 1000 ppm (decrease in body weight); levels tested 0, 3, 100, and 1000 ppm. Oncogenic LEL = 1000 ppm (increase in mammary tumors) Levels tested = 0, 3, 100 and 1000 ppm		Minimum 000575 Minimum 004542 005319 005508 005823
83-1(a) and 83-2(a) Feeding-2 year oral Species: rat Interntl. Res. and Develop. Co 382-007; 4/28/80	Propazine technical		Qualitative Risk Assessment: Significant dose-related trends are found for all mammary tumors combined, and for malignant mammary tumors combined. There is a significant pairwise comparison between control and high dose groups for all mammary tumors combined.		005894
83-3(a) Developmental Toxicity Study Species: rat Ciba-Geigy Corp. Inc. 227642; 11/24/76	Propazine tech	070544	Teratogenic NOEL > 600 mg/kg (HDT), Fetotoxic LEL = 300 mg/kg (decreased body weight), Fetotoxic NOEL = 100 mg/kg, Fetotoxic LEL = 300 mg/kg (decreased body weight), Maternal LEL = 300 mg/kg. (Decr. body wt.) Levels tested = 0, 30, 100, 300 and 600 mg/kg by intubation. Generalized edema, mandibular hypoplasia, unilateral anothalmia, lung hypolasia, anophthalmia, anasarca, delayed ossification of the calcanei.		Minimum 001450 Supplementary 005823
83-3(a) Developmental Toxicity Study Species: rat Toxigenics Inc. 450-1787; 5/8/85	Propazine technical 99.1% a.i. Lot #FL- 841648	073885 00150241	Pilot Study: Levels tested by gavage in Sprague-Dawley strain - 0, 300, 600, 800 and 1000 mg/kg. Maternal NOEL < 300 mg/kg (decreased body wt.) Developmental toxicity NOEL < 300 mg/kg (decreased body wt.) Crusty muzzle, urine soaked or yellow/brown stained fur, red substance on fur (perinal).		Acceptable 005226 005823
83-3(a) Developmental Toxicity Study Species: rat American Biogenics Corp. 450-1788; 5/8/85	Propazine tech 99.1% a.i. Lot #FL 841648	073885 00150241	Maternal NOEL = 10 mg/kg, Maternal LEL = 100 mg/kg (decreased food consumption and decreased body weight) Developmental toxicity NOEL = 10 mg/kg, Developmental toxicity LEL = 100 mg/kg (incomplete ossification of skeletal structures); A/D ratio = 10/10 = 1.0 Dose = 0, 10, 100, 500 mg/kg Levels tested by gavage in Sprague-Dawley strain.		Guideline 005226 005823

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-4 Reproduction-3 generation Species: rat Interntl. Res. and Develop. Co 382-010; 8/10/79	Propazine Tech batch #FL-761357	243356 00041409	Reproductive NOEL = 100 ppm, Reproductive LEL = 1000 ppm (HDT) (reduced mean pup body weights) Levels tested = 0, 3, 100 & 1000 ppm		Guideline 000575 Minimum 004542 005823
82-1(a) Feeding- 6 months Species: rat	Propazine 50W		Systemic NOEL < 250 mg/kg/day (LDT; retardation in weight gain) Levels tested = 0, 250, and 2500 mg/kg/day		001376
82-1(a) Feeding-3 month Species: rat	Propazine 80W		Systemic NOEL = 200 ppm, Systemic LEL = 1000 ppm (HDT; body weight loss, hyperirritability to handling) Levels = 0, 50, 200 and 1000 ppm.		001376
82-1(b) Feeding-3 month Species: dog	Propazine 80W		Systemic NOEL = 200 ppm, Systemic LEL = 1000 ppm (HDT; body weight loss) Levels tested = 0, 50, 200 and 1000 ppm		001376
82-2 Dermal-3 week Species: rabbit	80W (50% aqueous solution)		Mild erythema, drying, desquamation and thickening of skin at the application site. Levels tested = 1 gm/kg/day and 2 gm/kg/day. At 2 g/kg: severe body wt. loss, 20% mortality, generalized inactivity, anorexia and diarrhea.		001376
Dermal-5 day Species: rat	Propazine tech		No irritation effect noted at 140 mg/kg. Doses: 2.5%, 5% propazine.		001376
Feeding-28 day Species: rat	Propazine tech		No pathological changes noted at 2500 mg/kg Levels tested = 1250 and 2500 mg/kg/day		001376
84-2(b) Mutagenic-rec assay and rever. Species: Mutation Research, 40 p.19-30 1976	Propazine tech	070544	Negative for mutagenicity but no individual data on propazine was presented.		Supplementary 001450 Unacceptable 005823
84-4 Mutagenic nucleus anomaly Species: Chinese hamster Ciba-Geigy Corp. Inc. 831372; 8/10/84	G30028 technical propazine 100% a.i.	073885 00150622	Propazine was not mutagenic in this nucleus anomaly assay. Dosages = 0, 1250, 2500, 5000 mg/kg on two consecutive days.		Acceptable 005226 005823

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic-DNA (POL) repair Species: rat Ciba-Geigy Corp. Inc. 831371; 5/16/84	G30028 tech propazine 100% a.i., batch 909005	073885 00150623	Propazine was not mutagenic in the DNA repair assay. Assays were performed at 0.50, 2.5, 12.5, and 62.5 ug/ml		Acceptable 005226 005823
84-4 Mutagenic-DNA (POL) repair Species: human fibroblasts Ciba-Geigy Corp. Inc. 831373; 5/16/84	G30028 technical propazine 100% a.i. batch 909005	073885	Mutagenic potential could not be evaluated due to the following deficiencies: a) cell line not characterized, b) not tested in presence of activation, c) not stated how DNA synthesis was accounted for. Doses: 0.4, 20.0, 100 and 500 ug/ml		Unacceptable 005226 005823
84-4 Mutagenic Species: S. typhimurium Univ. of Penn. 100-551; 6/74	Technical 99% purity	79923	Propazine was not mutagenic (without activation) at doses of 0, 50, 250, 500 & 1000 ug impregnated discs.		Unacceptable 005823
84-4 Mutagenic-point mutation Species: Chinese hamster Ciba -Geigy Ltd.,Switz. 850624; 7/11/86	G30028 Tech. (Propazine) 100% purity; batch No. 08-909005	265162	Propazine produced a dose-related positive mutagenic response without activation and a weak (non-dose related) response with metab. activation. Doses: 100, 200, 600, 800 and 1000 ug/ml.		Acceptable 005611 005823
Registration standard	Propazine		Toxicology Chapter: 3/24/87 ..... Calculation of Worker Risk Assessment		005823 006566
Risk assessment-chronic Species: rat EPA 6/12/87	Propazine Tech.		Quantitative Risk Assessment. Q1* = 1.7 x 10-1 (mg/kg/day)-1 in human equivalents using Weibull's 82 model (time to tumor), based on ALL mammary tumors combined in female rats. Two-year Chronic oral study in rats (F) (IRDC report 382-007)- 4/28/80		006504
Exposure Assessment Species: worker EPA 1/88	Propazine		The potency estimate Q1* is 1.7 x 10exp-1 mg/kg/day-1 in human equivalent Worker exposed is estimated to be for: Ground-Grower = 10exp-4 to 10exp-3 Ground-Commercial = 10exp-4 to 10exp-3. Aerial-Closed system = 10exp-5 to 10exp-4. Aerial Pilot system = 10exp-6 to 10 exp-5. Aerial-Flagger = 10exp-5 to 10exp-4.		006566
Risk assessment-chronic Species: rat Interntl. Res. and Develop. Co 382-007; 4/28/80	Propazine tech.		Updated Qualitative Risk Assessment: 1.) Female rats at 1000 ppm had sig. lower mortality than controls and sig. incr. trend with dose. 2.) Sig. incr. incidence of malignant mammary tumors & combined malignant & benign mammary tumors at 1000 ppm compared to controls & a sig. incr. trend with dose. Also 3 ppm group had sig. more malignant mammary tumors.		006954

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Risk assessment-chronic Species: rat (female) Interntl. Res. and Develop. Co 382-007; 4/28/80	Propazine Tech.		2nd updated Qual. Risk assessment: Female rats had a sig. incr. dose trend with mortality. Sig. dose trend for all mammary tumors combined and also adenoma. Sig. pairwise comparison between control & high (1000 ppm) dose group for all mammary tumors combined.		006946
85-1 Metabolism Species: rat	14C-propazine		14C-propazine was recovered in urine (42.2%), feces (28%) and selected tissues (blood, kidney, liver heart, reprod. organs, muscle and fat; 8.6%).		001376
85-1 Metabolism Species: rat Ciba-Geigy Corp. Inc. 8F0687; 2/11/65	14C - propazine; specific activity not given	93339 111684	14C-propazine was recovered unchanged in feces (80 ppm) but not urine (< 0.05 ppm, LD); hydroxypropazine found equally in feces (1.1 ppm) and urine (1.2 ppm)		Supplementary 005823
Species: rabbit Cannon Labs Inc. 6/26/79	Flowable Propazine 44% Lot#071 41	240865	Application of 2g/kg. No mortalities. Erythema, nasal discharge, diarrhea, dark spots in lungs at necropsy.	3	Guideline 007419
81-1 Acute oral LD50 Species: mice Ciba-Geigy Corp. Inc. 8F0687; 6/14/63	Propazine technical	00111675	LD50 > 5 g/kg. Spasms, dypsnea, drowsiness and irregular breathing. Doses: 2.5, 5.0 gm/kg via stomach tube.	4	Supplementary 001376 005823
81-1 Acute oral LD50 Species: rat Ciba-Geigy Corp. Inc. 8F0687; 6/14/63	Propazine technical	00111674	LD50 > 5 g/kg. Doses: 2.5, 5.0 gm/kg via stomach tube.	4	Supplementary 001376 005823
81-1 Acute oral LD50 Species: rabbit Standard Oil of California	Triox liq. veg. killer		LD50 (M) = 3.9 (2.2-7.0) g/kg. LD50 (F) = 3.0 (1.3-6.7) g/kg Signs: lacrimation, salivation and ataxia.	3	Minimum 001377
81-1 Acute oral LD50 Species: rat Interntl. Res. and Develop. Co 382-043; 10/17/78	Propazine 18.7 % Metolachlor 36.3 % Milocep 5L		LD50 M&F) = 3868 (3142-4761) mg/kg. LD50 9M) = 4811 (3771-6139) mg/kg. LD50 (F) = 2944 (2185-3965) mg/kg. Signs: hypoactivity, ataxia, salivation, diarrhea, tremors, lacrimation, hypersensitivity to touch and prostration. Doses: 574, 2314, 3401, 5000, 7350, 10805 mg/kg.	3	Minimum 001378 Guideline 007418

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81-1 Acute oral LD50 Species: rat Stillmeadow Inc. 1131-79; 5/9/79	Propazine 90% (Milogard 90WDG)	238806 000111699	LD 50 > 5g/kg.	4	Guideline 001379 005823
81-1 Acute oral LD50 Species: rat Cannon Labs Inc. 7/18/79	Propazine 4L (44% a.i.)	240863	Doses: 3000, 4000, 4500, 5500, 6000 mg/kg LD50 (m)= 5800 (3752-8965) mg/kg LD50 (f)= 4600 (3893-5436) mg/kg Symptoms: Sedation, ptosis ,shallow respiration , piloerection , salvation ,abnormal defacation ,nasal discharge, oily ventral surface ,dried material around eyes.	3	Guideline 007419
81-2 Acute Dermal LD50 Species: rabbit	Propazine 80WP		LD50 > 10.2 g/kg (HDT). No skin irritation was noted. Doses: 3.0, 4.6, 6.8, 10.2 gm/kg	3	001376
81-2 Acute Dermal LD50 Species: rabbit Standard Oil of California	Triox liq. veg. killer		LD50 > 5 g/kg (single dose tested). Severe skin irritation.	3	Minimum 001377
81-2 Acute Dermal irritation Species: rabbit Standard Oil of California	Triox liq. veg. killer		PIS = 6.5/8.0. Eschar and moderate to severe edema. Irreversible erythema.	1	Minimum 001377
81-2 Acute Dermal LD50 Species: rat Interntl. Res. and Develop. Co 382-044; 10/17/78	Milocep		LD50 > 5 g/kg (single dose), slight to moderate irritation. Erythema, edema, atonia, desquamation coriaceousness, fissuring and blanching.	4	Minimum 001378 Guideline 007418
81-2 Acute Dermal irritation Species: rabbit Interntl. Res. and Develop. Co 382-046; 10/17/78	Milocep		PIS = 2.0/8.0. Eschar, edema; irritation still apparent at 72 hrs.	3	Minimum 001378 Guideline 007418
81-2 Acute Dermal LD50 Species: rabbit Stillmeadow Inc. 1132-79; 5/9/79	Propazine 90% (Milogard 90WDG)	238806 00111700	LD50 > 2 g/kg (HDT). Erythema and edema, zero by day 9.	3	Guideline 001379 005823

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81-2 Acute Dermal irritation Species: rabbit Stillmeadow Inc. 1133-79; 5/9/79	Propazine 90% (Milogard 90WDG)	238806 00111703	PIS = 3.94/8.0 - erythema, eschar and edema at all sites with improvement noted by 72 hours.	3	Guideline 001379 005823
81-3 Acute inhalation LC50 Species: rat	Propazine 80WP (0.5 % aq. sol.		LC 50 > 14.1 mg/L/4 hours.	4	001376
81-3 Acute inhalation LC50 Species: rat	Propazine 80 WP		LC 50 > 3.3 mg/L/1 hour	4	001376
81-3 Acute inhalation LC50 Species: rat Standard Oil of California	Triox liq. veg. killer		No gross pathological changes attributable to test material. Rapid diaphragmatic respiration observed during exposure to aerosol preparation		Minimum 001377
81-3 Acute inhalation LC50 Species: rat Interntl. Res. and Develop. Co 382-047; 11/3/78	Milocep		LC50 > 20.8 mg/L	4	Minimum 001378 Supplementaru 007418
81-3 Acute inhalation LC50 Species: rat Interntl. Res. and Develop. Co 382-076; 6/29/79	Propazine tech. 99.1 % a.i. (Milogard 90WDG)	238806 00111701	LC50 > 2.1 mg/L/4 hours. Bloody nasal discharge in 9/10 animals.	3	Minimum 001379 005823
81-3 Acute inhalation Species: rat Cannon Labs Inc. 7/2/79	Propazine 4L (44% a.i.) lot. # 07141	240864	All animals appeared normal during exposure period. Nnecropsy revealed no abnormalties. Actual atmospheric concentration (5.0mg/l) not high enough to define the appropriate toxicity category.		Supplementary 007419
81-4 Primary eye irritation Species: rabbit	Propazine 80 WP		Mildly irritating to the eyes. Dose: 50 mg undiluted test material.	3	001376

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Chemical:	**Propazine**
PC Code:	**080808**
HED File Code	**21200 CARC**
Memo Date:	**07/29/96**
File ID:	**DPD228305**
Accession Number:	**412-03-0019**

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