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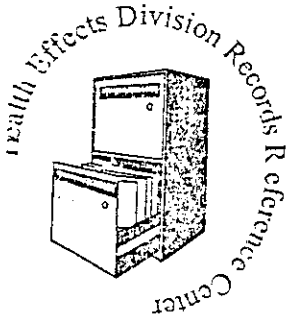
PC Code

080808 Propazine

Date of Package

8-6-96



Signature & Date

B Sjoblad 1-23-01

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

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 KB 7/29/96 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

012009

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.

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.

PROPAZINE, technical Mouse Carcinogenicity Study

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.

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) WRD 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.

1 of 31

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.

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.

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.

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.

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.

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.

Tox Chapter of 1987 Registration Standard

11

Ghali

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

SEP 12 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Propazine, Caswell No. 184. NOEL for 2-Year Rat Study

FROM: Toxicology Branch ADI Committee

TO: Robert Taylor, Product Manager #25
Registration Division (TS-767)

The data base on Propazine has been examined on several occassion by the Toxicology Branch ADI Committee. This Committee usually does not evaluate the actual data but bases its conclusion on existing DER's and checks the reviews and conclusions for consistency. In evaluating the DER of the 2 year rat study, the basis for the ADI/RfD for Propazine, an inconsistency was apparent since the review mentioned significant weight depression at 100 ppm and at the same time setting the NOEL at 100 pm. The Committee thus concluded that 3 ppm is the appropriate NOEL, as reflected in Dr. Dykstra's memo of 7/22/86.

However, one committee member subsequently evaluated the situation again, this time by looking at the data. His conclusion and report to the Committee was that the weight depression at both the 3 ppm and 100 ppm are not likely to be compound related since they were neither consistent throughout the study nor dose related. -- Therefore, the final conclusion is that 100 ppm is a NOEL for this study since the only compound related effects are apparent at 1000 ppm (HDT).

#14 9/12/86 sb

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM:

SUBJECT: Propazine; PP# 2F2618; Propazine in/on sorghum; Revised NOEL for 2-year rat study
Caswell No. 184

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

THRU: Edwin Budd, Section Head
Review Section II
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 7/22/86

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

William Dykstra 7/22/86

Recommendation:

1. For the two-year chronic/oncogenic rat feeding study (IRDC # 382-007; 4/28/80), the NOEL for chronic toxicity based on decreased body weight is considered to be 3.0 ppm (0.15 mg/kg/-day). The LEL is 100 ppm and the effect is decreased body weight in male and female rats.

2. The change of the NOEL from 100 ppm to 3 ppm is based on the re-evaluation of the propazine data base by the Toxicology Branch RFD/ADI committee. They concluded that decreased body weight was present at 100 ppm in rats for the major portion of the study and therefore could not be considered a NOEL.

cc: Dr. Ghali

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM:

SUBJECT: Propazine; PP# 2F2618; Propazine in/on sorghum; Revised NOEL for 2-year rat study
Caswell No. 184

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

THRU: Edwin Budd, Section Head
Review Section II
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 7/22/86

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

William Dykstra 7/22/86

Recommendation:

1. For the two-year chronic/oncogenic rat feeding study (IRDC # 382-007; 4/28/80), the NOEL for chronic toxicity based on decreased body weight is considered to be 3.0 ppm (0.15 mg/kg/-day). The LEL is 100 ppm and the effect is decreased body weight in male and female rats.

2. The change of the NOEL from 100 ppm to 3 ppm is based on the re-evaluation of the propazine data base by the Toxicology Branch RFD/ADI committee. They concluded that decreased body weight was present at 100 ppm in rats for the major portion of the study and therefore could not be considered a NOEL.

cc: Dr. Ghali

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

MEMORANDUM

004542

SUBJECT: PP# 2F2618; Propazine in/on sorghum; revised Section B and Section F
Caswell No. 184

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Robert P. Zendzian, Ph.D. 6/7/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 5/20/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

WDb 7.1.85

Requested Action:

Request to complete risk assessment for revised Section F, deleting sweet sorghum, and revised label adding restriction, "Do not use on sweet sorghum."

Conclusions:

1. The submitted studies are acceptable as core-minimum data. The oncogenic mouse study is negative for oncogenicity at doses up to 3000 ppm. The NOEL for the 3-generation reproduction study is 100 ppm.

2. In the two-year chronic feeding study in rats, propazine is considered oncogenic in female rats at the high-dose level of 1000 ppm. A significantly increased incidence of mammary gland tumors was observed.

Recommendation:

1. A quantitative risk assessment for dietary and applicator exposure is needed to complete the requested action.

Background:

Propazine was identified as a positive oncogen in female rats, producing a significant increase in tumor bearing animals at the high-dose of 1000 ppm.

On this basis, the review of propazine was referred to the Ad Hoc Committee on 6/16/84. The concesus of the committee was that a decision could not be reached based on the review of the studies. The committee requested that additional re-evaluation of the studies be performed and new reviews be presented. The presentation to the committee has been scheduled for May, 1985.

Review:

Section F Proposed Tolerances

Tolerances for residues of Propazine: 2-chloro-4,6-bis (isopropylamino)-s-triazine and its dealkylated metabolites determined as 2-amino-4-chloro-6-(isopropylamino)-s-triazine and 2,4-diamino-6-chloro-s-triazine in or on the following raw agricultural commodities are proposed;

1.0 ppm	Sorghum forage and fodder
0.02 ppm	Milk and eggs
0.05 ppm	Meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep, excluding kidney and liver
0.10 ppm	Liver and kidney of cattle, goats, hogs, horses, poultry, and sheep
0.25 ppm	sorghum, grain

1. Tolerances have been established in 40 CFR 180.243.

2. Two-year carcinogenicity study in mice with technical propazine (IRDC #: 382-004; April 24, 1980).

Test material: propazine technical; ARS No. 2046176; Batch No. FL-761357; 35 lbs., white powder.

Details of the materials and methods are attached as Appendix A.

004542

a. Study Author's results, and conclusions:

"No signs of overt toxicity were observed for any of the treated mice. No compound-related effects were observed with respect to the incidence of palpable masses, survival, group mean body weights or food consumption."

"No compound-related gross or microscopic changes were observed. The inflammatory, degenerative, proliferative and/or neoplastic changes described were considered of spontaneous nature, the prevalence of which were generally similar for both control and treatment groups and unrelated to compound administration. The slight increased incidence of lymphoreticular tumors seen initially among female mice at 3000-ppm treatment group was eliminated upon reevaluation of the data and examination of affected tissues in the 3 and 1000 ppm dietary levels." end of quote.

b. Reviewer's results and conclusions:

No compound-related toxic signs were recorded. Toxic signs observed most frequently in controls and test groups were pale skin, alopecia, tremors, corneal opacity, soft stools, altered posture, material on abdomen, ulcerations, and labored breathing. Mortality, body weight, and food consumption were unaffected by treatment.

The number of survivors in each group is shown below:

Survival at Termination of Study:

ppm	Males	Females
0	27	33
3	35	34
1000	37	27
3000	37	23

Palpable masses recorded did not display any compound-related findings.

The incidence of palpable masses in the study in shown below:

ppm	Male palpable masses/no. examined	Female palpable masses/no. examined
0	10/60	10/60
3	18/60	11/60
1000	3/60	15/60
3000	11/60	7/60

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Only three animals with palpable masses did not have a microscopic evaluation (3 ppm, male 24851 and male 25853; 1000 ppm, female 25062).

A good correlation of gross findings and microscopic findings was observed in all groups.

The incidence of amyloidosis in control and high-dose mice did not show any compound-related effect.

Amyloidosis in control and high-dose male and females is shown below:

Amyloidosis

No. affected/no. examined

ppm	Male	Female
0	53/59	56/60
3000	58/60	57/60

Other non-neoplastic lesions occurred at increased incidences in high-dose male and female mice.

In females, myocardial degeneration of the heart was increased as follows:

No. affected/no. examined

0 ppm	4/60
3000 ppm	17/59

For males, hemosiderin laden macrophages of the liver occurred in the follow manner.

No. affected/no. examined

0 ppm	3/60
3000 ppm	15/60

These non-neoplastic finding are considered compound-related.

Neoplastic lesions did not occur in a compound-related fashion.

Preliminary evaluation of the reticuloendothelial system indicated a significant increase in malignant lymphoma in females at 3000 ppm.

The distribution was as follows as reported in the study.

ppm	0	3	1000	3000
No. examined	61	49	45	59
malignant lymphoma	16	20	30	32*

*P<0.01

However, instead of counting the presence of malignant lymphoma as only one per animal, it was erroneously reported in terms of the total number of tumors per group.

A re-evaluation of the incidence of malignant lymphomas in female mice based on one per animal is presented below.

The following table also shows the lack of an effect of latency in tumor development in female mice.

Latency and Incidence of Malignant Lymphoma/Reticulum Cell Sarcoma

(Control)

*Animal number
a weeks on study

Female

0 ppm	Weeks	3 ppm	Weeks	1000 ppm	Weeks	3000 ppm	Weeks
24783*	105[a]	24903	85	25027	81	25149	85
24788	105	24908	76	25032	88	25152	89
24791	105	24922	96	25048	50	25172	20
24806	20	24923	51	25056	86	25174	105
24831	83	24942	105	25059	105	25177	27
24842	93	24951	102	25062	72	25183	84
25203	105	24952	80	25064	82	6	
7		24960	105	25065	105		
		8		25072	90		
				25078	40		
				10			

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Conclusion:

Propazine was not oncogenic in mice. The presence of significant incidences of non-neoplastic lesions in high-dose males were hemosiderin laden macrophages and myocardial degeneration in high-dose females. The NOEL is 100 ppm. The LOEL is 3000 ppm HED
Classification: Core minimum data.

3. Two-year chronic oral toxicity study in rats (IRDC # 382-007; 4/28/80).

Test material: Propazine technical; ARS No. 2046/26; Batch No. FL-761357; 35 pounds; white powder.

I. Details of the Materials and Methods are attached as Appendix B.

a. Study author's results and conclusions.

"A slight increase in subcutaneous nodules and masses in female rats from the 1000-ppm group was considered possibly compound-related. No organ weight variations of toxicological significance were observed. There was an increase in the number of adenomas in the mid- and high- dose group, in the number of papillary carcinomas in the low- and high- dose group and in adenocarcinomas in all treated groups without any dose relationship. None of these increases were statistically significant and none were considered treatment related." end of quote.

b. Reviewer's Results and Conclusions.

No treatment-related toxic signs were observed in any group. No compound-related effect on survival was observed. At termination of the study the following animals survived.

ppm	males	females
0	31	36
3	42*	37
100	46	46
1000	38	25

Body weight of males and females of the high-dose were significantly decreased in comparison to controls.

Food consumption was significantly decreased in high-dose male and female rats. However, this finding was not considered totally responsible for the decreased body weight differences in these groups.

No compound-related effects were noted in hematology, clinical chemistry or urinalyses in controls and the 1000 ppm groups.

Gross necropsy findings showed an increase of subcutaneous masses and nodules in females of 1000 ppm group. These increased nodules correlated with the increased microscopic finding of mammany gland neoplasms.

Organ weights at terminal sacrifice showed an increased relative liver weight in females 1000 ppm, a decreased absolute kidney weight in 1000 ppm males and a decreased absolute brain weight in females of the 1000 ppm group.

At termination of the study, the following animals were examined.

Group	Dosage Level	sex	terminal sacrifice	moriburd sacrifice and deaths	total evaluated
I	control	m	26	18	44
		f	36	19	55
II	3 ppm	m	36	10	46
		f	37	20	57
III	100 ppm	m	42	11	53
		f	44	16	60
IV	1000 ppm	m	36	18	54
		f	25	30	55

There was a good correlation between gross and microscopic findings.

Neoplasms involving the mammary gland included adenomas, adenocarcinomas, fibroadenomas, papillary adenomas and papillary carcinomas.

Mammary gland tumors were increased in high-dose female rats as follows:

ppm	No. of tumor-bearing animals/ no. examined
0	27/56
3	33/57
100	32/60
1000	39/55 *P<0.05

The increase in tumor-bearings animals is significant and considered compound-related.

The most frequent mammary tumor was fibroadenoma.

The distribution and type of mammary gland tumors in control and high-dose female rats is presented in Table I.

Additionally, no treatment-related non-neoplastic lesions were observed.

Conclusion: A compound - related increase in mammary gland tumors in female rats was observed. Other toxicological parameters examined did not show any treatment-related findings. NOEL = 100 ppm ; LEL = 1000 ppm ; positive for oncogenicity at 1000 ppm.

Classification: Core minimum data.

WHO

Table 1

Mammary Tumors in Female Rats Fed Propazine

* Number of tumor-bearing animals

	Group I - control					Group IV - 1000 ppm				
	Terminal	Moribund	Deaths	Total	%	Terminal	Moribund	Deaths	Total	%
No. examined	36	8	12	56		25	15	15	55	
Papillary carcinomas	2*	1	0	3	5.4	6	1	3	10	5.4
Fibroadenoma	13	0	3	19	33.9	8	5	3	16	29.0
Papillary adenoma	1	0	0	1	1.8	0	1	1	2	3.6
Adeno carcinoma carcinoma	5	1	0	6	10.7	6	3	1	10	18.1
Ductular adenoma	0	0	0	0	0	0	1	0	1	1.8
Cystadenoma	1	0	0	1	1.8	0	0	0	0	0
Adenoma	1	0	0	1	1.8	0	0	0	0	0

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4. Three generation reproduction study in rats with propazine technical (IRDC # 382-010; 8/10/79).

Test material: Propazine technical; ARS. No. 2046/76; Batch No. FL-76/357; 35 lbs; white powder.

Details of the materials and methods are attached as Appendix C.

a. Study author's results and conclusions:

"No biologically meaningful differences were seen in the food consumption values in all F_0, male treatment groups, in the 3 and 100 ppm F_0, F_1, and F_2 females, and in the 1000 ppm F_1 females when compared to the control values. A slight reduction in food consumption was observed in the 1000 ppm dosage groups of the F_0 and F_2 females and in all treatment groups of the F_1 and F_2 males when compared to the control group."

"No treatment-related differences were seen between the treated and control groups with regard to the male and female fertility indices, length of the gestation periods and the viability and survival of the pups."

"No biologically meaningful differences were seen in the mean pup body weights of the litters in the 3- and 100- ppm treatment groups when compared to the control litters. At the 1000-ppm treatment level, the mean pup body weights of each of the six litters produced were consistently lower than the mean weights of the control pups."

"No gross or microscopic pathological lesions which were considered compound-related were observed in the F_0, F_1, F_2 parental rats or F_{3b} weanling rats. The changes described among these rats were considered of spontaneous nature, not uncommon to rats of this age, and were present in most instances among control and 1000-ppm dose level rats."

"A dose level of 100 ppm Propazine technical or less produced no biologically meaningful signs of parental or pup toxicity when administered in the diet during a three-generation reproduction study in rats. Therefore, the no observable effect level (NOEL) in this study was 100 ppm." end of quote.

b. Reveiwer's Results and Conclusions.

No compound-related effects in toxic signs and mortality were observed during the study.

At 1000 ppm during the study, decreased body weight was observed in male and female parental animals.

Food consumption was reduced at 1000 ppm in the F_0 and F_2 females and at 3,100, and 1000 ppm of the F_1 and F_2 male groups.

No compound-related effects in male fetility, female fertility, gestation length, pup viability and pup survival were observed in any litter during the study.

Mean body weights of male and female pups at day 21 of lactation were significantly reduced at 1000 ppm in the F_{1b}, F_{2a}, F_{2b}, F_{3a} and F_{3b} litters. This finding in considered compound-related.

At necopsy of parental animals and 21-day old pups, no treatment-related effects were recorded. Absolute and relative organ weight variations were observed in parental animals.

In the F_0 animals, males showed an increased relative testicular and relative heart weight at 1000 ppm.

Males of the F_1 parental group at 1000 ppm displayed increased relative liver and heart weight.

In the F_2 parental animals at 1000 ppm, males and females had decreased absolute liver weight, males had decreased relative liver weight, decreased relative testicular weight, and decreased absolute kidney weight.

At 100 ppm, females had decreased absolute and relative ovarian weight. This finding is not considered compound-related since it was not observed at 1000 ppm.

At 3 ppm, females had an increased relative liver weight. This finding is not considered compound-related, since females at higher dosage level did not show this finding.

No histological effects were present in parental animals which could further explain the organ weight variations.

Additionally, no effects in incidence or grade of histological findings were present in F_0, F_1, and F_2 parental animals and F_{3b} weanlings at 1000 ppm in comparison to controls.

Conclusion: The NOEL for reproductive parameters is 100 ppm. At 1000 ppm, the LEL, decreased pup body weights at day 21 of lactation were significantly reduced in the F_{1b}, F_{2a}, F_{2b}, F_{3a} and F_{3b} litters of both males and females.

Organ weight variation at 1000 ppm was also recorded in parental animals. No histological findings were obsrved in parental or weanling animals.

Classification: Core minimum data.

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

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) WSD for LDC 6/10/81

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

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.

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.

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.

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.

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.

The basal laboratory diet was ground Purina Laboratory Chow. The rats were identified individually with numbered ear tags. Beginning on July 26, 1977, ear tag verifications were recorded at each cage change, before and after blood and urine sample collection and before necropsy. The study was initiated on July 27, 1976; there were two interim sacrifices, one at 12 months and a second at 13 months of study because of the following experimental procedure.

Ten additional male and 10 additional female rats were initiated in the control and high-dose groups; of these additional animals, five of each sex were sacrificed and necropsied after 12 months of study. The remaining five of each sex were placed into a compound-withdrawal group and fed a control diet for 4 weeks and then sacrificed and necropsied. During 4 week of study, Group III female 38160 replaced 39644 which died. The study was terminated on July 26-28, 1978.

Propazine technical was fed in the diet at the following dosage levels:

Dosage Level ppm	Number of Rats	
	Male	Female
0 (control)	70	70
3	60	60
100	60	60
1000	70	70

The rats were observed twice daily for signs of overt toxicity, moribundity and mortality. Detailed observations were recorded weekly.

Individual body weights were recorded weekly for the first 3 months and monthly thereafter. After one year of study individual body weights and food consumption were recorded weekly for rats placed on withdrawal.

Individual food with compound consumption values (for 10 rats/sex/group) were recorded weekly for the first 3 months and monthly thereafter. After one year of study, individual food consumption values were recorded weekly for the rats placed on withdrawal. Food efficiency was calculated through 30 weeks of study.

Blood and urine samples were obtained from 10 rats/sex for both the control and high-dose groups at 3, 6, 12, 18 and 24 months of study. Prior to sample collection the rats were housed overnight in metabolism cages (without food or water). The blood was obtained by the orbital sinus technique.

Hematologic tests included hemoglobin, hematocrit, total and differential WBC, total RBC, total platelet count, prothrombin time, and partial thromboplastin time.

Biochemical tests included fasting blood glucose, BUN, SGOT, SGPT, SAP, serum total protein and total cholesterol.

Urinalyses included a description of appearance, measurement of volume.

Five male and five female rats from the control group and the 1000 ppm group were sacrificed with carbon dioxide asphyxiation and necropsied after 12 months of compound feeding.

The five male and five female rats from these groups which were placed in compound withdrawal were sacrificed and necropsied after 4 weeks of compound withdrawal. All remaining rats were sacrificed and necropsied after 2 years of compound withdrawal. At necropsy, an examination was made of the external body surface and body orifices. The rat was then opened and the contents of the body cavities were examined in situ, removed and again examined. Liver, kidneys, spleen, heart and testes were weighed fresh at necropsy.

Representative tissues and organs from each rat were collected and fixed in phosphate buffered neutral 10% formalin. Adrenal glands, thyroid and ovaries were weighed after fixation.

Rats which died or were sacrificed in extremis during the course of the study were necropsied as above except no organs were weighed.

Hematoxylin and eosin stained paraffin sections were prepared at IRDC by standard histologic methods and examined microscopically from all rats from the control and 1000 ppm groups which were sacrificed after 12 months of study or which died or were sacrificed in extremis during the first 12 months of study.

adrenal gland
aorta
bone marrow
brain (cerebrum, cerebellum, pons)
cecum
colonm
esophagus
eye
gonads
harderian gland
peripheral nerve (sciatic)
pituitary gland
prostate
salivary gland (submaxillary)
skin
small intestines (duodenum, jejunum, ileum)
spinal cord
heart
kidney
liver
lung
lymph node (cervical and mes.)
mammary gland
muscle
optic nerve
pancreas
parathyoid
spleen
sternum
stomach (cardia, fundus, pylorus)
thyroid
trachea
urinary bladder
uterus
any other tissue with gross lesions

The above tissues from rats which were sacrificed at termination or which died or which were sacrificed in extremis during the period 12-24 months were delivered to Experimental Pathology Laboratories, Inc., Herndon, Virginia for histologic processing and microscopic examination.

Statistical analyses of the data were performed.

Results:

No signs of overt toxicity were observed among treated animals. Incidental findings seen occasionally among control and treated rats included skin lesions, hair loss, material around eyes and nose, material around anogenital region, lacrimation, corneal opacity, labored breathing and respiratory congestion, discolored urine, soft stools, swollen hind feet (hard to the touch in several cases), raised pink areas on ventral surfaces, exposed areas of skin and eyes pale, excessive salivation and ventral neck swollen.

Palpable masses were observed and recorded in all groups; there were no greater numbers of masses in treated rats than in controls. The number of palpable masses in the rats at 104 weeks of the study were as follows:

	I (0)		II (3 ppm)		III (100 ppm)		IV (1000 ppm)	
	Male	Female	Male	Female	Male	Female	Male	Female
o. of masses	9	57	19	75	18	75	15	82
urvival (104 wks)	31/60	36/60	42/60	37/60	46/60	46/60	38/60	25/60
rats with masses	19	75	31	73	30	72	32	92
with single masses	67	37	69	37	71	36	92	30
vith multiple masses	33	63	31	63	29	64	8	70

All groups generally showed a decrease in rate of body weight gain with an increase in dosage of compound. A t-test comparison between means and the ratio of change in body weights of control and treated groups showed that for female rats of the low-dose (3 ppm), a statistically significant decrease occurred between weeks 26 through 65; for female rats of the middle-dose (100 ppm), a statistically significant decrease occurred between weeks 0 through 104; for female rats of the high-dose (1000 ppm), a statistically significant decrease occurred between weeks 0 through 104. Similarly, for male rats at the low-dose (3 ppm), a statistically significant decrease occurred between weeks 0 through 104; for male rats at the middle-dose (100 ppm), a decrease (though not statistically significant) occurred though most of the weeks from 0 to 104; and for high-dose (1000 ppm) male rats, a statistically significant decrease occurred through weeks 0 to 104.

There was little difference in the amount of food consumed per day between the control and treated rats, although a slight decrease was noted for both males and females in the high-dose group. This slight decrease in food consumption was not enough to account for the significant decrease in body weights. There were no compound-related effects in hematologic tests, biochemical tests and urinalyses; although a few values were statistically significant, all were within the expected ranges, and no trends of increase or decrease were evident.

Although statistical variations occurred in sex group mean weights of a number of organs of rats in the treated groups, there was no dose response evident and the organs which had statistical weight variations were not the site of compound-related gross or microscopic morphologic lesions. These weight variations therefore were not considered of toxicological significance.

The number of subcutaneous masses and nodules in female rats from the 1000 ppm group was slightly increased when compared to the control group at gross necropsy.

12-Month Interim Sacrifices, Deaths 0-12 Months

No microscopic pathologic lesions which were considered related to Propazine feeding were seen in any tissues examined from rats from the 1000 ppm group which were sacrificed at the 12-month interim or which died or were sacrificed in extremis during the first 12 months of study. Microscopic findings in these rats were those which commonly occur in untreated rats of this age and strain. They were primarily lesions of mild inflammatory conditions or early degenerative changes and they occurred with similar frequency and severity in rats from the control group and 1000 ppm group.

Terminal Sacrifices, Deaths 12-Months to Termination

A variety of microscopic changes was observed in most of the organs and tissues in both the control and high-dose (1000 ppm) groups of rats. These occurred either infrequently or with similar distribution between the two groups and are considered unrelated to the exposure to the compound. These changes were most evident in the lungs and kidneys. The lung changes were representative of the chronic respiratory disease complex (Murine Respiratory Mycoplasmosis). These changes included varying degrees of mutifocal to diffuse pneumonitis with peribronchial and perivascular lymphnoid cell accumulations and focal accumulations of foamy macrophages. Multifocal hemorrhages of the lung were also observed in both the control and treated rats changes related to this complex were also observed in the tracheas and hearts of individual rats in both the control and treated groups.

The changes in the kidneys were compatible with the microscopic lesions of the chronic progressive glomerulonephrosis and nephritis observed in most rat strains.

Incidental changes were present in the livers from both control and treated rats. A low incidence of hepatocellular carcinoma and adenoma occurred in both the control and treated rats. Other hepatic changes, seen with a higher frequency but with similar distribution in the control and treated rats, included bile duct hyperplasia, multifocal hepatocytomegaly and multifocal to diffuse vacuolation.

A generally low incidence of neoplasms was observed in most organs and tissues from both the control and treated groups except for the pituitary, testes and mammary gland. Pituitary adenomas and carcinomas were commonly observed, although evenly distributed among the control and treated groups, there was a higher incidence in the female rats. Interstitial cell tumors occurred in the testes of some rats in the control and treated groups. There was a slightly higher incidence of this tumor in the high-dose group of rats (8/64, control vs. 12/64, high-dose) which was considered to be a biological variation and not a treated-related change.

Three was a high incidence of hyperplastic mammary gland changes in the control and all three test groups of female rats. The severity of these hyperplasia changes of the mammary glands made it difficult in individual rats with mammary gland neoplasms to classify the type of mammary gland tumor present in the animal. Areas of glandular hyperplasia (lobular) were present in areas of relatively normal mammary gland as well as within the benign adenomas and fibroadenomas observed in both the control and all three groups of treated animals. The classification of mammary gland tumors used in the report is set forth in the Pathology of Tumors in Laboratory Animals, Volume I, Tumours of the Rats, Part I by V.S. Turusov. Individual animals, the histological differentiation between adenomas and well differentiated carcinomas of the mammary gland was made difficult due to the degree of hyperplastic change present. Classification of the tumors as adenocarcinomas or papillary carcinomas was used when one or more of the following criteria was present within the tumor: (1) loss of normal glandular architecture; (2) pronounced variability in cytologic features; (3) prominent nucleoli; (4) numerous mitotic figures; (5) multiple layering of the epithelium; (6) lack of cellular orientation; and (7) local invasion.

The male rats in this study had very few tumors of the mammary gland. No tumors of the mammary glands were present in the male or female rats which died before the twelve-month sacrifice. The female control rats and rats exposed for a longer period of time had a high incidence of mammary gland tumors. The distribution of the mammary gland tumors in the female rats from the two-year sacrifice is presented in Table I.

TABLE I
Distribution of Mammary Gland Tumors

	Group I Control	Group II 3 ppm	Group III 100 ppm	Group IV 1000 ppm
No. Examined	(55)	(57)	(60)	(55)
TYPE OF TUMORS				
Adenomas No./Rat	3/3	3/3	5/5	10/10
Fibroadenoma No./Rat	34/22	37/22	31/24	35/24
Adenocarcinoma No./Rat	9/6	12/11	11/8	13/9
Papillary Carcinoma No./Rat	4/4	12/7	4/3	12/8
MALIGNANT TUMORS				
Total/Rat	13/9	24/17	15/10	25/14*
Average Tumor/Rat	1.44	1.41	1.50	1.78
Percentage of Tumor-Bearing Rats	16.4%	29.8%	16.7%	25.5%
BENIGN TUMORS				
Total/Rat	37/24	40/25	36/26	45/30**
Average Tumor/Rat	1.54	1.60	1.38	1.50
Percentage of Tumor-Bearing Rats	43.6%	43.9%	43.3%	54.5%
TOTAL MAMMARY GLAND TUMORS				
Total/Rat	50/28	64/33	51/32	70/40***
Average Tumor/Rat	1.78	1.94	1.69	1.75
Percentage of Tumor-Bearing Rats	50.9%	57.9%	53.3%	72.7%

*Twelve tumors in two rats.
**Nine tumors in two rats.
***Twenty-one tumors in four rats.

The most frequent mammary gland tumor present in female rats was the fibroadenoma which had a fairly equal distribution among the control and the three treatment groups.

Adenomas had a similar distribution in the control and treatement Groups II (3 ppm) and III (100 ppm) while there was an increase in the number of adenomas in Group IV (1000 ppm). Adenocarcinomas were fairly equally distributed among the control and three treatment groups.

Papillary carcinomas were similar in occurrence in the control group and Group III (100 ppm) with an increased incidence in Group II (3 ppm) and Group IV (1000 ppm).

A comparison of the number of female rats having mammary gland tumors shows a higher incidence of animals with mammary gland tumors in the high dose group (1000 ppm) when compared to the control group. The increase is due to an increase in the incidence in both benign and malignant tumor-bearing animals in the high-dose group.

A difference in the number of tumor-bearing animals is not observed between the low (3 ppm), middle (100 ppm) and control group of female rats in this study. A comparison of the number of tumors per individual animal does not show any substantial difference between these ratios in the control and the three treated groups of rats with respect to the total number of mammary gland tumors, malignant tumors or benign tumors. However, evaluation of the individual animals in the high dose group (1000 ppm) shows two animals (No. 39814 and No. 39832) with twelve malignant mammary gland tumors (seven and five tumors, respectively) and two animals (No. 39799 and No. 39804) with nine benign tumors (five and four, respectively). This is a total of twenty-one tumors in four rats from the high dose group. Even though there is an apparent increase incidence of mammary gland tumors in the high dose group, it may be difficult to conclude that this increased incidence of mammary gland tumors was related to the exposure to 1000 ppm of Propazine technical. A high incidence of mammary gland tumors occurred in all groups of female rats in this study. Instances of fifty-five percent, sixty-two percent, sixty-four percent and as high as eighty-five percent have been reported in Sprague-Dawley rats (Sher, Sanford P., Toxicology and Applied Pharmacology, 22 (1972); pp. 562-588.) These data, however, did not come from IRDC.

Conclusions:

A statistically significant (Fisher's Exact test, P = 0.015) increase in rats bearing mammary tumors occurred in the high-dose female rats. The increase in the total number of tumor-bearing animals in the high-dose group may reflect a biological variation in Sprague-Dawley rats. The historical control data of mammary tumors in Charles River CD rats at IRDC from 1975-1979 has been submitted by the registrant and the number of female rats bearing mammary tumors compared to the number of female rats examined is 769/1528 (50.3%). The historical control data was compared to the high-dose female rats using 2x2 contingency Chi-Square analysis. A statistically significant increase (p = .0011) was seen in the mammary adenomas and number of tumoring bearing rats in the T-III females (1000 ppm).

Therefore it can be concluded that Propazine technical at dietary levels of 1000 ppm was weakly oncogenic to female rats producing increased mammary gland tumors.

Test for Significance of Differences Between Proportions 11/15/80

Mammary neoplasms in rats

ppm	# +DSP	Total	% +/-2(S.E.)	One Tail P Statistic Fisher's
0.000	28	55	50.91+/-(14.12)	
3.000	33	57	57.89+/-(13.69)	0.290
100.000	32	60	53.33+/-(13.46)	0.471
1000.000	40	55	72.73+/-(12.68)	0.015

Test for Linear Trend in Proportions P = 0.015

The pathologist for the study had difficulties in attributing these findings to administration of propazine for the following reasons:

1) Most of the mammary glands in the rats in this study (control and treated) had some degree of hyperplastic change probably due to some extent to the large number of pituitary tumors in the rats in this study.

2) A high incidence of mammary gland tumors occurred in all groups of female rats in this study. Instances of fifty-five percent, sixty-two percent, sixty-four percent and as high as eighty-five percent have been reported in Sprague-Dawley rats (Sher, Sanford P: 1972, Tox. Appl. Pharmacol. 22: 562-588.

3) There was an absence of any significant increase in the number of tumors in the mammary glands of male rats or in any of the rats sacrificed prior to twelve months on study.

4) A similar distribution and incidence of mammary gland tumors in the control group and in Group III (100 ppm) demonstrated a lack of dosage-related response.

Classification: Core-Minimum Data

3. Three-Generation Reproduction Study in Rats with Propazine Technical (IRDC Report No. 382-010; August 10, 1979)

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

Forty male (weighing from 121 to 175 gm) and 80 female (weighing from 96 to 148 gm) Charles River CD rats were initiated on this study. The rats were evenly distributed among each of three treatment groups and one control group (10 males/group and 20 females/group). Placement of the rats was made so initial group mean body weights for each sex were similar. Littermates, by sex, were evenly distributed among the groups.

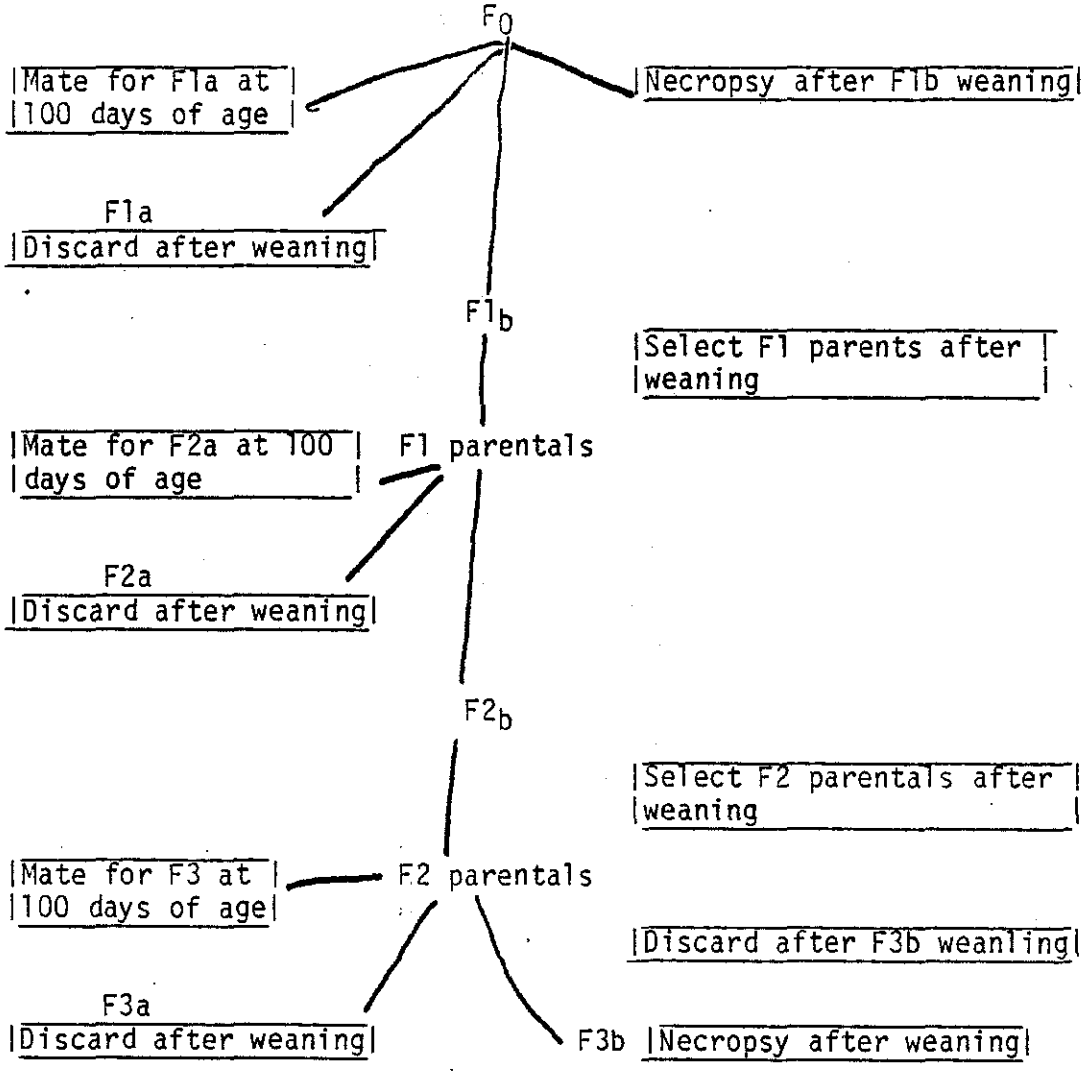
Except during mating and through lactation, the rats were individually housed in hanging wire-mesh cages. During the initial mating periods, the rats were housed in units of one male and two females in plastic boxes on ground corn-cob bedding.

During the second or third remating periods, some males were housed with one female. Following the mating periods and during lactation, the females were individually housed in plastic boxes on ground corn-cob bedding and the males in hanging wire-mesh cages. Throughout the span of this study, the rats were housed in a temperature-, humidity-, and light- (12 hours on/off) controlled room. Tap water and the control and test diets were available ad libitum.

The study was initiated on September 7, 1976 and terminated with the last sacrifice on July 3, 1978.

Propazine technical was administered in the diet at fixed percentages to achieve dosage levels of 3, 100 and 1000 ppm . Ten male and 20 female rats were initiated at each treatment level and one control group.

Shown below is the breeding schematic used in the study.



The control and treated rats were maintained on their respective diets throughout the duration of the first generation (F_0). After 77 days of treatment and at approximately one hundred days of age, the F_0 parental rats were initially housed in units of one male and two females within the same treatment group to produce the $F1_a$ litters. The rats were housed together for a maximum of 21 days. The females were vaginally smeared daily during this period until sperm or a copulatory plug was observed. This finding was designated gestation day 0.

If no evidence of mating was observed after two estrous cycles (appproximately ten days), those females were housed with a different male within the same treatment group for an additional 10 days. This procedure was repeated once. No more than three different males were used with each female during the mating period. Just prior to expected parturition or at the end of the maximum mating period, the rats were separated and individually housed. The females were allowed to deliver. The day all pups in a litter were found was designated lactation day 0. During lactation, the pups were counted, sexed and weighed at designated intervals. At weaning, the Fla pups were examined for external abnormalities, sacrificed and discarded.

After weaning, the F_0 parental females were allowed a minimum 10-day rest period and then mated a second time to produce the F_{1b} litters. The mating procedure was identical to the F_{1a} mating, except the females were housed with different males within the same treatment group.

The rats were housed together for a maximum of 30 days. The females were vaginally smeared daily during this period until sperm or a copulatory plug was observed (gestation day 0).

If no evidence of mating was observed after two estrous cycles, those females were housed with a different male within the same group for an additional 10 days. This procedure was repeated once. No more than three different males were used with each female during the mating period.

Just prior to expected parturition or at the conclusion of the maximum mating period, the rats were separated and individually housed. The females were allowed to deliver.

The day all pups in a litter were found was designated lactation day 0. The F_{1b} pups were counted, sexes and weighed on designated days during lactation. After weaning, 10 male and 20 female F_{1b} pups were selected from each group to comprise the second generation (F_1) parents. Also after weaning and following approximately 33 weeks on test, all surviving male from each group were sacrificed and necropsied. Any F_{1b} pups not selected for study continuation and the remaining parental females were sacrificed and discarded.

The F_1 parental rats, selected from the F_{1b} litters, remained on their respective control or treated diets during the span of this generation. At approximately 100 days of age, the parental rats were mated to produce the F_{2a} litters. The mating procedure was identical to the F_{1a} mating with avoidance of brother-sister matings. The rats were housed together for a maximum of 30 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1a}. At weaning, the F_{2a} pups were examined for external abnormalities, sacrificed and discarded.

Following a minimum of 10 days after weaning, the F_1 parental rats were mated a second time in a manner identical to the F_{1b} mating and avoiding brother-sister matings to produce the F_{2b} litters. The rats were housed together for a maximum of 31 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1b}.

After weaning, 10 male and 20 female F_{2b} pups were selected from each group to comprise the third generation (F_2) parents. Also after weaning, all surviving male and 10 female F_1 parental rats from each group were sacrificed and necropsied. Any F_{2b} pups not selected for study continuation and the remaining parental females were sacrificed and discarded.

The F_2 parental rats, selected from the F_{2b} litters, remained on their respective control or treated diets until termination of the study.

At approximately 100 days of age, the parental rats were mated to produce the F_{3a} litters. The mating procedure was identical to the F_{1a} mating with avoidance of brother-sister matings. The rats were housed together for a maximum of 31 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1a}. At weaning, the F_{3a} pups were examined for external abnormalities, sacrificed and discarded. Following a minimum of 10 days after weaning, the F_2 parental rats were mated a second time in a manner identical to the F_{1b} mating and avoiding brother-sister matings to produce the F_{3b} litters. The rats were housed together for a maximum of 30 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1b}.

After weaning, 10 male and 10 female F_{3b} pups were selected from each group, sacrificed and necropsied. Also after weaning, all surviving males and 10 female F_2 parental rats from each group were sacrificed and necropsied. The remaining parental females and F_{3b} pups were sacrificed and discarded.

The parental rats and pups were observed daily for signs of overt toxicity, changes in general behavior and appearance and mortality. Detailed observations, individual body weights and food consumption were recorded on a weekly basis for the parental rats. Specific observations for the reproduction aspects of the study included male and female fertility, length of the gestation period, numers of male and female pups at weaning and the viability, growth and survival of the pups through weaning. The number of pups surviving at lactation days 0, 5, 14 and 21 were recorded. Litter size was reduced to 10 pups of equal sex ratio, if possible, on day 5 of lactation. Individual pup body weights were recorded on day 21 of lactation.

As mentioned previously, at intervals during the study, 10 male and 10 female F_0, F_1 and F_2 parental rats from each group were sacrificed with carbon dioxide and necropsied. Ten male and 10 female rats from each group from the F_{3b} generation were also sacrificed at the conclusion of the study. At necropsy, contents of the cranium, thorax and abdomen were examined in situ and after removal. Representative tissues from each rat were collected and fixed with buffered 10% neutral formalin. All pups and parental rats which died during the course of study were also necropsied. Hematoxylin and eosin stained paraffin sections of the following tissues were prepared and examined from rats in the control and high dose group of the F_0, F_1 and F_2 parental rats and the F_{3b} weanling rats:

adrenal gland
bone marrow (sterum and femur)
brain (cerebrum, cerebellum, pons)
large intestine (2 levels)
esophages
eye
heart
kidney
liver
lymph node (cervical and mesenteric)
mammary gland
optic nerve
ovary
pancreas
parathyroid
peripheral nerve (sciatic)
pituitary gland
prostate
salivary gland (parotid, sublingual, submaxillary)
seminal vesicles
small intestines (3 levels)
spinal cord (3 levels)
spleen
stomach
testes
thyroid
trachea
urinary bladder
uterus
lung

Organs underlined above were weighed at necropsy.

Statistical analyses of the data were performed.

Results:

No changes considered to be related to treatment of Propazine technical were seen in parental rats in relation to the general behavior, appearance or survival of the treated rats when compared to the controls. No difference were seen between the pups in the control and treated groups with respect to the general behavior, appearance or survival which was considered treatment related. Differences in the mean body weights of the parental rats receiving Propazine technical at dosage levels of 3 and 100 were not considered treatment related. At study week 63, mean body weights of the F_2 100 ppm parental females were statistically significant higher than the control females. This difference was not considered treatment related. At the 1000 ppm treatment level, the parental mean body weights of both the males and females were generally lower than the control group throughout treatment of Propazine technical. Statistical significance of these differences were not evident at all points of analysis. At this treatment level, the mean body weights of the F_0 females at study weeks 10 and 33; the F_1 males at study week 63, the F_1 females at study weeks 41 and 63 and the F_2 females at study weeks 72 and 95 were statistically significantly lower than their respective control group.

No treatment-related differences were seen between the control and treated groups with respect to male and female fertility, the length of the gestation periods and the viability and survival of the pups through weaning. The gestation survival index of the F_{2b} litters in the 100 ppm treatment group was statistically significant higher than the control group, but this difference was not considered a result of treatment. No biologically meaningful or statistical significant differences were seen in the mean pup body weights of the litters at lactation day 21 in the 3 and 100 ppm treatment groups when compared to the control itters. The mean pup body weights of each of the six litters producted (F_{1a}, F_{1b}, F_{2a}, F_{2b}, F_{3a}, F_{3b}) at the 1000 ppm treatment level were consistently lower than the mean weights of the control pups. Statistical significance was noted in all but the F_{1a} litters at this treatment level.

No gross pathological lesions or abnormalities which are considered compound-related were seen at necropsy in any F_0, F_1, F_2 parental rats or F_{3b} weanling rats which were sacrificed at termination or which died during the course of study and were examined.

Statistiical analysis or organ weights showed the following significantly different means in the treatment groups when compared with the control groups. In the absence of any morphologic change, the biological significance of these organ weight variations is unknown.

Organ	Dosage Level ppm	Sex	Weight	Change	p <
F_0 Generation					
testes	1000	M	relative	increase	0.05
heart	1000	M	relative	increase	0.05
F_1 Generation					
liver	1000	M	relative	increase	0.05
heart	1000	M	relative	increase	0.05
F_2 Generation					
liver	3	F	relative	decrease	0.05
	1000	M	absolute, relative	decrease	0.01, 0.05
	1000	F	absolute	decrease	0.05
kidneys	1000	M	absolute	decrease	0.05
testes	1000	M	relative	increase	0.01
ovaries	100	F	absolute, relative	decrease	0.01, 0.01

No microscopic morphological changes considered compound-related were seen in the F_0, F_1, F_2 parental rats or F_{3b} weanling rats sacrificed at termination.

Conclusion:

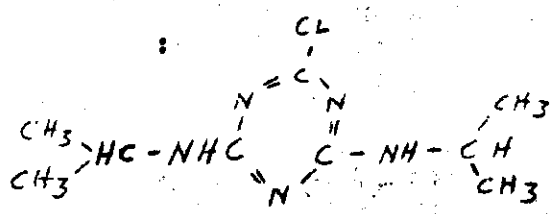
The NOEL for reproductive parameters in the study is 100 ppm. The LEL is 1000 ppm and the reproductive effect was statistically significantly reduced mean pup body weights in five of six litters.

Classification: Core-Guideline Data

TS-769:th:TOX/HED:WDykstra:6-8-81:#1

184

RDCoberly:bjc
August 7, 1968

Chemical Name	:	2 - Chloro-4,6-bis-(isopropylamino) s-triazine.
Trade Name	:	**Propazine**
Chemical Structure	:	
Physical State	:	**Solid**
Use	:	Herbicide
Company	:	Geigy

SUMMARY

These data indicate that the material has a low degree of acute lethal toxicity by the oral dermal and inhalation routes of exposure. The subacute studies also indicate a low degree of toxicity.

This material should not create an undue hazard when used as a herbicide.

Acute Mouse Oral	:	LD_{50} = >5.0 gm/KG
Acute Rat Oral	:	LD_{50} = >5.0 gm/KG
Acute Rabbit Dermal (80W)	:	LD_{50} = >10.2 gm/KG No effects noted.
Acute Rat Inhalation (80W) (4 hrs.)	:	LC_{50} = >0.07 mg/L of active ingredient
Rabbit Eye Irritation (80W)	:	Mildly irritating
Acute Rat Inhalation (80W)	:	LC_{50} = >3.3 mg/KG
Subacute Rat Dermal (50W) (5 days)	:	No effects were noted at levels tested ie: 60 and 130 mg/KG.
21 Day Rabbit Dermal (80W)	:	Levels tested were 1.0 and 2.0 gm/KG. Effects noted at 2.0 gm/KG.
28 Day Rat Oral	:	Levels tested were 1250 and 2500 mg/KG. Weight retardation noted at both levels.
90-180 Day Rat Oral (50W)	:	Mortality at 2500 mg/KG. Possible effects at 250 mg/KG.
90 Day Dog Feeding (80W)	:	Levels tested were 50, 200, and 1000 ppm. Body weight loss at 1000 ppm.
90 Day Rat Feeding (80W)	:	Levels tested were 50, 200, and 1000 ppm. Body weight loss at 1000 ppm.
Metabolic Study (Rats)	:	Propazine is absorbed and excreted mainly in the urine and feces.
Metabolism Study (Rat)	:	See Report.

PROPAZINE

Acute Mouse Oral

10 mice were tested per dosage level of 2.5 and 5.0 gm/KG. Both male and female mice were used. Observation period was 8 days.

Results

LD_{50} = >5.0 gm/KG. The 2.5 gm/KG level produced slight dyspena and mild drowsiness. The high level produced 30% death accompanied by spasms, dyspena, drowsiness, irregular breathing.

Acute Rat Oral

10 animals were tested per dosage level of 2.5 and 5.0 gm/KG. Both male and female animals were used. Animals were observed for 8 days.

Results

LD_{50} = >5.0 gm/KG. Neither level showed toxic symptoms.

Acute Rabbit Dermal (80W)

2 male and 2 female rabbits were tested per dosage level of 3.0, 4.6, 6.8, and 10.2 gm/KG. The test material remained in contact with the skin for 24 hours.

Results

No deaths or untoward behavioral reactions were observed. No evidence of local skin irritation was noted.

Acute Rat Inhalation (80W)

5 males and 5 females were tested at a concentration of 14.1 mg/L of air of a 0.5 aqueous suspension. Particle sizes varied from 0.5 to 20 microns in size. Exposure was for 4 hours.

Results

No deaths or untoward behavior reactions were noted at the aerosol concentration of 14.1 mg/L of air of a 0.5% aqueous suspension (equal to 0.07 mg/L of active ingredient).

Rabbit Eye Irritation (80W)

Exactly 50 mg of undiluted test material was instilled into the conjunctival sac of the right eye of 5 rabbits. Animals were observed at interim times up to and including 7 days.

Results

The material was mildly irritating to the eye.

Acute Rat Inhalation (80W)

10 rats were exposed to an aerosol concentration of 3.3 mg/L of the 8% wettable powder. Exposure time was 1 hr. The apparatus used in this study allowed the animal to be outside the chamber with only their nostrils exposed to the dust within the chamber.

Results

No deaths or signs of toxicological or pharmacological effects were noted. Thus the LC_{50} = >3.3 mg/L.

5 Day Rat Dermal

Suspensions in gum arabic were prepared with the active ingredient and also with the 50% wettable powder, the concentrations being 5% and 2.5% propazine respectively. 0.4 ml of the suspension was applied for 5 consecutive days on 5 animals per dosage level. This corresponds to 60-70 mg/KG and 130-140 mg/KG of active ingredient.

Results

No symptoms were noted in any of the animals. No local irritation or systemic toxic effects were noted.

21 Day Rabbit Dermal (80W)

10 males and 10 females (half abraded) were tested per dosage level of 1.0 and 2.0 gm/KG. The skin applications of the test material were made in the form of a 50% aqueous suspension on a 7 hours/day 5 days/wk for 3 weeks. The control received the inerts contained in the test material.

Results

The animals receiving 2.0 gm/KG/day showed severe body weight loss. This group also showed 20% mortality in the intact group and also 20% mortality in the abraded group. The lower dosage level showed no mortality.

No significant untoward behavioral reactions were noted in the animals receiving 1.0 gm/KG/day. Generalized inactivity, anorixea and diarrhea were noted at the 2.0 gm/KG/day level.

These reactions appeared after 3-6 applications and progressed to severe within 21 days.

Local skin reactions first became evident after the 3rd or 4th application. These reactions were characterized by mild erythema, drying, desquamation and thickening of the skin at the application site.

The only tissue disclosing any significant pathologic alteration was the skin of all the test animals. This was confined to local inflamatory reactions.

No significant differences were noted between the control and test groups with respect to the organand body weight ratio data.

28 Day Rat Oral

The active ingredient was given by stomach tube to 2 groups of 5 male and 5 female rats on a 6 day a week basis for 4 weeks. The dosage levels employed were 1250, and 2500 mg/KG/day.

Results

No deaths occurred in the low level and only 1 death occurred in 2500 mg/KG/day level. Both test levels showed a distinct retardation in the rate of weight increase but exhibited no symptoms. Histological examination of the liver, kidney, spleen, pancreas, lung, intestines and gonads revealed no pathological changes which could be attributed to the

administration of the test material.

90-180 Day Rat Oral (50W)

12 males and 12 females were tested per dosage of 250 and 2500 mg/KG/day. 2 control groups were used, 1 received the inactive excipients at the dosage level of 2500 mg/KG/day and the 2nd control group received water at 5 ml/KG/day.

This high level group was terminated after 90 days, the remaining animals were continued for 180 days.

Results

The animals receiving the test material at the dosage level of 2500 mg/KG/day showed a marked reduction in food intake. Up to the 90th day the weight gain in the control groups was practically identical. The animals receiving 250 mg/KG/day showed a slight retardation in weight gain and those of the high level showed a distinct retardation in weight growth. However by the end of the 180th day there was a slight difference in weight gain between the 2 control groups. This may indicate an effect of the inactive excipients. There was no difference between the low level and the control receiving the inactive excipients.

There were 3 deaths in 1 control group and 1 death in the 2nd control group. There were 3 deaths in the low level animals and 16 deaths in the high level animals.

Histological examination revealed that the administration in the daily dose of 250 mg/KG produced no degenerative modifications in the major parenchymatous organs. There were however indications of atrophy in 6 out of the 11 animals with 1 exhibiting severe edema. The ovaries of the corresponding females appeared normal. It should be noted that testicular atrophy was also observed in 1 of the control animals which received the inactive excipients.

Of the 8 surviving animals of the 2500 mg/KG group only 1 exhibited perilobular fatty degeneration of the liver. All other organs appeared to be unchanged.

Note - The testicular atrophy noted in the 250 mg/KG does not appear to extend into the high level. Thus we have the possibility that this effect is not dose related. We must also consider that 1 animal in the control group also showed testicular atrophy.

90 Day Dog Feeding (80W)

12 male and 12 female adult dogs were tested per dosage level of 50, 200 and 1000 ppm.

Results

No compound related pharmacodynamic signs were noted. 4 dogs receiving the 1000 ppm dietary level showed body weight loss during the course of the study. There appeared to be nocorresponding reduction in their food intake.

No compound related alterations and hematology, plasma biochemistry, liver function tests or urinalyses were seen.

No compound related gross or microscopic pathologic lesions or variations in organ weights were noted.

90 Day Rat Feeding (80W)

20 males and 20 females were tested per dosage level of 50, 200, and 1000 ppm.

Results

The male and female rats receiving 1000 ppm in their diet showed hyperirritability to handling during the 8th and 11th weeks of the study. No other pharmacodynamic effects were noted. Only 1 female death occurred at this level.

The body weight gains of the 1000 ppm animals were significantly lower than the corresponding control animals.

No compound related alterations in hematology, plasma biochemistry, liver function tests or urinalysis were noted.

No compound related gross or microscopic pathologic lesions or variations in organ weights occurred in any test rat.

Metabolic Fate C^{14} - Propazine

The results of a radiotracer study in albino rats to determine the metabolic fate of propazine following oral administration

indicated that propazine was absorbed. The administered C^{14} propazine was recovered from urine, feces, selected tissues and organs of the test animals, whereas nothing was recovered from the expired air samples.

The amount of the dose recovered from the urine was between 28.9 and 42.2% and from the feces between 14.2 and 28.1%. Radioassays of selected tissues and organs accounted for an additional 2.6-8.6% of the given dose.

The selected tissues included blood, kidney, liver, heart, reproductive organs, muscle and fat.

Metabolism of Propazine and Prometryne in Rats

The metabolic breakdown products of C^{14} propazine and C^{14}-prometryne fed orally to rats were compared using extraction, ion exchange gradient elution and paper chromatographic techniques.

3 common metabolites, other than hydroxy-propazine, were found in the urine of rats fed either propazine or prometryne. Both the urine and feces from rats fed either compound contained hydroxy-propazine. Unchanged propazine or prometryne was found in the feces but not in the urine. It can be concluded that propazine and prometryne follow similar metabolic pathways.

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Tox Chem No. Propazine 184 File Last Updated 10/1/84 Current Date

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - rat; Ciba-Geigy; #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 Maternal toxic LEL = 300 mg/kg Maternal toxic NOEL = 100 mg/kg Levels tested = 0, 30, 100, 300 and 600 mg/kg		Supplementary 001450
3 Generation reproduction- rat; IRDC; #382-010 08/10/79	Tech Batch#FL-76/357	243356	Reproductive NOEL = 100 ppm Reproductive LEL = 1,000 ppm (HDT) (reduced mean pup body weights) Levels tested = 0, 3, 100 and 1000 ppm		Guideline 000575 Minimum 004542
5 Day dermal- rat	Tech		No irritation effect noted at 140 mg/kg		001376
21 Day dermal- rabbit	80W (50% aqueous solution)		Mild erythema, drying, desquamation and thickening of skin at the application site Levels testted = 1 gm/kg/day and 2 gm/kg/day		001376
28 Day feeding- rat	Tech		No pathological changes noted at 2500 mg/kg Levels tested = 1250 and 2500 mg/kg /day		001376
90-180 Day feeding- rat	50W		Systemic NOEL < 250 mg/kg (LDT; retardation in weight gain) Levels tested = 0, 250, and 2500 mg /kg/day		001376

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Tox Chem No. Propazine 184

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90 Day feeding- dog	80W		Systemic NOEL = 200 ppm Systemic LEL = 1000 ppm (HDT; body weight loss) Levels tested = 0, 50, 200 and 1000 ppm		001376
90 Day feeding- rat	80W		Systemic NOEL = 200 ppm Systemic LEL - 1,000 ppm (HDT; body weight loss) Levels tested = 0, 50, 200 and 1000 ppm		001376
2 Year feeding/oncogenic - mice; IRDC; #382-004 04/24/80	Tech Batch # FL-76.1357	243350	Systemic NOEL = 100 ppm Systemic LEL = 3,000 ppm (HDT); (increased focal myocardial fibrosis, focal myocardial degeneration.) Oncogenic NOEL > 3,000 ppm (HDT) Levels tested = 0, 3, 100 and 3000 ppm in CD-1 strain.		minimum 000575 Minimum 004542
2 Year feeding/oncogenic - rat; IRDC; #382-007; 04/28/80	Tech Batch # FI-76157	243353	Systemic NOEL = 100 ppm Systemic LEL = 1000 ppm (decrease in body weight) Oncogenic NOEL = 100 ppm Oncogenic LEL = 1000 ppm (increase in mammary tumors) Levels tested = 0, 3, 100 and 1000 ppm		minimum 000575 Minimum 004542
Metabolism- rat	^{14}C-propazine		^{14}C-propazine was recovered in urine (42.2%), feces (28%) and selected tissues (blood, kidney		001376

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Tox Chem No. Propazine 184

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic, rec-assay + reversin assay; Mutation Research; 140; 1970; pp. 19-30	Propazine tech	070544	Negative for mutagenicity but no individual data on propazine was presented.		Supplementary 001450
Acute oral LD_{50} - mice	Tech		LD_{50} > 5 gm/kg spasms, dypsnea and drowsiness	IV	001376
Acute oral LD_{50} - rat	Tech		LD_{50} > 5 gm/kg	IV	001376
Acute dermal LD_{50} - rabbit	80W		LD_{50} > 10.2 gm/kg (HDT) No skin irritation was noted	III	001376
Acute inhalation LC_{50} - rat	80W (0.5% aqueous suspension)		LC_{50} >14 mg/L/4 hours	IV	001376
Primary eye irritation - rabbit	80W		Mildly irritating to the eyes	III	001376
Acute aerosol inhalation LC_{50}- rat	80W		LC_5^0 > 3.3 mg/L/1 hour	IV	001376
Acute oral LD_{50}- rat; Std. Oil Co. of Calif.	Triox liquid Vegetation killer		LD_{50} = 3.9 gm/kg Symptoms: lacrimation, soliration and ataxia	III	001377
Acute dermal LD_{50}- rabbit; Std. Oil Co. of Calif.	Triox liquid Vegetation Killer		LD_{50} > 5 gm/kg (single dose tested)	III	001377
Primary eye irritation- rabbit; Std. Oil Co. of Calif.	Triox liquid vegetation killer		No corneal opacity or iritis was noted.	III	001377

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation- rabbit; Std. Oil Co. of Calif.	Triox liquid vegetation killer		PIS = 6.5/8.0 Eschar and moderate to severe edema. Irreversible erythema.	I	001377
Acute inhalation LC_{50}- rat; Std. Oil Co. of Calif.	Triox liquid vegetation killer		No gross pathological changes attributable to the test material		001377
Acute oral LD_{50}- rat; IRDC;#382-043; 10/17/78	Milocep (metolachlor 36.3% Propazine 18.7%		LD^{50} = 4,811 mg/kg (male) LD_{50} = 2, 944 mg/kg (female) Symptoms: hypoactivity and ataxia	III	minimum 001378
Acute dermal LD_{50}- rat; IRDC;#382-044; 10/17/78	Milocep		LD_{50} > 5 gm/kg (single dose) slight to moderate irritation	IV	minimum 001378
Primary eye irritation - rabbit; IRDC;#382-045; 10/17/78	Milocep		Corneal opacity persisted through 7 days in unwashed eyes	I	minimum 001378
Primary dermal irritation - rabbit; IRDC; #382-046; 10/17/78	Milocep		PIS = 2.0/8.0	III	Minimum 001378
Acute inhalation LC_{50} - rat; IRDC; #382-047; 11/3/78	Milocep		LC_{50} > 20.8 mg/L	IV	minimum 001378
Acute oral LD_{50}- rat; Stillmeadow;#1131-79; 05/09/79	Propazine 90%	238806	LD_{50} > 5gm/kg (HDT)	IV	guideline 001379
Acute dermal LD_{50} - rabbit; Stillmeadow; #1132-79; 5/9/79	Propazine 90%	238806	LD_{50} > 2 gm/kg (HDT)	III	guideline 001379

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Tox Chem No. Propazine 184

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; Stillmeadow; # 1134-79; 5/9/79	Propazine 90%	238806	No corneal opacity - some conjunctival irritation	III	guideline 001379
Primary dermal irritation- rabbit; Stillmeadow;#1133-79; 05/09/79	Propazine 90%	238806	PIS = 3.94/8.0 - erythema, eschar, and edema at all sites with improvement noted by 72 hours.	III	guideline 001379
Acute inhalation LC_{50} - rat; IRDC; 6/29/79	Propazine 90%	238806	LC_{50} > 2.1 mg/L/4 hours	III	minimum 001379

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM:

SUBJECT: Propazine; PP# 2F2618; Propazine in/on sorghum; Revised NOEL for 2-year rat study
Caswell No. 184

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

THRU: Edwin Budd, Section Head
Review Section II
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 7/22/86

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

William Dykstra 7/22/86

Recommendation:

1. For the two-year chronic/oncogenic rat feeding study (IRDC # 382-007; 4/28/80), the NOEL for chronic toxicity based on decreased body weight is considered to be 3.0 ppm (0.15 mg/kg/-day). The LEL is 100 ppm and the effect is decreased body weight in male and female rats.

2. The change of the NOEL from 100 ppm to 3 ppm is based on the re-evaluation of the propazine data base by the Toxicology Branch RFD/ADI committee. They concluded that decreased body weight was present at 100 ppm in rats for the major portion of the study and therefore could not be considered a NOEL.

cc: Dr. Ghali

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

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) WHD for LOC 6/10/81

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

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.

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.

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.

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.

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.

The basal laboratory diet was ground Purina Laboratory Chow. The rats were identified individually with numbered ear tags. Beginning on July 26, 1977, ear tag verifications were recorded at each cage change, before and after blood and urine sample collection and before necropsy. The study was initiated on July 27, 1976; there were two interim sacrifices, one at 12 months and a second at 13 months of study because of the following experimental procedure.

Ten additional male and 10 additional female rats were initiated in the control and high-dose groups; of these additional animals, five of each sex were sacrificed and necropsied after 12 months of study. The remaining five of each sex were placed into a compound-withdrawal group and fed a control diet for 4 weeks and then sacrificed and necropsied. During 4 week of study, Group III female 38160 replaced 39644 which died. The study was terminated on July 26-28, 1978.

Propazine technical was fed in the diet at the following dosage levels:

Dosage Level ppm	Number of Rats	
	Male	Female
0 (control)	70	70
3	60	60
100	60	60
1000	70	70

The rats were observed twice daily for signs of overt toxicity, moribundity and mortality. Detailed observations were recorded weekly.

Individual body weights were recorded weekly for the first 3 months and monthly thereafter. After one year of study individual body weights and food consumption were recorded weekly for rats placed on withdrawal.

Individual food with compound consumption values (for 10 rats/sex/group) were recorded weekly for the first 3 months and monthly thereafter. After one year of study, individual food consumption values were recorded weekly for the rats placed on withdrawal. Food efficiency was calculated through 30 weeks of study.

Blood and urine samples were obtained from 10 rats/sex for both the control and high-dose groups at 3, 6, 12, 18 and 24 months of study. Prior to sample collection the rats were housed overnight in metabolism cages (without food or water). The blood was obtained by the orbital sinus technique.

Hematologic tests included hemoglobin, hematocrit, total and differential WBC, total RBC, total platelet count, prothrombin time, and partial thromboplastin time.

Biochemical tests included fasting blood glucose, BUN, SGOT, SGPT, SAP, serum total protein and total cholesterol.

Urinalyses included a description of appearance, measurement of volume.

Five male and five female rats from the control group and the 1000 ppm group were sacrificed with carbon dioxide asphyxiation and necropsied after 12 months of compound feeding.

The five male and five female rats from these groups which were placed in compound withdrawal were sacrificed and necropsied after 4 weeks of compound withdrawal. All remaining rats were sacrificed and necropsied after 2 years of compound withdrawal. At necropsy, an examination was made of the external body surface and body orifices. The rat was then opened and the contents of the body cavities were examined in situ, removed and again examined. Liver, kidneys, spleen, heart and testes were weighed fresh at necropsy.

Representative tissues and organs from each rat were collected and fixed in phosphate buffered neutral 10% formalin. Adrenal glands, thyroid and ovaries were weighed after fixation.

Rats which died or were sacrificed in extremis during the course of the study were necropsied as above except no organs were weighed.

Hematoxylin and eosin stained paraffin sections were prepared at IRDC by standard histologic methods and examined microscopically from all rats from the control and 1000 ppm groups which were sacrificed after 12 months of study or which died or were sacrificed in extremis during the first 12 months of study.

Palpable masses were observed and recorded in all groups; there were no greater numbers of masses in treated rats than in controls. The number of palpable masses in the rats at 104 weeks of the study were as follows:

	I (0)		II (3 ppm)		III (100 ppm)		IV (1000 ppm)	
	Male	Female	Male	Female	Male	Female	Male	Female
o. of masses	9	57	19	75	18	75	15	82
urvival (104 wks)	31/60	36/60	42/60	37/60	46/60	46/60	38/60	25/60
rats with masses	19	75	31	73	30	72	32	92
with single masses	67	37	69	37	71	36	92	30
vith multiple masses	33	63	31	63	29	64	8	70

All groups generally showed a decrease in rate of body weight gain with an increase in dosage of compound. A t-test comparison between means and the ratio of change in body weights of control and treated groups showed that for female rats of the low-dose (3 ppm), a statistically significant decrease occurred between weeks 26 through 65; for female rats of the middle-dose (100 ppm), a statistically significant decrease occurred between weeks 0 through 104; for female rats of the high-dose (1000 ppm), a statistically significant decrease occurred between weeks 0 through 104. Similarly, for male rats at the low-dose (3 ppm), a statistically significant decrease occurred between weeks 0 through 104; for male rats at the middle-dose (100 ppm), a decrease (though not statistically significant) occurred though most of the weeks from 0 to 104; and for high-dose (1000 ppm) male rats, a statistically significant decrease occurred through weeks 0 to 104.

There was little difference in the amount of food consumed per day between the control and treated rats, although a slight decrease was noted for both males and females in the high-dose group. This slight decrease in food consumption was not enough to account for the significant decrease in body weights. There were no compound-related effects in hematologic tests, biochemical tests and urinalyses; although a few values were statistically significant, all were within the expected ranges, and no trends of increase or decrease were evident.

Although statistical variations occurred in sex group mean weights of a number of organs of rats in the treated groups, there was no dose response evident and the organs which had statistical weight variations were not the site of compound-related gross or microscopic morphologic lesions. These weight variations therefore were not considered of toxicological significance.

The number of subcutaneous masses and nodules in female rats from the 1000 ppm group was slightly increased when compared to the control group at gross necropsy.

12-Month Interim Sacrifices, Deaths 0-12 Months

No microscopic pathologic lesions which were considered related to Propazine feeding were seen in any tissues examined from rats from the 1000 ppm group which were sacrificed at the 12-month interim or which died or were sacrificed in extremis during the first 12 months of study. Microscopic findings in these rats were those which commonly occur in untreated rats of this age and strain. They were primarily lesions of mild inflammatory conditions or early degenerative changes and they occurred with similar frequency and severity in rats from the control group and 1000 ppm group.

Terminal Sacrifices, Deaths 12-Months to Termination

A variety of microscopic changes was observed in most of the organs and tissues in both the control and high-dose (1000 ppm) groups of rats. These occurred either infrequently or with similar distribution between the two groups and are considered unrelated to the exposure to the compound. These changes were most evident in the lungs and kidneys. The lung changes were representative of the chronic respiratory disease complex (Murine Respiratory Mycoplasmosis). These changes included varying degrees of mutifocal to diffuse pneumonitis with peribronchial and perivascular lymphnoid cell accumulations and focal accumulations of foamy macrophages. Multifocal hemorrhages of the lung were also observed in both the control and treated rats changes related to this complex were also observed in the tracheas and hearts of individual rats in both the control and treated groups.

The changes in the kidneys were compatible with the microscopic lesions of the chronic progressive glomerulonephrosis and nephritis observed in most rat strains.

Incidental changes were present in the livers from both control and treated rats. A low incidence of hepatocellular carcinoma and adenoma occurred in both the control and treated rats. Other hepatic changes, seen with a higher frequency but with similar distribution in the control and treated rats, included bile duct hyperplasia, multifocal hepatocytomegaly and multifocal to diffuse vacuolation.

A generally low incidence of neoplasms was observed in most organs and tissues from both the control and treated groups except for the pituitary, testes and mammary gland. Pituitary adenomas and carcinomas were commonly observed, although evenly distributed among the control and treated groups, there was a higher incidence in the female rats. Interstitial cell tumors occurred in the testes of some rats in the control and treated groups. There was a slightly higher incidence of this tumor in the high-dose group of rats (8/64, control vs. 12/64, high-dose) which was considered to be a biological variation and not a treated-related change.

Three was a high incidence of hyperplastic mammary gland changes in the control and all three test groups of female rats. The severity of these hyperplasia changes of the mammary glands made it difficult in individual rats with mammary gland neoplasms to classify the type of mammary gland tumor present in the animal. Areas of glandular hyperplasia (lobular) were present in areas of relatively normal mammary gland as well as within the benign adenomas and fibroadenomas observed in both the control and all three groups of treated animals. The classification of mammary gland tumors used in the report is set forth in the Pathology of Tumors in Laboratory Animals, Volume I, Tumours of the Rats, Part I by V.S. Turusov. Individual animals, the histological differentiation between adenomas and well differentiated carcinomas of the mammary gland was made difficult due to the degree of hyperplastic change present. Classification of the tumors as adenocarcinomas or papillary carcinomas was used when one or more of the following criteria was present within the tumor: (1) loss of normal glandular architecture; (2) pronounced variability in cytologic features; (3) prominent nucleoli; (4) numerous mitotic figures; (5) multiple layering of the epithelium; (6) lack of cellular orientation; and (7) local invasion.

The male rats in this study had very few tumors of the mammary gland. No tumors of the mammary glands were present in the male or female rats which died before the twelve-month sacrifice. The female control rats and rats exposed for a longer period of time had a high incidence of mammary gland tumors. The distribution of the mammary gland tumors in the female rats from the two-year sacrifice is presented in Table I.

TABLE I
Distribution of Mammary Gland Tumors

	Group I Control	Group II 3 ppm	Group III 100 ppm	Group IV 1000 ppm
No. Examined	(55)	(57)	(60)	(55)
TYPE OF TUMORS				
Adenomas No./Rat	3/3	3/3	5/5	10/10
Fibroadenoma No./Rat	34/22	37/22	31/24	35/24
Adenocarcinoma No./Rat	9/6	12/11	11/8	13/9
Papillary Carcinoma No./Rat	4/4	12/7	4/3	12/8
MALIGNANT TUMORS				
Total/Rat	13/9	24/17	15/10	25/14*
Average Tumor/Rat	1.44	1.41	1.50	1.78
Percentage of Tumor-Bearing Rats	16.4%	29.8%	16.7%	25.5%
BENIGN TUMORS				
Total/Rat	37/24	40/25	36/26	45/30**
Average Tumor/Rat	1.54	1.60	1.38	1.50
Percentage of Tumor-Bearing Rats	43.6%	43.9%	43.3%	54.5%
TOTAL MAMMARY GLAND TUMORS				
Total/Rat	50/28	64/33	51/32	70/40***
Average Tumor/Rat	1.78	1.94	1.69	1.75
Percentage of Tumor-Bearing Rats	50.9%	57.9%	53.3%	72.7%

*Twelve tumors in two rats.
**Nine tumors in two rats.
***Twenty-one tumors in four rats.

The most frequent mammary gland tumor present in female rats was the fibroadenoma which had a fairly equal distribution among the control and the three treatment groups.

Adenomas had a similar distribution in the control and treatement Groups II (3 ppm) and III (100 ppm) while there was an increase in the number of adenomas in Group IV (1000 ppm). Adenocarcinomas were fairly equally distributed among the control and three treatment groups.

Papillary carcinomas were similar in occurrence in the control group and Group III (100 ppm) with an increased incidence in Group II (3 ppm) and Group IV (1000 ppm).

A comparison of the number of female rats having mammary gland tumors shows a higher incidence of animals with mammary gland tumors in the high dose group (1000 ppm) when compared to the control group. The increase is due to an increase in the incidence in both benign and malignant tumor-bearing animals in the high-dose group.

A difference in the number of tumor-bearing animals is not observed between the low (3 ppm), middle (100 ppm) and control group of female rats in this study. A comparison of the number of tumors per individual animal does not show any substantial difference between these ratios in the control and the three treated groups of rats with respect to the total number of mammary gland tumors, malignant tumors or benign tumors. However, evaluation of the individual animals in the high dose group (1000 ppm) shows two animals (No. 39814 and No. 39832) with twelve malignant mammary gland tumors (seven and five tumors, respectively) and two animals (No. 39799 and No. 39804) with nine benign tumors (five and four, respectively). This is a total of twenty-one tumors in four rats from the high dose group. Even though there is an apparent increase incidence of mammary gland tumors in the high dose group, it may be difficult to conclude that this increased incidence of mammary gland tumors was related to the exposure to 1000 ppm of Propazine technical. A high incidence of mammary gland tumors occurred in all groups of female rats in this study. Instances of fifty-five percent, sixty-two percent, sixty-four percent and as high as eighty-five percent have been reported in Sprague-Dawley rats (Sher, Sanford P., Toxicology and Applied Pharmacology, 22 (1972); pp. 562-588.) These data, however, did not come from IRDC.

Conclusions:

A statistically significant (Fisher's Exact test, P = 0.015) increase in rats bearing mammary tumors occurred in the high-dose female rats. The increase in the total number of tumor-bearing animals in the high-dose group may reflect a biological variation in Sprague-Dawley rats. The historical control data of mammary tumors in Charles River CD rats at IRDC from 1975-1979 has been submitted by the registrant and the number of female rats bearing mammary tumors compared to the number of female rats examined is 769/1528 (50.3%). The historical control data was compared to the high-dose female rats using 2x2 contingency Chi-Square analysis. A statistically significant increase (p = .0011) was seen in the mammary adenomas and number of tumoring bearing rats in the T-III females (1000 ppm).

Therefore it can be concluded that Propazine technical at dietary levels of 1000 ppm was weakly oncogenic to female rats producing increased mammary gland tumors.

Test for Significance of Differences Between Proportions 11/15/90

Summary neoplasms in rats

ppm	# -ESP Total	% +/-2(S.E.)	One Tail P Statistic Fisher's
0.000	28 55	50.91+/-(14.12)	
3.000	33 57	57.89+/-(13.59)	0.296
100.000	32 60	53.33+/-(13.46)	0.471
1000.000	40 55	72.73+/-(12.68)	0.015

Test for Linear Trend in Proportions P = 0.015

The pathologist for the study had difficulties in attributing these findings to administration of propazine for the following reasons:

1) Most of the mammary glands in the rats in this study (control and treated) had some degree of hyperplastic change probably due to some extent to the large number of pituitary tumors in the rats in this study.

2) A high incidence of mammary gland tumors occurred in all groups of female rats in this study. Instances of fifty-five percent, sixty-two percent, sixty-four percent and as high as eighty-five percent have been reported in Sprague-Dawley rats (Sher, Sanford P: 1972, Tox. Appl. Pharmacol. 22: 562-588.

3) There was an absence of any significant increase in the number of tumors in the mammary glands of male rats or in any of the rats sacrificed prior to twelve months on study.

4) A similar distribution and incidence of mammary gland tumors in the control group and in Group III (100 ppm) demonstrated a lack of dosage-related response.

Classification: Core-Minimum Data

3. Three-Generation Reproduction Study in Rats with Propazine Technical (IRDC Report No. 382-010; August 10, 1979)

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

Forty male (weighing from 121 to 175 gm) and 80 female (weighing from 96 to 148 gm) Charles River CD rats were initiated on this study. The rats were evenly distributed among each of three treatment groups and one control group (10 males/group and 20 females/group). Placement of the rats was made so initial group mean body weights for each sex were similar. Littermates, by sex, were evenly distributed among the groups.

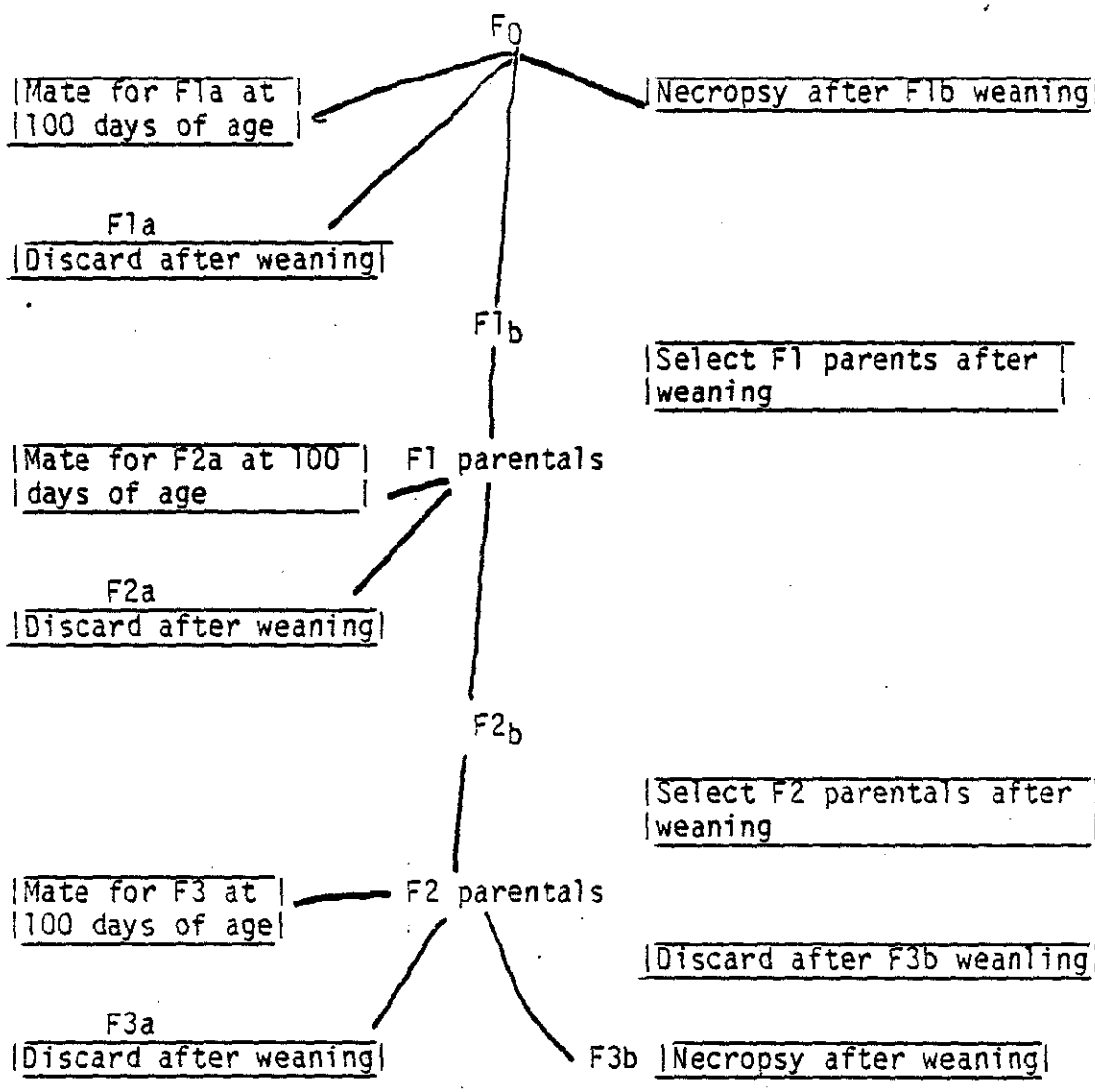
Except during mating and through lactation, the rats were individually housed in hanging wire-mesh cages. During the initial mating periods, the rats were housed in units of one male and two females in plastic boxes on ground corn-cob bedding.

During the second or third remating periods, some males were housed with one female. Following the mating periods and during lactation, the females were individually housed in plastic boxes on ground corn-cob bedding and the males in hanging wire-mesh cages. Throughout the span of this study, the rats were housed in a temperature-, humidity-, and light- (12 hours on/off) controlled room. Tap water and the control and test diets were available ad libitum.

The study was initiated on September 7, 1976 and terminated with the last sacrifice on July 3, 1978.

Propazine technical was administered in the diet at fixed percentages to achieve dosage levels of 3, 100 and 1000 ppm . Ten male and 20 female rats were initiated at each treatment level and one control group.

Shown below is the breeding schematic used in the study.



The control and treated rats were maintained on their respective diets throughout the duration of the first generation (F_0). After 77 days of treatment and at approximately one hundred days of age, the F_0 parental rats were initially housed in units of one male and two females within the same treatment group to produce the $F1_a$ litters. The rats were housed together for a maximum of 21 days. The females were vaginally smeared daily during this period until sperm or a copulatory plug was observed. This finding was designated gestation day 0.

If no evidence of mating was observed after two estrous cycles (appproximately ten days), those females were housed with a different male within the same treatment group for an additional 10 days. This procedure was repeated once. No more than three different males were used with each female during the mating period. Just prior to expected parturition or at the end of the maximum mating period, the rats were separated and individually housed. The females were allowed to deliver. The day all pups in a litter were found was designated lactation day 0. During lactation, the pups were counted, sexed and weighed at designated intervals. At weaning, the F1a pups were examined for external abnormalities, sacrificed and discarded.

After weaning, the F_0 parental females were allowed a minimum 10-day rest period and then mated a second time to produce the F_{1b} litters. The mating procedure was identical to the F_{1a} mating, except the females were housed with different males within the same treatment group.

The rats were housed together for a maximum of 30 days. The females were vaginally smeared daily during this period until sperm or a copulatory plug was observed (gestation day 0).

If no evidence of mating was observed after two estrous cycles, those females were housed with a different male within the same group for an additional 10 days. This procedure was repeated once. No more than three different males were used with each female during the mating period.

Just prior to expected parturition or at the conclusion of the maximum mating period, the rats were separated and individually housed. The females were allowed to deliver.

The day all pups in a litter were found was designated lactation day 0. The F_{1b} pups were counted, sexes and weighed on designated days during lactation. After weaning, 10 male and 20 female F_{1b} pups were selected from each group to comprise the second generation (F_1) parents. Also after weaning and following approximately 33 weeks on test, all surviving male from each group were sacrificed and necropsied. Any F_{1b} pups not selected for study continuation and the remaining parental females were sacrificed and discarded.

The F_1 parental rats, selected from the F_{1b} litters, remained on their respective control or treated diets during the span of this generation. At approximately 100 days of age, the parental rats were mated to produce the F_{2a} litters. The mating procedure was identical to the F_{1a} mating with avoidance of brother-sister matings. The rats were housed together for a maximum of 30 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1a}. At weaning, the F_{2a} pups were examined for external abnormalities, sacrificed and discarded.

Following a minimum of 10 days after weaning, the F_1 parental rats were mated a second time in a manner identical to the F_{1b} mating and avoiding brother-sister matings to produce the F_{2b} litters. The rats were housed together for a maximum of 31 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1b}.

After weaning, 10 male and 20 female F_{2b} pups were selected from each group to comprise the third generation (F_2) parents. Also after weaning, all surviving male and 10 female F_1 parental rats from each group were sacrificed and necropsied. Any F_{2b} pups not selected for study continuation and the remaining parental females were sacrificed and discarded.

The F_2 parental rats, selected from the F_{2b} litters, remained on their respective control or treated diets until termination of the study.

At approximately 100 days of age, the parental rats were mated to produce the F_{3a} litters. The mating procedure was identical to the F_{1a} mating with avoidance of brother-sister matings. The rats were housed together for a maximum of 31 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1a}. At weaning, the F_{3a} pups were examined for external abnormalities, sacrificed and discarded. Following a minimum of 10 days after weaning, the F_2 parental rats were mated a second time in a manner identical to the F_{1b} mating and avoiding brother-sister matings to produce the F_{3b} litters. The rats were housed together for a maximum of 30 days. Parental and pup observations conducted during the gestation and lactation periods were identical to those employed for the F_{1b}.

After weaning, 10 male and 10 female F_{3b} pups were selected from each group, sacrificed and necropsied. Also after weaning, all surviving males and 10 female F_2 parental rats from each group were sacrificed and necropsied. The remaining parental females and F_{3b} pups were sacrificed and discarded.

The parental rats and pups were observed daily for signs of overt toxicity, changes in general behavior and appearance and mortality. Detailed observations, individual body weights and food consumption were recorded on a weekly basis for the parental rats. Specific observations for the reproduction aspects of the study included male and female fertility, length of the gestation period, numers of male and female pups at weaning and the viability, growth and survival of the pups through weaning. The number of pups surviving at lactation days 0, 5, 14 and 21 were recorded. Litter size was reduced to 10 pups of equal sex ratio, if possible, on day 5 of lactation. Individual pup body weights were recorded on day 21 of lactation.

As mentioned previously, at intervals during the study, 10 male and 10 female F_0, F_1 and F_2 parental rats from each group were sacrificed with carbon dioxide and necropsied. Ten male and 10 female rats from each group from the F_{3b} generation were also sacrificed at the conclusion of the study. At necropsy, contents of the cranium, thorax and abdomen were examined in situ and after removal. Representative tissues from each rat were collected and fixed with buffered 10% neutral formalin. All pups and parental rats which died during the course of study were also necropsied. Hematoxylin and eosin stained paraffin sections of the following tissues were prepared and examined from rats in the control and high dose group of the F_0, F_1 and F_2 parental rats and the F_{3b} weanling rats:

adrenal gland
bone marrow (sterum and femur)
brain (cerebrum, cerebellum, pons)
large intestine (2 levels)
esophages
eye
heart
kidney
liver
lymph node (cervical and mesenteric)
mammary gland
optic nerve
ovary
pancreas
parathyroid
peripheral nerve (sciatic)
pituitary gland
prostate
salivary gland (parotid, sublingual, submaxillary)
seminal vesicles
small intestines (3 levels)
spinal cord (3 levels)
spleen
stomach
testes
thyroid
trachea
urinary bladder
uterus
lung

Organs underlined above were weighed at necropsy.

Statistical analyses of the data were performed.

Results:

No changes considered to be related to treatment of Propazine technical were seen in parental rats in relation to the general behavior, appearance or survival of the treated rats when compared to the controls. No difference were seen between the pups in the control and treated groups with respect to the general behavior, appearance or survival which was considered treatment related. Differences in the mean body weights of the parental rats receiving Propazine technical at dosage levels of 3 and 100 were not considered treatment related. At study week 63, mean body weights of the F_2 100 ppm parental females were statistically significant higher than the control females. This difference was not considered treatment related. At the 1000 ppm treatment level, the parental mean body weights of both the males and females were generally lower than the control group throughout treatment of Propazine technical. Statistical significance of these differences were not evident at all points of analysis. At this treatment level, the mean body weights of the F_0 females at study weeks 10 and 33; the F_1 males at study week 63, the F_1 females at study weeks 41 and 63 and the F_2 females at study weeks 72 and 95 were statistically significantly lower than their respective control group.

No treatment-related differences were seen between the control and treated groups with respect to male and female fertility, the length of the gestation periods and the viability and survival of the pups through weaning. The gestation survival index of the F_{2b} litters in the 100 ppm treatment group was statistically significant higher than the control group, but this difference was not considered a result of treatment. No biologically meaningful or statistical significant differences were seen in the mean pup body weights of the litters at lactation day 21 in the 3 and 100 ppm treatment groups when compared to the control itters. The mean pup body weights of each of the six litters producted (F_{1a}, F_{1b}, F_{2a}, F_{2b}, F_{3a}, F_{3b}) at the 1000 ppm treatment level were consistently lower than the mean weights of the control pups. Statistical significance was noted in all but the F_{1a} litters at this treatment level.

No gross pathological lesions or abnormalities which are considered compound-related were seen at necropsy in any F_0, F_1, F_2 parental rats or F_{3b} weanling rats which were sacrificed at termination or which died during the course of study and were examined.

Statistiical analysis or organ weights showed the following significantly different means in the treatment groups when compared with the control groups. In the absence of any morphologic change, the biological significance of these organ weight variations is unknown.

Organ	Dosage Level ppm	Sex	Weight	Change	p <
F_0 Generation					
testes	1000	M	relative	increase	0.05
heart	1000	M	relative	increase	0.05
F_1 Generation					
liver	1000	M	relative	increase	0.05
heart	1000	M	relative	increase	0.05
F_2 Generation					
liver	3	F	relative	decrease	0.05
	1000	M	absolute, relative	decrease	0.01, 0.05
	1000	F	absolute	decrease	0.05
kidneys	1000	M	absolute	decrease	0.05
testes	1000	M	relative	increase	0.01
ovaries	100	F	absolute, relative	decrease	0.01, 0.01

No microscopic morphological changes considered compound-related were seen in the F_0, F_1, F_2 parental rats or F_{3b} weanling rats sacrificed at termination.

Conclusion:

The NOEL for reproductive parameters in the study is 100 ppm. The LEL is 1000 ppm and the reproductive effect was statistically significantly reduced mean pup body weights in five of six litters.

Classification: Core-Guideline Data

TS-769:th:TOX/HED:WDykstra:6-8-81:#1

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Tox Chem No. Propazine 184 File Last Updated 10/1/84 Current Date

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - rat; Ciba-Geigy; #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 Maternal toxic LEL = 300 mg/kg Maternal toxic NOEL = 100 mg/kg Levels tested = 0, 30, 100, 300 and 600 mg/kg		Supple-mentary 001450
3 Generation repro-duction- rat; IRDC; #382-010 08/10/79	Tech Batch#FL-76/357	243356	Reproductive NOEL = 100 ppm Reproductive LEL = 1,000 ppm (HDT) (reduced mean pup body weights) Levels tested = 0, 3, 100 and 1000 ppm		Guideline 000575 Minimum 004542
5 Day dermal- rat	Tech		No irritation effect noted at 140 mg/kg		001376
21 Day dermal- rabbit	80W (50% aqueous solution)		Mild erythema, drying, desquamation and thickening of skin at the application site Levels testted = 1 gm/kg/day and 2 gm/kg/day		001376
28 Day feeding- rat	Tech		No pathological changes noted at 2500 mg/kg Levels tested = 1250 and 2500 mg/kg /day		001376
90-180 Day feeding- rat	50W		Systemic NOEL < 250 mg/kg (LDT; retardation in weight gain) Levels tested = 0, 250, and 2500 mg /kg/day		001376

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Tox Chem No. Propazine 184

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90 Day feeding- dog	80W		Systemic NOEL = 200 ppm Systemic LEL = 1000 ppm (HDT; body weight loss) Levels tested = 0, 50, 200 and 1000 ppm		001376
90 Day feeding- rat	80W		Systemic NOEL = 200 ppm Systemic LEL - 1,000 ppm (HDT; body weight loss) Levels tested = 0, 50, 200 and 1000 ppm		001376
2 Year feeding/oncogenic - mice; IRDC; #382-004 04/24/80	Tech Batch # FL-761357	243350	Systemic NOEL = 100 ppm Systemic LEL = 3,000 ppm (HDT); (increased focal myocardial fibrosis, focal myocardial degeneration.) Oncogenic NOEL > 3,000 ppm (HDT) Levels tested = 0, 3, 100 and 3000 ppm in CD-1 strain.		minimum 000575 Minimum 004542
2 Year feeding/oncogenic - rat; IRDC; #382-007; 04/28/80	Tech Batch # F1-76157	243353	Systemic NOEL = 100 ppm Systemic LEL = 1000 ppm (decrease in body weight) Oncogenic NOEL = 100 ppm Oncogenic LEL = 1000 ppm (increase in mammary tumors) Levels tested = 0, 3, 100 and 1000 ppm		minimum 000575 Minimum 004542
Metabolism- rat	^{14}C-propazine		^{14}C-propazine was recovered in urine (42.2%), feces (28%) and selected tissues (blood, kidney		001376

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic, rec-assay + reversin assay; Mutation Research; 140; 1970; pp. 19-30	Propazine tech	070544	Negative for mutagenicity but no individual data on propazine was presented.		Supplementary 001450
Acute oral LD_{50} - mice	Tech		LD_{50} > 5 gm/kg spasms, dypsnea and drowsiness	IV	001376
Acute oral LD_{50} - rat	Tech		LD_{50} > 5 gm/kg	IV	001376
Acute dermal LD_{50} - rabbit	80W		LD_{50} > 10.2 gm/kg (HDT) No skin irritation was noted	III	001376
Acute inhalation LC_{50} - rat	80W (0.5% aqueous suspension)		LC_{50} >14 mg/L/4 hours	IV	001376
Primary eye irritation - rabbit	80W		Mildly irritating to the eyes	III	001376
Acute aerosol inhalation LC_{50}- rat	80W		LC_{50} > 3.3 mg/L/1 hour	IV	001376
Acute oral LD_{50}- rat; Std. Oil Co. of Calif.	Triox liquid Vegetation killer		LD_{50} = 3.9 gm/kg Symptoms: lacrimation, soliration and ataxia	III	001377
Acute dermal LD_{50}- rabbit; Std. Oil Co. of Calif.	Triox liquid Vegetation Killer		LD_{50} > 5 gm/kg (single dose tested)	III	001377
Primary eye irritation- rabbit; Std. Oil Co. of Calif.	Triox liquid vegetation killer		No corneal opacity or iritis was noted.	III	001377

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary dermal irritation- rabbit; Std. Oil Co. of Calif.	Triox liquid vegetation killer		PIS = 6.5/8.0 Eschar and moderate to severe edema. Irreversible erythema.	I	001377
Acute inhalation LC_{50}- rat; Std. Oil Co. of Calif.	Triox liquid vegetation killer		No gross pathological changes attributable to the test material		001377
Acute oral LD_{50}- rat; IRDC;#382-043; 10/17/78	Milocep (metolachlor 36.3% Propazine 18.7%		LD^{50} = 4,811 mg/kg (male) LD_{50} = 2, 944 mg/kg (female) Symptoms: hypoactivity and ataxia	III	minimum 001378
Acute dermal LD_{50}- rat; IRDC;#382-044; 10/17/78	Milocep		LD_{50} > 5 gm/kg (single dose) slight to moderate irritation	IV	minimum 001378
Primary eye irritation - rabbit; IRDC;#382-045; 10/17/78	Milocep		Corneal opacity persisted through 7 days in unwashed eyes	I	minimum 001378
Primary dermal irritation - rabbit; IRDC; #382-046; 10/17/78	Milocep		PIS = 2.0/8.0	III	Minimum 001378
Acute inhalation LC_{50} - rat; IRDC; #382-047; 11/3/78	Milocep		LC_{50} > 20.8 mg/L	IV	minimum 001378
Acute oral LD_{50}- rat; Stillmeadow;#1131-79; 05/09/79	Propazine 90%	238806	LD_{50} > 5gm/kg (HDT)	IV	guideline 001379
Acute dermal LD_{50} - rabbit; Stillmeadow; #1132-79; 5/9/79	Propazine 90%	238806	LD_{50} > 2 gm/kg (HDT)	III	guideline 001379

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary eye irritation - rabbit; Stillmeadow; # 1134-79; 5/9/79	Propazine 90%	238806	No corneal opacity - some conjunctival irritation	III	guideline 001379
Primary dermal irritation- rabbit; Stillmeadow;#1133-79; 05/09/79	Propazine 90%	238806	PIS = 3.94/8.0 - erythema, eschar, and edema at all sites with improvement noted by 72 hours.	III	guideline 001379
Acute inhalation LC_{50} - rat; IRDC; 6/29/79	Propazine 90%	238806	LC_{50} > 2.1 mg/L/4 hours	III	minimum 001379

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REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Propazine

CAS #: 139-40-2
Caswell #: 184

Carcinogenicity: Preliminary evidence of oncogenicity in female rats (increased incidence of mammory tumors) is under review.

Systemic Toxicity: See below.

Preparation Date: 3/20/87

Endpoint	Experimental Doses	UF	MF	RfD
IRDC (1980) 2-Year Rat Feeding/ Oncogenicity Study decrease in body weight	100 ppm (5 mg/kg/day) Systemic NOEL 1000 ppm (50 mg/kg/day) Systemic LEL	300	--	0.02 mg/kg/day

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

2-Year Rat Feeding/Oncogenicity Study
IRDC
Report No. 382-007; April 28, 1980

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100, and 1000 ppm of propazine in their diets for 2 years. At 1000 ppm there was a significant decrease in body weight in both sexes. There was an significant increase in mammary tumors in females at 1000 ppm. The NOEL for Systemic effects is 100 ppm (5 mg/kg/day).

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Uncertainty Factors (UFs):

An uncertainty factor of 100 was used to account for the inter- and intraspecies differences. An additional UF was used to account for the fact that the data base on chronic toxicity lacks an adequate second mammalian bioassy (e.g. a chronic feeding study in the dog may yield a more sensitive toxicological endpoint. However, since the 90-day studies in rats and dogs do not show an order of magnitude of difference, an additional 3-fold UF was considered appropriate.

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Modifying Factors (MFs):

None

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Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat NOEL = 100 ppm (5 mg/kg/day), LEL = 1000 ppm (50 mg/kg/day)(decreased body weight); Oncogenic NOEL = 100 ppm, Oncogenic LEL = 1000 ppm (increase in mammary tumors); Core grade minimum

2) 3-Generation Reproduction - Rat NOEL = 5 mg/kg, LEL = 50 mg/kg; reduced mean pup body weight; Core grade minimum

3) Teratology - Rat Fetotoxic NOEL = 100 mg/kg, Fetotoxic LEL = 300 mg/kg; Maternal toxic NOEL = 100 mg/kg, Maternal toxic LEL = 300 mg/kg; Core grade supplementary

4) 90-Day Feeding - Dog NOEL = 200 ppm (5 mg/kg/day), LEL = 1000 ppm (HDT)(25 mg/kg/day)(decreased body weight); No core grade

5) 90-Day Feeding - Rat Systemic NOEL = 200 ppm (10 mg/kg/day), Systemic LEL = 1000 ppm (50 mg/kg/day)(HDT; body weight loss); No core grade

Data Gap(s)

1) Chronic Dog Feeding Study
2) Rabbit Teratology Study

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice NOEL = 15 mg/kg; LEL = 450 mg/kg; increased focal myocardial fibrosis and focal myocardial degeneration; negative for oncogenicity up to 450 mg/kg; Core grade minimum

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The critical study appears to be of fair quality and is given a medium confidence rating. Additional studies are supportive but since there are data gaps existing the data base and RfD are given medium confidence ratings.

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Documentation of RfD and Review:

Registration Files

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Agency RfD Review:

First Review: 9/29/86
Second Review: 5/20/87
Verification Date: 5/20/87

U.S. EPA Contact:

Primary: William Dykstra FTS 557-7432

Secondary: George Ghali FTS 557-7490

7/18/86

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Propazine

CAS #: 139-40-2
Caswell #: 184

Carcinogenicity: Preliminary evidence of oncogenicity in female rats (increased incidence of mammory tumors) is under review.

Systemic Toxicity: See below.

Preparation Date: 6/27/86

Endpoint	Experimental Doses	UF	MF	RfD
IRDC (1980)	3 ppm (0.15 mg/kg/day) Systemic NOEL	100	10	0.00015 mg/kg/day
2-Year Rat Feeding/ Oncogenicity Study	100 ppm (5 mg/kg/day) Systemic LEL			
Decrease in body weight	100 ppm Oncogenic NOEL			
increased in mammary tumors	1000 ppm Oncogenic LEL			

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

2-Year Rat Feeding/Oncogenicity Study
IRDC
Report No. 382-007; April 28, 1980

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100, and 1000 ppm of propazine in their diets for 2 years. All groups generally showed a decrease in the rate of body weight gain with an increase in dosage of the test substance. A significant decrease in body weights occurred between weeks 0 through 104 for females at 100 ppm and 1000 ppm for males. There was an significant increase in mammary tumors in females at 1000 ppm. The NOEL for Systemic effects is 3.0 ppm (0.15 mg/kg/day).

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Uncertainty Factors (UFs):

Based on a chronic exposure study, an uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

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Modifying Factors (MFs):

An additional MF of 10 was used to account for the fact that the data base on chronic toxicity is incomplete and, therefore, the most sensitive toxicological endpoint can not be established.

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Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat (NOEL = 0.15 mg/kg, LEL = 5 mg/kg; decreased body weight; Oncogenic NOEL = 100 ppm, Oncogenic LEL = 1000 ppm (increase in mammary tumors); minimum)

2) 3-Generation Reproduction - Rat (NOEL = 5 mg/kg, LEL = 50 mg/kg; reduced mean pup body weight; minimum)

3) Teratology - Rat (Fetotoxic NOEL = 100 mg/kg, Fetotoxic LEL = 300 mg/kg; Maternal toxic NOEL = 100 mg/kg, Maternal toxic LEL = 300 mg/kg; supplementary)

4) 90-Day Feeding - Dog (NOEL = 200 ppm (5 mg/kg/day), LEL = 1000 ppm (HDT)(25 mg/kg/day)(decreased body weight); no core grade)

Data Gap(s)

1) Chronic Dog Feeding Study
2) Rat Teratology Study
3) Rabbit Teratology Study

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (NOEL = 15 mg/kg; LEL = 450 mg/kg; increased focal myocardial fibrosis and focal myocardial degeneration; negative for oncogenicity up to 450 mg/kg; minimum)

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The critical study appears to be of fair quality and is given a medium confidence rating. Additional studies are supportive but since there are data gaps existing the RfD is given a medium confidence rating.

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Documentation of RfD and Review:

Registration Files

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Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary: William Dykstra FTS 557-7491

Secondary: George Ghali FTS 557-4382

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Propazine

CAS #: 139-40-2
Caswell #: 184

Carcinogenicity: Preliminary evidence of oncogenicity in female rats (increased incidence of mammory tumors) is under review.

Systemic Toxicity: See below.

Preparation Date: 6/27/86

Endpoint	Experimental Doses	UF	MF	RfD
IRDC (1980) 2-Year Rat Feeding/ Oncogenicity Study decrease in body weight	100 ppm (5 mg/kg/day) Systemic NOEL 1000 ppm (50 mg/kg/day) Systemic LEL	300	~~10~~	0.02 ~~0.005 mg/kg/day~~

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

2-Year Rat Feeding/Oncogenicity Study
IRDC
Report No. 382-007; April 28, 1980

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100, and 1000 ppm of propazine in their diets for 2 years. At 1000 ppm there was a significant decrease in body weight in both sexes. There was an significant increase in mammary tumors in females at 1000 ppm. The NOEL for Systemic effects is 100 ppm (5 mg/kg/day).

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Uncertainty Factors (UFs):

Based on a chronic exposure study, an uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

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Modifying Factors (MFs):

An additional ~~MF~~ UF of ~~10~~ 3 was used to account for the fact that the data base on chronic toxicity is incomplete and a chronic feeding study in the dog may yield a more sensitive toxicological endpoint, however, since the 90-day studies in rats and dogs did not show a significant species difference an additional 10 fold UF was not necessary.

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Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat (NOEL = 100 ppm (5 mg/kg/day), LEL = 1000 ppm (50 mg/kg/day)(decreased body weight); Oncogenic NOEL = 100 ppm, Oncogenic LEL = 1000 ppm (increase in mammary tumors); minimum)

2) 3-Generation Reproduction - Rat (NOEL = 5 mg/kg, LEL = 50 mg/kg; reduced mean pup body weight; minimum)

3) Teratology - Rat (Fetotoxic NOEL = 100 mg/kg, Fetotoxic LEL = 300 mg/kg; Maternal toxic NOEL = 100 mg/kg, Maternal toxic LEL = 300 mg/kg; supplementary)

4) 90-Day Feeding - Dog (NOEL = 200 ppm (5 mg/kg/day), LEL = 1000 ppm (HDT)(25 mg/kg/day)(decreased body weight); no core grade) similar

(5) 90-Day rat NOE a 200 ppm = 10 mg/kg/day

Data Gap(s)

1) Chronic Dog Feeding Study
~~2) Rat Teratology Study~~
3) Rabbit Teratology Study

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (NOEL = 15 mg/kg; LEL = 450 mg/kg; increased focal myocardial fibrosis and focal myocardial degeneration; negative for oncogenicity up to 450 mg/kg; minimum)

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Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The critical study appears to be of fair quality and is given a medium confidence rating. Additional studies are supportive but since there are data gaps existing the RfD is given a medium confidence rating.

.....

Documentation of RfD and Review:

Registration Files

.....

Agency RfD Review:

First Review: 8/19/86
Second Review: 9/29/86
Verification Date: 8/29/86

U.S. EPA Contact:

Primary: William Dykstra FTS 557-7491

Secondary: George Ghali FTS 557-4382

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Propazine

CAS #: 139-40-2
Caswell #: 184

Carcinogenicity: Preliminary evidence of oncogenicity in female rats (increased incidence of mammory tumors) is under review.

Systemic Toxicity: See below.

Preparation Date: 6/27/86

Endpoint	Experimental Doses	UF	MF	RfD
IRDC (1980) 2-Year Rat Feeding/ Oncogenicity Study Increase in body weight	3 ppm (0.15 mg/kg/day) Systemic NOEL 100 ppm (5 mg/kg/day) Systemic LEL	100	10	0.005 mg/kg/day

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

2-Year Rat Feeding/Oncogenicity Study
IRDC
Report No. 382-007; April 28, 1980

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100, and 1000 ppm of propazine in their diets for 2 years. All groups generally showed a decrease in the rate of body weight gain with an increase in dosage of the test substance. A significant decrease in body weights occurred between weeks 0 through 104 for females at 100 ppm and 1000 ppm for males. There was an significant increase in mammary tumors in females at 1000 ppm. The NOEL for Systemic effects is 3.0 ppm (0.15 mg/kg/day).

.....

Uncertainty Factors (UFs):

Based on a chronic exposure study, an uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

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Modifying Factors (MFs):

An additional MF of 10 was used to account for the fact that the data base on chronic toxicity is incomplete and, therefore, the most sensitive toxicological endpoint can not be established.

.....

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat (NOEL = 0.15 mg/kg, LEL = 5 mg/kg; decreased body weight; Oncogenic NOEL = 100 ppm, Oncogenic LEL = 1000 ppm (increase in mammary tumors); minimum)

2) 3-Generation Reproduction - Rat (NOEL = 5 mg/kg, LEL = 50 mg/kg; reduced mean pup body weight; minimum)

3) Teratology - Rat (Fetotoxic NOEL = 100 mg/kg, Fetotoxic LEL = 300 mg/kg; Maternal toxic NOEL = 100 mg/kg, Maternal toxic LEL = 300 mg/kg; supplementary)

4) 90-Day Feeding - Dog (NOEL = 200 ppm (5 mg/kg/day), LEL = 1000 ppm (HDT)(25 mg/kg/day)(decreased body weight); no core grade)

Data Gap(s)

1) Chronic Dog Feeding Study
2) Rat Teratology Study
3) Rabbit Teratology Study

Other Data Considered

1) 2-Year Feeding/Oncogenic - Mice (NOEL = 15 mg/kg; LEL = 450 mg/kg; increased focal myocardial fibrosis and focal myocardial degeneration; negative for oncogenicity up to 450 mg/kg; minimum)

.....

.....

Confidence in the RfD:

Study: Medium Data Base: Medium RfD: Medium

The critical study appears to be of fair quality and is given a medium confidence rating. Additional studies are supportive but since there are data gaps existing the RfD is given a medium confidence rating.

.....

Documentation of RfD and Review:

Registration Files

.....

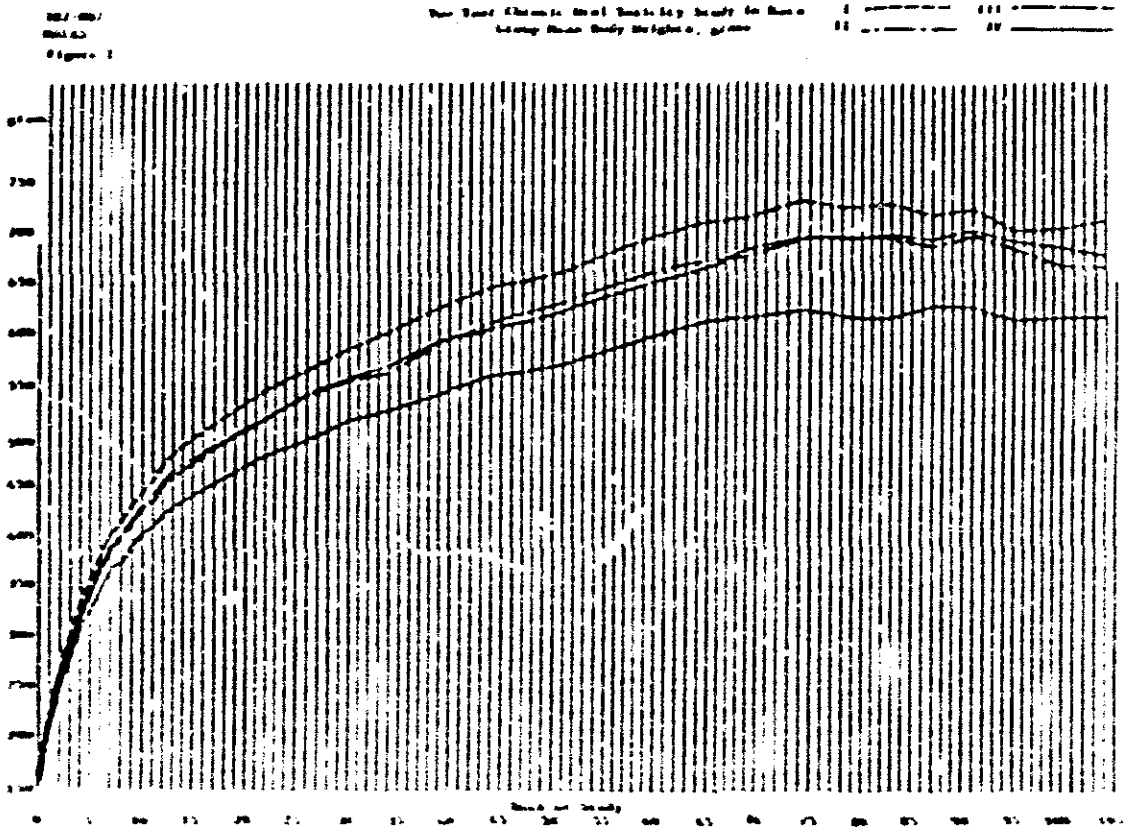
Agency RfD Review:

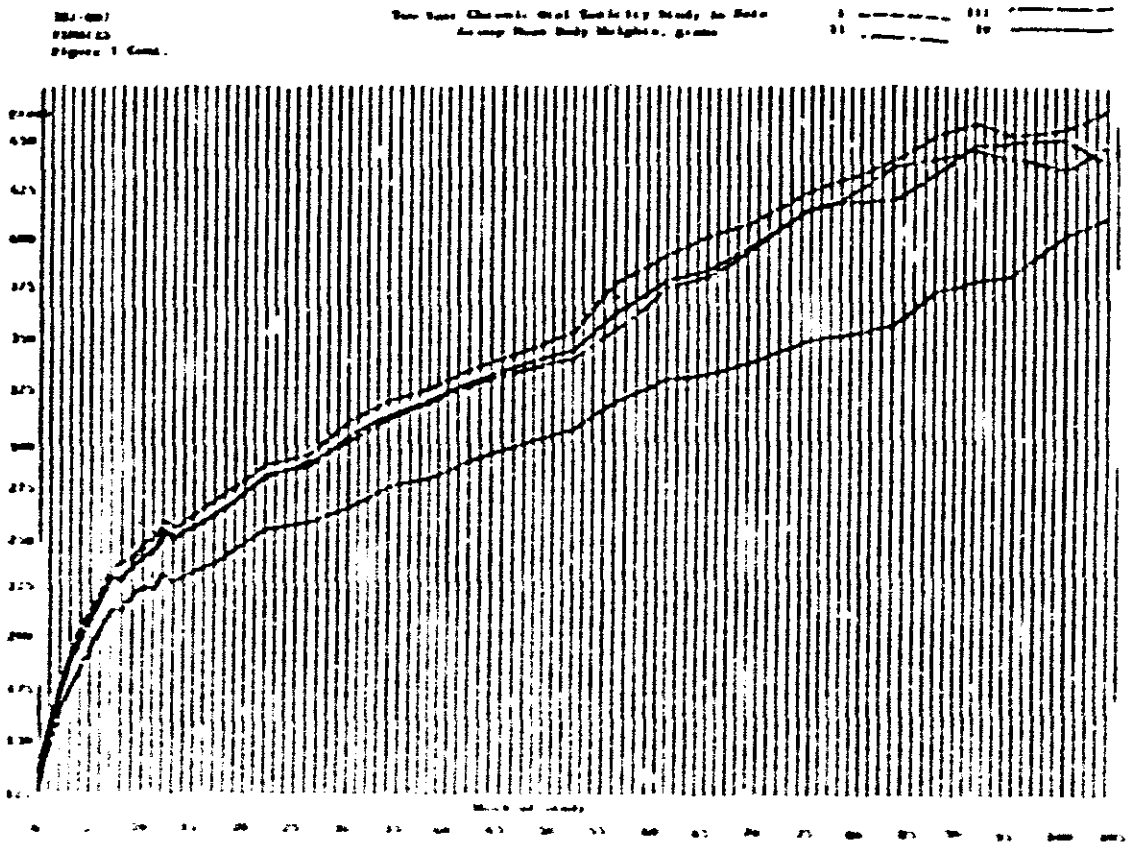
First Review:
Second Review:
Verification Date:

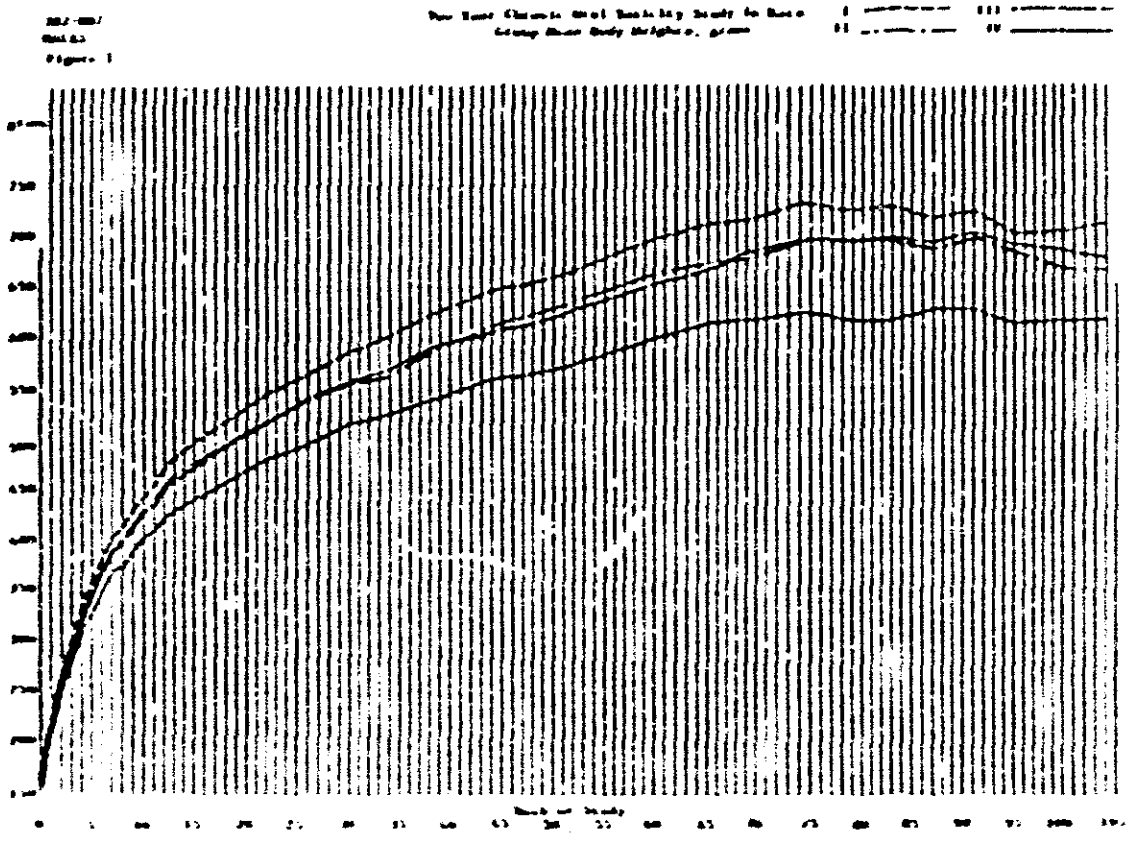
U.S. EPA Contact:

Primary: William Dykstra FTS 557-7491

Secondary: George Ghali FTS 557-4382







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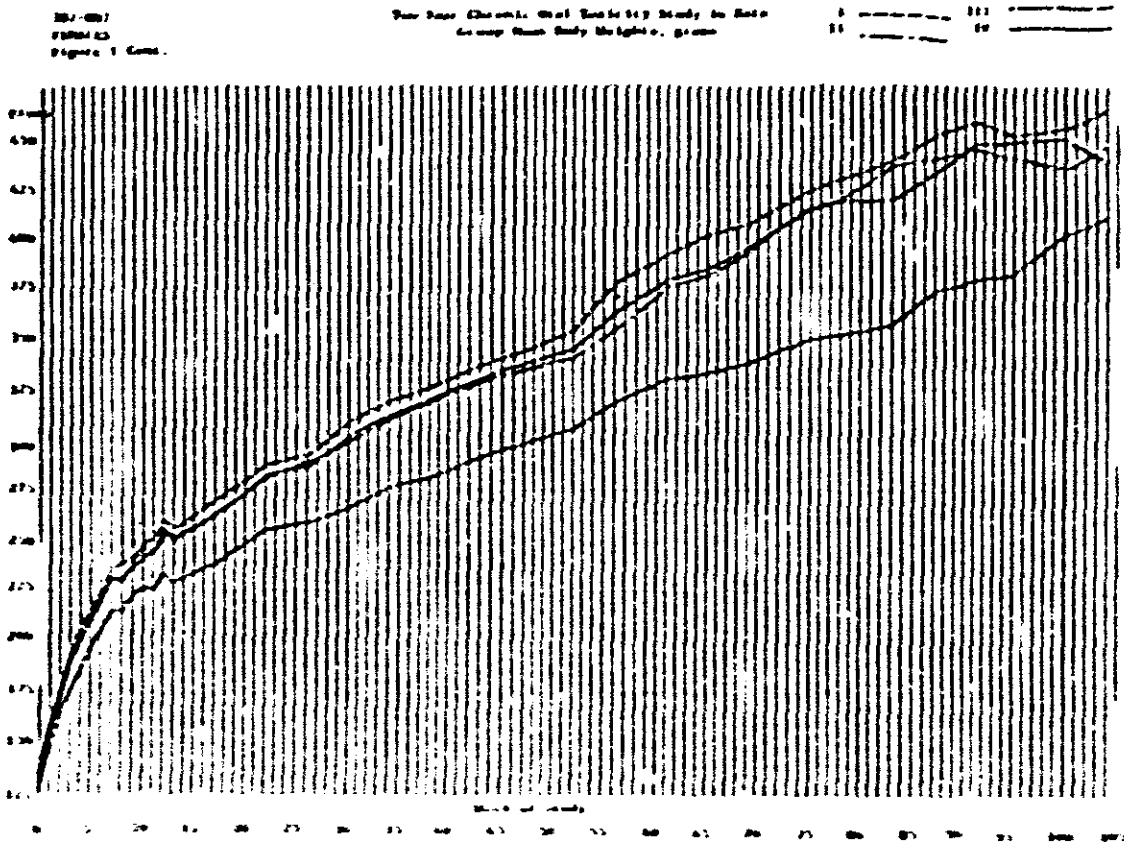


APPENDIX 52
PROPAZINE GUIDANCE LEVEL

1.0 CHEMICAL IDENTIFICATION

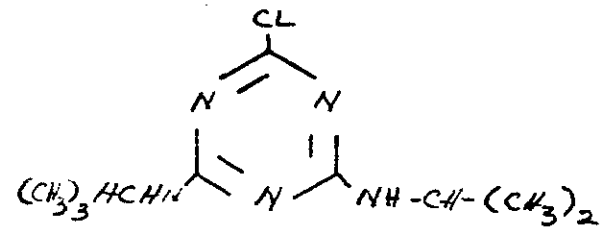
Common Name: Propazine

Chemical Name: 1,3,5-Triazine-2,4-diamine, 6-chloro-N,N'-bis(1-methylethyl)-

Synonyms: Geigy 30,028; Gesamil; Milogard; Plantulin; Primatol P; Propasin; Prozinex

CAS Number: 139-40-2

Chemical Structure:



2.0 PHYSICOCHEMICAL PROPERTIES

Physical State:	Colorless crystals (Meister 1983).
Solubility (Water):	8.6 mg/L (20°C) (Meister 1983).
Stability (Water):	Stable in neutral, slightly acid, or alkaline media, but is hydrolyzed by stronger acids and alkalis (Hayes 1982).
Melting point:	212-214°C (Meister 1983).
Boiling point:	No value available.
Density:	No value available.
Vapor pressure:	2.9×10^{-8} mm Hg at 20°C (TDB 1985).
Log Kow:	-1.21 (calculated; CHEMLAB 1985).
Henry's Law constant:	No value available.
Activated carbon adsorption:	No information available.

3.0 USES

Selective preemergence and preplant herbicide used for the control of most annual broadleaf weeds and annual grasses in milo and sweet sorghum (Meister 1983).

4.0 CHEMICAL FATE

4.1 Environmental Fate

Propazine is more readily adsorbed on soils containing high clay and organic matter content (TDB 1985). Adsorption is not irreversible and desorption will occur readily, depending on temperature, moisture, and pH (TDB 1985). Microorganisms affect the rate of propazine degradation via influencing hydroxylation and dealkylation (TDB 1985).

4.2 Pharmacokinetics

Propazine is readily absorbed from the gastrointestinal tract and is primarily excreted in the urine (TDB 1985). In animals, the dominant metabolic reaction is N-dealkylation (NAS 1977).

5.0 HEALTH EFFECTS IN HUMANS

5.1 Summary

Contact dermatitis was reported in workers involved in Propazine manufacutre (Hayes 1983).

5.2 Key OPP Studies

None identified.

6.0 HEALTH EFFECTS IN ANIMALS

6.1 Summary

Reinhardt and Brittelli (1981) reported the following acute toxicity values for propazine: mouse oral LD50, 5000 mg/kg; rat oral LD50, >5000 mg/kg; rabbit dermal LD50, >10,200 mg/kg. RTECS (1985) reported the acute oral LD50 in the rat, mouse, and guinea pig as 3840, 3180, and 1200 mg/kg, respectively.

Propazine at 250 mg/kg for 130 days produced no gross signs of toxicity or pathologic changes (species not specified) (WSSA 1974).

In a 90-day feeding study, no signs of toxicity were observed in beagle dogs receiving 50, 200, or 1000 ppm (1.25, 5, or 25 mg/kg/day) of propazine 80w (TDB 1985).

Mice fed propazine for 80 weeks at 46.4 mg/kg/day displayed a 5.7% incidence of hepatomas (4.2% in controls) (Innes et al. 1969).

6.2 Key OPP Studies (File Last Updated 10-1-84)

Reference (OPP Accession Number)	Brief Description
Ciba-Geigy 1976** (ACC. NO. 070544)	Teratology - rat Teratogenic NOEL > 600 mg/kg (HDT); Fetotoxic LEL = 300 mg/kg (decreased body weight); Fetotoxic NOEL = 100 mg/kg; Maternal toxic LEL = 300 mg/kg; Maternal toxic NOEL = 100 mg/kg; Levels tested: 0, 30, 100, 300, and 600 mg/kg.
IRDC 1979* (ACC. NO. 243356)	3-Generation Reproduction - rat Reproductive NOEL = 100 ppm (5 mg/kg/day); Reproductive LEL = 1000 ppm (50 mg/kg/day; HDT) (reduced mean pup body weights); Levels tested: 0, 3, 100, and 1000 ppm (0, 0.15, and 50 mg/kg/day).
Not stated**	90-to-180-Day Feeding - rat Systemic NOEL < 250 mg/kg (LDT) (retardation in weight gain); Levels tested: 0, 250, and 2500 mg/kg/day.
Not stated**	90-Day Feeding - dog Systemic NOEL = 200 ppm (5 mg/kg/day); Systemic LEL = 1000 ppm (25 mg/kg/day; HDT) (body weight loss); Levels tested: 0, 50, 200, and 1000 ppm (0, 1.25, 5, and 25 mg/kg/day).
Not stated**	90-Day Feeding - rat Systemic NOEL = 200 ppm (10 mg/kg/day); Systemic LEL = 1000 ppm (50 mg/kg/day; HDT) (body weight loss); Levels tested: 0, 50, 200, and 1000 ppm (0, 2.5, 10, and 50 mg/kg/day).
IRDC 1980* (ACC. NO. 243350)	2-Year Feeding/Oncogenic - rat Systemic NOEL = 1000 ppm (50 mg/kg/day); Systemic LEL = 3000 ppm (150 mg/kg/day; HDT) (increased focal myocardial fibrosis, focal myocardial degeneration); Oncogenic NOEL > 3000 ppm (HDT); Levels tested: 0, 3, 100, and 3000 ppm (0, 0.15, 5, and 150 mg/kg/day).

* Study determined by OPP to be valid for regulatory purposes.

** Validity of study not reported in OPP file, or study considered by OPP to be insufficient for regulatory purposes.

(7/19/85)

Reference (OPP Accession Number)	Brief Description
IRDC* (ACC. NO. 243353)	2-Year Feeding/Oncogenic - rat Systemic NOEL < 3 ppm (lowest dose tested; significant decrease in body weight in both male and female rats); Oncogenic NOEL = 100 ppm (5 mg/kg/day); Oncogenic LEL = 1000 ppm (50 mg/kg/day; increase in mammary tumors); Levels tested: 0, 3, 100, and 1000 ppm (0, 0.15, 5, and 50 mg/kg/day).

7.0 EXISTING CRITERIA AND GUIDELINES

Organization	Guidance Level Type	Value	Rationale
Long-Term:			
NAS	ADI	0.0464 mg/kg/day	Based on a NOAEL of 46.4 mg/kg/day identified in an 80-week feeding study in mice (Innes et al., 1969) and an uncertainty factor of 1,000 (NAS 1977).
NAS	Suggested-No-Adverse-Effect-Level	0.32 mg/L	Based on ADI of 0.0464 mg/kg/day; 70 kg adult consuming 2 L/day; and a source contribution factor of 20% (NAS 1977).

8.0 TREATMENT

No information on treatment processes for this compound were available. Refer to Section 2.0 for physical and chemical properties that may affect treatment processes.

9.0 REFERENCES

CHEMLAB. 1985. The Chemical Information System, CIS, Inc.

Hayes WJ. 1982. Pesticides studied in man. Baltimore, MD: Williams and Wilkins.

Innes JRM, Viland MG, Valerio L, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary note. J. Nat. Cancer Inst. 42:1101-1114. Cited in: NAS. 1977. National Academy of Sciences. Drinking Water and Health. Washington, DC: National Academy of Sciences.

* Study determined by OPP to be valid for regulatory purposes.

(7/19/85)

Meister R, ed. 1983. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.

NAS. 1977. National Academy of Sciences. Drinking water and health. Washington, DC: National Academy Press.

Reinhardt CF, Brittelli MR. 1981. Heterocyclic and miscellaneous nitrogen compounds. In: Clayton GD, Clayton FE, eds. 1981. Patty's industrial hygiene and toxicology. 3rd revised ed. New York: John Wiley and Sons.

RTECS. 1985. National Institute for Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. National Library of Medicine Online File.

TDB. 1985. Toxicology Data Bank. MEDLARS II. National Library of Medicine's National Interactive Retrieval Service.

WSSA. 1983. Weed Society of America. Herbicide Handbook. Champaign, IL: Weed Society of America.

HEALTH ADVISORY SUMMARY

Propazine

What is a Health Advisory?

Health Advisories are guidance documents issued by the U.S. Environmental Protection Agency to assist federal, state, and local officials in responding to drinking water contamination. The Health Advisories contain information on health risks and treatment technologies, and specify levels of chemical concentrations in water that are acceptable for drinking. In preparing Health Advisories, EPA reviews available human data and experimental animal studies in evaluating potential human health effects. The Health Advisories are updated as new information becomes available. This summary presents key highlights from the Health Advisory for Propazine.

What is Propazine?

Propazine, also known as Gesomil®, Milogard®, or Primatol P®, is a herbicide used for the control of annual broadleaf weeds and annual grasses in sorghum.

What Health Effects Might Be Caused by Propazine in My Water?

Non-Cancer Effects. EPA has set a Lifetime Health Advisory level for Propazine in drinking water at ***10 micrograms per liter****. This level includes a margin of safety to protect human health and should be regarded as a guideline. EPA believes that water containing Propazine at or below this level is acceptable for drinking every day over the course of one's lifetime, and does not pose any health concerns.

However, consuming Propazine at high levels well above the Lifetime Health Advisory level over a long period of time has been shown to result in decreased fetal weight gain and delayed fetal bone development in animal studies.

Cancer Risk. Propazine is considered by EPA to be a possible human carcinogen (cancer causing agent). There is limited or uncertain information indicating that Propazine causes cancer in animals receiving high doses of the chemical over the course of their lifetimes. Because Propazine in drinking water may possibly increase the risk of cancer in humans, the Lifetime Health Advisory includes an additional margin of safety.

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* Micrograms per liter are the units of measurement for contaminants in water, equivalent to parts per billion.

What Actions Should I Take?

Your first step should be to get the advice of your state or county health officials. Other experts in your state environmental agency or agriculture department may also be helpful to you.

These people are likely to recommend that you retest your well to get an accurate overall picture of the water quality. Seasonal precipitation changes and changes in pesticide use can cause wide variations in the amount of pesticides found in your well.

Upon retesting, if Propazine is detected in your drinking well at or below 10 micrograms per liter, you should continue to retest your well periodically. Your state or county health officials can refer you to approved testing services, advise you on the cost of testing, and recommend how often you should retest.

If Propazine is detected in your water and confirmed by retesting at a level above 10 micrograms per liter, once again consult your state or county health officials. They may advise you to continue periodic retesting, or in some cases, to use an alternative drinking water supply (such as bottled water) or dig a new or deeper well. At present, EPA has no information on the effectiveness of treatment technologies in removing Propazine from water, although activated carbon adsorption and reverse osmosis may be effective.

Where Can I Get More Information?

In addition to your state and county experts, EPA has two toll-free lines you can call. For further information on drinking water quality, treatment technologies, and EPA's Health Advisories, please contact EPA's toll-free Safe Drinking Water Hotline, Monday thru Friday, 8:30 A.M. to 4:30 P.M. E.S.T. at 1-800-426-4791.

Additional information on the health effects of pesticides is available from the National Pesticide Telecommunications Network, toll-free, 24 hours a day, 1-800-858-7378.

August, 1988

PROPAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

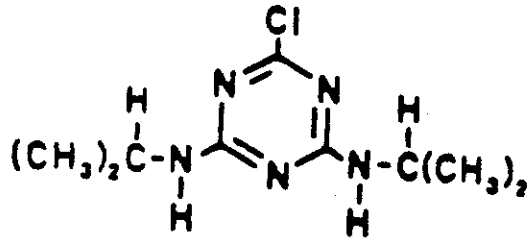
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 139-40-2

Structural Formula



6-Chloro-N,N'-bis(1-methylethyl)-1-3,5-triazine-2,4-diamine

Synonyms

- Geigy 30,028; Gesomil; Milogard; Plantulin; Primatol P; Propasin; Prozinex (Meister, 1983).

Uses

- Selective preemergence and preplant herbicide used for the control of most annual broadleaf weeds and annual grasses in milo and sweet sorghum (Meister, 1983).

Properties (Meister, 1983; IPC, 1984; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_9H_{16}N_5Cl$
Molecular Weight	230.09
Physical State (25°C)	Colorless crystals
Boiling Point	--
Melting Point	212 to 214°C
Density	--
Vapor Pressure (20°C)	2.9×10^{-8} mm Hg
Water Solubility (29°C)	8.6 mg/L
Octanol/Water Partition Coefficient	-1.21
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Propazine has been found in 33 of 1,097 surface water samples analyzed and in 15 of 906 ground water samples (STORET, 1988). Samples were collected at 244 surface water locations and 607 ground water locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 0.2 ug/L in ground water sources. The maximum concentration found was 13 ug/L in surface water and 300 ug/L in ground water. Propazine was found in five States in surface water and in four States in ground water. This information is provided to give a general impression of the occurrence of this chemical in

ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Propazine was detected in ground water in California at trace levels (<0.1 ppb) (U.S.G.S., 1985).

Environmental Fate

The following data were submitted by Ciba-Geigy and reviewed by the Agency (U.S. EPA, 1987):

- Hydrolysis studies show propazine to be resistant to hydrolysis. After 28 days, at pH 5, 60% remains; at pH 7, 92% remains; and at pH 9, 100% remains. Hydroxypropazine (2-hydroxy-4,6-bis-isopropylamino)-s-triazine) is the hydrolysis product.

- Propazine at 2.5 ppm in aqueous solution was exposed to natural sunlight for 17 days. In that time, 5% degraded to hydroxy-propazine.

- Under aerobic conditions, 10 ppm propazine was applied to a loamy sand (German) soil with 2.2% organic carbon. The soil was incubated at 25°C in the dark and kept at 70% of field capacity. Propazine degraded with a half-life of 15 weeks. Hydroxypropazine was the major degradate from aerobic soil metabolism; its concentration increased from 14% at 12 weeks to a maximum of 31% after 52 weeks of incubation. Trapped volatiles identified as CO_2 accounted for 1% of the applied propazine after 52 weeks. Bound residues increased up to 35% after 12 weeks of incubation.

- Under anaerobic conditions, further degradation of propazine was slight.

- Freundlich soil-water partition coefficient (Kd) values for propazine and hydroxypropazine were determined for four soils: a sand loam (0.7% OM), a sand loam (1.4% OM), a loam soil (2.9% OM) and a clay loam (8.3% OM). The Kd values were: 0.34, 1.13, 2.69 and 3.19, respectively, for propazine. On the same four soils the Kd values for hydroxypropazine were: 1.13, 2.94, 31.8 and 10.6, respectively. All Kd values have units of ml/gm.

- Leaching studies for propazine performed on four soils under worst-case conditions (30-cm columns leached with 20 inches of water) for propazine indicate propazine's mobility in soil-water systems. In a loamy sand (0.7% OM), a sandy loam (1.4% OM), a loam (1.7% OM), and a silt loam (2.4% OM), 82.5%, 18%, 69.5%, and 23.6% leached, respectively.

- In column studies using aged propazine, degradation products leached from a loamy sand soil with 2.2% OM. About 25% of the aged propazine added to the columns leached. In a loam soil with 3.6% OM, <0.05% of the aged propazine added to the columns leached.

- In field dissipation studies, propazine was found at 18 inches the deepest depth in the soil sampled. Hydroxypropazine was found at all depths and sites up to 3 years after application. Field half-lives for propazine were 5 to 33 weeks in the 0- to 6-inch depth, and 17 to 51 weeks at the 6 to 12 inch depth.

III. PHARMACOKINETICS

Absorption

- Bakke et al. (1967) administered single oral doses of ring-labeled ^{14}C-propazine to Sprague-Dawley rats. After 72 hours, about 23% of the label was recovered in the feces and about 66% was excreted in the urine. This indicates that gastrointestinal absorption was at least 77% complete.

Distribution

- Bakke et al. (1967) administered ring-labeled ^{14}C-propazine (41 to 56 mg/kg) to rats by gastric intubation. Radioactivity in a variety of tissues was observed to decrease from an average of 46.7 ppm 2 days posttreatment to 22.3 ppm after 8 days. Radioactivity was detected in the lung (30 ppm), spleen (25 ppm) heart (27 ppm), kidney (17 ppm) and brain (13 ppm) for up to 8 days. After 12 days, the only detectable quantities were in hide and hair (3.35% of administered dose), viscera (0.1%) and carcass (2.22%).

Metabolism

- Eighteen metabolites of propazine have been identified in the urine of rats given single oral doses of ^{14}C-propazine (Bakke et al., 1967). No other details were provided. Based on metabolites found in urine, Bakke et al. (1967) reported that dealkylation is one reaction in the metabolism of propazine. No other details were provided.

Excretion

- Bakke et al. (1967) administered single oral doses of ^{14}C-ring-labeled propazine to rats. Most of the radioactivity was excreted in the urine (65.8%) and feces (23%) within 72 hours. Excretion of propazine and/or metabolites was most rapid during the first 24 hours after administration, decreasing to smaller amounts at 72 hours.

IV. HEALTH EFFECTS

Humans

- Contact dermatitis was reported in workers involved in propazine manufacturing (Hayes, 1982). No other information on the health effects of propazine in humans was found in the available literature.

Animals

Short-term Exposure

- The reported acute oral LD_{50} values for propazine (purity not specified) were >5,000 mg/kg in mice (Stenger and Kindler, 1963b) and 1,200 mg/kg in guinea pigs (NIOSH, 1987).

- Stenger and Kindler (1963a) reported that dietary administration of propazine (purity not specified) to rats (five/sex/dose) at doses of 1,250 or 2,500 mg/kg for 4 weeks resulted in a decrease in body weight, but there were no pathological alterations in organs or tissues. No other details were provided.

Dermal/Ocular Effects

- The acute dermal LD_{50} value in rabbits for propazine (90% water dispersible granules) was reported as >2,000 mg/kg (Cannelongo et al., 1979).

- Stenger and Huber (1961) reported that rats were unaffected when a 5% gum arabic suspension of propazine (0.4 mL/animal) was applied once a day for 5 consecutive days to shaved and intact skin of five rats then washed away 3 hours after application.

- Palazzolo (1964) reported that propazine (1 or 2 g/kg/day) applied to intact or abraded skin of albino rabbits (five/sex/dose) for 7 hours produced mild erythema, drying, desquamation and thickening of the skin. Body weights, mortality, behavior, hematology, clinical chemistry and pathology of the treated and untreated groups were similar.

Long-term Exposure

- In 90-day feeding studies by Wazeter et al. (1967a), beagle dogs (12/sex/dose) were fed propazine (80 WP) in the diet at 0, 50, 200 or 1,000 ppm active ingredient. Based on the assumption that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959) these doses correspond to 0, 1.25, 5.0 or 25 mg/kg/day. No compound-related changes were observed in general appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology or histopathology at any dose tested. In the 1,000 ppm dose group, four dogs lost 0.3 to 1.1 kg in body weight, which the author suggested may have been compound-related (no p value reported). Based on these results, a No-Observed-Adverse-Effect Level (NOAEL) of 200 ppm (5 mg/kg/day) and a LOAEL of 1,000 ppm (25 mg/kg/day) were identified.

- Wazeter et al. (1967b) supplied CD rats (80/sex/dose) with propazine (80 WP) in the diet for 90 days at dose levels of 0, 50, 200 or 1,000 ppm active ingredient. Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 0, 2.5, 10 or 50 mg/kg/day. No compound-related changes were observed in appearance, general behavior, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. There was

a 12% reduction ($p < 0.01$) in body weight of females at 1,000 ppm (50 mg/kg/day) at the end of the study. Based on body weight loss, a NOAEL of 200 ppm (10 mg/kg/day) and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 1,000 ppm (50 mg/kg/day) were identified.

- Geigy (1960) dosed rats (12/sex/dose) of an unspecified strain with propazine (50% a.i.) by stomach tube for 90 days at 0, 250 or 2,500 mg/kg/day (a.i.) or for 180 days at 0 or 250 mg/kg/day (a.i.). In the 90-day study, a reduction in body weight and feed consumption were reported at 2,500 mg/kg/day, but no effects were seen at 250 mg/kg/day. No histopathological evaluations were performed at the high-dose level. After 180 days, rats administered propazine at 250 mg/kg/day were similar to untreated controls in growth rates, daily food consumption, gross appearance and behavior, mortality, gross pathology and histopathology. This study identified a NOAEL of 250 mg/kg/day and a LOAEL of 2,500 mg/kg/day.

- Jessup et al. (1980a) fed CD mice (60/sex/dose) technical propazine (purity not specified) for 2 years at dose levels of 0, 3, 1,000 or 3,000 ppm. Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 0.45, 150 or 450 mg/kg/day. The general appearance, behavior, survival rate, body weights, organ weights, food consumption and incidence of inflammatory, degenerative or proliferative alterations in various tissues and organs did not differ significantly from untreated controls. The author identified a NOAEL of 3,000 ppm (450 mg/kg/day, the highest dose tested).

- Jessup et al. (1980b) fed CD rats (60 to 70/sex/dose) technical propazine (purity not specified) in the diet for 2 years at dose levels of 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. No compound-related effects were observed in behavior, appearance, survival, feed consumption, hematology, urinalysis and in nonneoplastic alterations in various tissues and organs. Mean body weight gains appeared to be lower in the treatment groups than the control groups. Body weights at 104 weeks were lower than controls at all dose levels. The percent decreases in males and females were as follows: -6.3 and -3.9% (3 ppm); -4.6 and -5.6% (100 ppm); -13.1 and -11.4% (1,000 ppm). These decreases were statistically significant in males at 3 and 1,000 ppm, and in females at 100 and 1,000 ppm. The decreases at 3 or 100 ppm appeared to be so small that they may not be considered biologically significant; a NOAEL was identified at 100 ppm (5 mg/kg/day).

Reproductive Effects

- Jessup et al. (1979) conducted a three-generation study in which CD rats (20 females and 10 males/dose) were administered technical propazine in the diet at 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. No compound-related effects were observed in any dose group in

general behavior, appearance or survival of parental rats or pups. The mean parental body weights were statistically lower at 1,000 ppm (50 mg/kg/day). No differences were reported in feed consumption for treated and control animals. No treatment-related effects were observed in fertility, length of gestation or viability and surivival of the pups through weaning. Mean pup weights at lactation were not adversely affected at 3 or 100 ppm (0.15 or 5 mg/kg/day). However, at 1,000 ppm (50 mg/kg/day), there was a statistically significant decrease in mean pup weights for all generations except F_{1a}. Based on these data, a NOAEL of 100 ppm (5 mg/kg/day) was identified.

Developmental Effects

- Fritz (1976) administered technical propazine (0, 30, 100, 300 or 600 mg/kg/bw) orally by intubation to pregnant Sprague-Dawley rats (25/dose) on days 6 through 15 of gestation. No maternal toxicity, fetotoxicity or teratogenic effects were observed at 100 mg/kg/day or lower. Maternal body weight and feed consumption were reduced at 300 mg/kg/day or higher. Fetal body weight was reduced, and there was delayed skeletal ossification (of calcanei) at 300 mg/kg/day or higher. Based on body weights, a maternal NOAEL of 100 mg/kg/day and a fetal NOAEL of 100 mg/kg/day were identified.

- Salamon (1985) dosed pregnant CD rats (21 to 23 animals per dose group) with technical propazine (99.1% pure) by gavage at dose levels of 0, 10, 100 or 500 mg/kg/day on days 6 through 15 of gestation. Maternal body weight and feed consumption were statistically significantly ($p < 0.05$) decreased at doses of 100 mg/kg/day or higher. Fetal body weight was reduced, and ossification of cranial structures was delayed at 500 mg/kg/day. Based on maternal toxicity, a NOAEL of 100 mg/kg/day was identified.

Mutagenicity

- Puri (1984a) reported that propazine (0, 0.4, 20, 100 or 500 ug/mL) did not produce DNA damage in human fibroblasts in vitro.

- Puri (1984b) reported that propazine (0, 0.50, 2.5, 12.5 or 62.5 ug/mL) did not cause DNA damage in rat hepatocytes in vitro.

- Strasser (1984) reported that propazine administered to Chinese hamsters by gavage (0, 1,250, 2,500 or 5,000 mg/kg) did not cause anomalies in nuclei of somatic interphase cells.

Carcinogenicity

- Innes et al. (1969) fed propazine in the diet to 72 mice (C57BL/6 x AKR)F_1 or (C57BL/6 x C3H/ANf)F_1 for 18 months at a dose level of 0 or 46.4 mg/kg/day. Based on histopathological examination of tissues (no data reported), the authors stated that propazine, at the one dose tested, did not cause a statistically significant increase in the frequency of any tumor type in any sex-strain subgroup or combination of groups.

- Jessup et al. (1980b) fed CD rats (60 to 70/sex/dose) technical propazine (purity not specified) in the diet for 2 years at dose levels of 0, 3, 100 or 1,000 ppm. Based on the assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.15, 5 or 50 mg/kg/day. Tumor incidence was evaluated for a variety of organs and tissues. The most commonly occurring tumors were mammary gland tumors in female rats. At the highest dose tested (1,000 ppm, 50 mg/kg/day), the authors reported an increase in adenomas (10/55, 18%), adenocarcinomas (9/55, 16%) and papillary carcinomas (8/55, 15%) compared to corresponding tumor levels in untreated controls (3/55, 5%), (6/55, 11%) and (4/55, 7%), respectively. Also, it was reported that the percentage of tumor-bearing rats was 73% in the high-dose treated group compared to 50% in corresponding untreated controls. The authors did not consider these increases to be statistically significant. However, in 1981, Somers reported historical control values of 122/1,248 (10%) for adenomas and of 769/1,528 (50%) for percentage of tumor-bearing animals. Further evaluations by Somers (1981) of the above data (control and treated) and historical control data indicated that the increase in mammary gland adenomas and the number of rats bearing one or more tumor was statistically significant ($p < 0.02$).

- Jessup et al. (1980a) fed CD mice (60/sex/dose) technical propazine (purity not stated) for 2 years at dose levels of 0, 3, 1,000 or 3,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 0.45, 150 or 450 mg/kg/day. The incidence of proliferative and neoplastic alterations in the treated groups did not differ significantly from the control group at any dose level.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (BW)}{(UF) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L} \ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000), in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for propazine. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, 1.0 mg/L (1,000 ug/L, calculated below), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Salamon (1985) has been selected to serve as the basis for the determination of Ten-day HA value for propazine. In this teratogenicity study in rats, body weight was decreased in dams dosed on days 6 to 15 of gestation with 100 mg/kg/day or greater. No adverse effects were observed in either dams or fetuses at 100 mg/kg/day. The rat study by Fritz (1976) reported maternal and fetal toxicity at 300 mg/kg/day, but not at 100 mg/kg/day. This NOAEL was not selected, since maternal weight loss was noted at this dose by Salamon (1985).

Using a NOAEL of 10 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of maternal and developmental toxicity in rats exposed to propazine by gavage on days 6 through 15 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in dogs by Wazeter et al. (1967a) has been selected to serve as the basis for the Longer-term HA for propazine. In this study, body weight loss occurred at 1,000 ppm (25 mg/kg). A NOAEL of 200 ppm (5 mg/kg/day) was identified. This is supported by the 90-day rat feeding study by Wazeter et al. (1967b), which identified a NOAEL of 10 mg/kg/day and a LOAEL of 50 mg/kg/day. The 90-day study in rats by Geigy (1960) has not been selected, since the NOAEL (250 mg/kg/day) is higher than the LOAEL values reported above.

Using a NOAEL of 5 mg/kg/day, the Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.5 \text{ mg/L } (500 \text{ ug/L})$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology, histopathology and body weight gain in dogs exposed to propazine via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(5\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 1.75\ \text{mg/L}\ (2{,}000\ \text{ug/L})$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on appearance, behavior, hematology, urinalysis, clinical chemistry, gross pathology, histopathology and body weight gain in dogs exposed to propazine via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking

water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Jessup et al. (1980b) has been selected to serve as the basis for determination of the Lifetime HA for propazine. No effects were detected on behavior, appearance, mortality, food consumption, hematology, urinalysis or body weight gain at doses of 5 mg/kg/day. At 50 mg/kg/day, decreased weight gain was noted, and there was evidence of increased tumor frequency in the mammary gland. This NOAEL value (5 mg/kg/day) is supported by the NOAEL of 5 mg/kg/day in the three-generation reproduction study in rats by Jessup et al. (1979). The 2-year feeding study in mice by Jessup et al. (1980a) has not been selected, since the data suggest that the mouse is less sensitive than the rat.

The Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(5\ mg/kg/day)}{(100)\ (3)} = 0.02\ mg/kg/day$$

where:

5 mg/kg/day = NOAEL, based on absence of effects on behavior, appearance, mortality, hematology, urinalysis or body weight gain in rats exposed to propazine via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = additional uncertainity factor to account for data gaps (chronic feeding dog study) in the propazine database.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.02\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.70\ mg/L\ (700\ ug/L)$$

where:

0.02 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.70 \text{ mg/L})\ (20\%)}{(10)} = 0.014 \text{ mg/L } (10 \text{ ug/L})$$

where:

0.70 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- No evidence of increased tumor frequency was detected in a 2-year feeding study in mice at doses up to 450 mg/kg/day (Jessup et al., 1980a) or in an 18-month feeding study in mice at a dose of 46.4 mg/kg/day (Innes et al., 1969).

- Jessup et al. (1980b) reported that the occurrence of mammary gland tumors in female rats administered technical propazine in the diet for 2 years at 1,000 ppm (50 mg/kg/day) was increased but did not differ significantly from concurrent controls. However, a reevaluation of the data by Somers (1981) that considered historical control data indicated that the increase in mammary gland adenomas and the number of rats bearing one or more tumors was statistically significant ($p < 0.02$).

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of propazine.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), propazine may be classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1986b) has established residue tolerances of 0.25 ppm for propazine in or on various agricultural commodities (negligible) based on a Provisionary Acceptable Daily Intake (PADI) of 0.005 mg/kg/day.

- NAS (1977) determined an Acceptable Daily Intake (ADI) of 0.464 mg/kg/day, based on a NOAEL of 46.4 mg/kg identified in an 80-week feeding study in mice with an uncertainty factor of 1,000.

- NAS (1977) calculated a chronic Suggested-No-Adverse-Effect-Level (SNARL) of 0.32 mg/L, based on an ADI of 0.0464 mg/kg/day and a relative source contribution factor of 20%.

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VII. ANALYTICAL METHODS

- Analysis of propazine is by a gas chromatographic (GC) using method #507, a method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. This method has been validated in a single laboratory and the limit of detection for propazine was 0.13 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information regarding treatment technologies applicable to the removal of propazine from contaminated water was found in the available literature.

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*Confidential Business Information submitted to the Office of Pesticide Programs.

E X T O X N E T

EXTENSION TOXICOLOGY NETWORK

A Pesticide Information Project of Cooperative Extension Offices of
Cornell University, The University of California, Michigan State University, and Oregon State University

PROPAZINE

TRADE OR OTHER NAMES

Gesamil, Milogard, Primatol, Geigy 30028, Plantulin, Propazin, G-30028, Milo-Pro, Prozinex. Due to changing regulations, these names may not be up-to-date; check with most recent Farm Chemicals Handbook for current trade names.

REGULATORY STATUS

Propazine is classified as a general use herbicide by the U.S. Environmental Protection Agency (EPA). Check with specific state regulations for local restrictions which may apply.

INTRODUCTION

Propazine is an herbicide, a chemical used to kill and control undesirable plants. It is used as a preemergence herbicide, before a crop comes up, for control of broadleaf and grass weeds in sweet sorghum and milo; it is applied as a spray at the time of planting or immediately following planting, but prior to weed or sorghum emergence. It is also used as a selective herbicide, after crops are up (postemergence), on carrots, celery and fennel (20, 21). Like atrazine, an herbicide with similar chemical characteristics, propazine has minor activity against fungi and some worms, 'nematodes'; it does not have insecticidal activity however (20). Containers of propazine formulations bear the EPA signal word "CAUTION," indicating that it is slightly poisonous, or toxic (1).

TOXICOLOGICAL EFFECTS

Acute Toxicity (Effects of one, or short-term, exposure)

Propazine is classified as a moderately toxic herbicide. The amount of this material that could be deadly in humans if taken by mouth is 0.5 to 5 grams per kilogram (g/kg) of body weight, or between one ounce and one pint for a 150-pound person. This quantity of propazine is referred to as its probable oral lethal dose (4). It is mildly irritating to the skin, eyes, and upper respiratory tract (10). Contact dermatitis has been reported among workers manufacturing propazine (7). No cases of poisoning from human ingestion of the herbicide have been recorded Skin and eye contact with propazine should be avoided; inhalation should also be avoided (20).

The amount of propazine that is lethal to one-half (50%) of experimental animals given short term exposure to it is referred to as the acute lethal dose fifty, or LD_{50}, of this herbicide. The oral LD_{50} in rats is 3,840 - 5,000 milligrams per kilogram (mg/kg); in mice, it is 3,180 mg/kg; in guinea pigs, it is 1,200 mg/kg (11). Slight irritation was noted after propazine was applied to the skin of rabbits (1); its dermal LD_{50} in rats is10,200 mg/kg (1). Eye applications of 400 mg caused mild eye irritation in these animals (11). Symptoms of dizziness, cramping, labored and irregular breathing are evident in mice given 5,000 mg/kg orally (20). It has also been observed to cause convulsions or coma, as well as liver and/or kidney damage in experimental animals (3).

EXTOXNET is a collaborative educational project intended to convey pesticide-related information in easily understood terms. Information is provided in two types of documents: Pesticide Information Profiles (PIPs), on the health and environmental effects of specific pesticides, and Toxicology Information Briefs (TIBs), short descriptions of a variety of issues that pertain to pesticides, such as carcinogenicity, ecological effects, and epidemiology. The TIBs are intended to assist in the understanding and interpretation of information in the PIPs. Data presented through EXTOXNET documents are not based on an exhaustive literature search.

Chronic Toxicity (Effects of long-term, repeated exposure)

When given daily to rabbits for one to four months, oral doses of 500 mg/kg propazine were reported to cause a type of **anemia** (4). No gross signs of toxicity or pathologic changes were evident in rats that received daily doses of 250 mg/kg of propazine for 130 consecutive days. No clinical or physical toxic symptoms resulted in beagle dogs fed 50, 200, or 1,000 parts per million (ppm) of propazine formulation in 90-day feeding studies (20).

Reproductive Effects (Effects of exposure on reproduction)

There was an increase in the number of deaths of newborns produced by female rats that were given five mg/kg of propazine during 18 days of pregnancy, or 'gestation' (15).

Teratogenic Effects (Birth defects related to exposure)

No information was found on this aspect of propazine.

Mutagenic Effects (Permanent changes in hereditary material related to exposure)

Some tests indicate that propazine does not have mutagenic effects (1).

Carcinogenic Effects (Cancer production related to exposure)

One of propazine's suspected effects is cancer production, 'carcinogenesis' (5). It is not certain as to whether propazine can cause tumor production (11). One series of studies suggested that propazine is not tumorigenic, or tumor-forming (7).

Organ Toxicity (Harmful effects on organs)

Liver damage is one of the suspected effects of propazine (5). The functioning of certain liver processes was decreased in rats that were given 2,500 mg/kg propazine (4).

Fate in Humans and Animals

Triazines, the family of chemicals within which propazine is included, may disturb the **metabolism** of some of the B vitamins, thiamine (B_1) and riboflavin (B_2). They may also concentrate and accumulate in the fat of humans and animals (5). Propazine is readily absorbed and metabolized in the body (4). There is 42-46% elimination of a metabolized form of the herbicide within 24 hours of oral administration (6). Urine was the major route of propazine excretion in lab animals given oral doses of the herbicide (17).

ECOLOGICAL EFFECTS

Harmful Effects on Birds

Propazine is slightly toxic to birds (21). The lethal concentration fifty, or LC_{50}, is that concentration of a chemical in air or water that kills half of the experimental animals exposed to it for a given time period. The eight-day dietary LC_{50} is over 10,000 ppm for both bobwhite quail and mallard ducks (20).

Harmful Effects on Fish

The 96-hour LC_{50} is 18 ppm for rainbow trout and over 100 ppm for bluegill sunfish (6, 20).

Harmful Effects on Other Animals/Insects (Nontarget species)

Propazine is considered to be practically nontoxic to bees (6).

ENVIRONMENTAL FATE

Breakdown of Chemical in Soil and Groundwater

Propazine readily binds, or **adsorbs**, to soils that contain high clay and organic matter content. However, it can become unbound as readily, depending on soil temperature, moisture, pH, etc. Propazine is not adsorbed as much as other commercial herbicides of its class (s-triazines). Its movement with soil moisture, **'leaching'**, is limited by its adsorption to various soil particles, as well as its low

water solubility (20). In other words, because of its poor solubility in water it remains in the soil for a long time without decomposition (9). However, propazine is one of the pesticide compounds considered by the EPA to have the greatest potential for leaching into groundwater (18). Leaching of propazine does occur with irrigation and/or high rainfall, especially in sandy soils (20). A national groundwater survey did not detect propazine in groundwater (19).

A significant portion of the herbicide may be broken down, or decomposed, by tiny organisms in the soil. Several soil microorganisms are thought to utilize propazine as a source of energy or nitrogen. While it is not fully understood, the breakdown of this herbicide by ultraviolet light from the sun, through a process called 'photodecomposition', is not considered to be an important factor in propazine dissipation. Similarly, the changing of propazine into a gaseous form, in a process called volatilization, is not thought important in its breakdown (20).

Depending on the growing region, propazine-treated soils can be replanted with sorghum, corn, or cotton 12 months following application. Propazine will persist longer in dry or cold soil conditions that inhibit its degradation (20). When it was applied at 0.5 pounds/acre, propazine persisted for 11 to 24 weeks (13).

Breakdown of Chemical in Water

Propazine has been detected in drinking water in the United States (12).

Breakdown of Chemical in Vegetation

Propazine is absorbed principally through plant roots; it has very little postemergence activity. After absorption, it is moved, or translocated, upward into the plant where it accumulates in the apical meristems and leaves of plants (20). This type of herbicide inhibits photosynthesis, the process by which plants derive and create energy from the ultraviolet (UV) light from the sun (2).

The breakdown of propazine in plants is assumed to be similar to the metabolism of two other herbicides, atrazine and simazine. Propazine accumulates, and causes death, in those plants that are unable to readily metabolize propazine into a nonpoisonous, or 'non-phytotoxic' compound. At high dosages propazine damages carrots, especially when humidity is high. Sugar beets are also very sensitive to this herbicide (20).

PHYSICAL PROPERTIES/GUIDELINES

Propazine is a white crystalline substance that forms colorless crystals; the technical material is more than 95% pure (7, 9). It is stable in neutral, slightly acid, or alkaline media, but it is hydrolyzed by stronger acids and alkalis (7). It is nonflammable. Propazine is very stable over several years of shelf life, with only slight sensitivity to light and extreme temperatures which would normally occur (20).

It is available as 80% wettable and four pounds/gallon liquified; 90% water dispersible granule; 50% wettable powder (Berg,1987). It is compatible with most pesticides and fertilizers when used at normal rates. It is noncorrosive under normal use conditions (20).

BASIC MANUFACTURER

Ciba-Geigy Corp.
Agricultural Division
P.O. Box 18300
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GLOSSARY

ADI: Acceptable Daily Intake; the maximum dose of a substance that is anticipated to be without lifetime risk to humans, when taken daily.

ADSORB: the process by which chemicals are held (bound) on the surface of something (e.g. soil particles).

ANEMIA: a condition in which blood is low in red blood cells, total volume, or hemoglobin, the part of blood which contains iron.

APICAL MERISTEMS: the areas of tissue at or near the tip of a plant structure, where new tissue cells are formed.

CONTACT DERMATITIS: skin swelling due to either initial acute irritation from short-term contact with a substance, or from chronic sensitization that develops from long-term skin contact with an irritating substance.

Kd: soil-water adsorption coefficient, calculated by using measurements of pesticide distribution between soil and water.

Koc: soil-adsorption measure; a measure of the tendency for organics to be adsorbed by soil and sediment. The Koc is chemical specific and is largely independent of soil properties.

Kow: octanol-water partition coefficient; an indicator of soil adsorption and bioaccumulation, calculated by using measurements of pesticide distribution between octanol and water. High octanol-water coefficient compounds are likely to bioaccumulate.

LD_{50} (ORAL, DERMAL, or RESPIRATORY): lethal dose fifty; the dose of a poisonous substance (given by mouth, absorbed through the skin, or inhaled, respectively) that causes death in half (50%) of the test population. A value used to show the toxicity of a chemical, expressed in milligrams (mg) of toxic chemical per kilogram (kg) of body weight: mg/kg. The lower the LD_{50}, the more toxic the chemical. LD_{50}s do not indicate the dosages necessary to produce poisoning symptoms, disease conditions, or other nonlethal effects on health. A high LD_{50} can not be interpreted as an indication of safety or a lack of having the capacity to poison.

LEACHING: the movement of a pesticide, chemical, or other substance through soil as a result of water movement, potentially causing contamination of groundwater resources with "leachate". The tendency for a material to leach is generally affected by its adsorption to soil particles and its solubility: the less a material adsorbs to soil and the more soluble a material is, the more likely it will be to leach.

METABOLISM: the process of chemical changes by which energy is provided in living cells.

pH: a measure of the acidity or alkalinity of a substance. A pH above 7 represents alkalinity (baseness) in an aqueous medium; a pH below 7 indicates acidity; pH 7 is neutral.

pka: equivalent to pH.

PPM: parts per million; the number of parts of toxicant per million parts of the substance in question; may represent the percentage or residue in soil, water, or whole animals, for example.

RESPIRATORY TRACT: all the passages through which air is taken in and out of the body with breathing, including the nose, trachea, larynx, bronchii, and lungs, where an exchange of oxygen and carbon dioxide takes place.

SELECTIVE HERBICIDE: one that kills specific undesirable plants/insects, sparing other desirable plants; this is done through different types of toxic action or by the manner in which the material is used (its formulation, dosage, timing, placement, etc.).

SOLUBILITY: the concentration of a substance that dissolves in a given solvent. HIGH SOLUBILITY: readily dissolves. LOW SOLUBILITY: does not dissolve very well.

VAPOR PRESSURE: the pressure exerted by a gas that is in equilibrium with its solid or liquid form; a relative measure of the volatility of a chemical in its pure state. The higher the vapor pressure of a chemical, the more likely it will be to evaporate.

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Please refer to Toxicology Information Brief for a detailed description of the information that follows.

CAS # 139-40-2

Physical Properties:

H_2O solubility -- 8.6 ppm at 20°C (20, 1, 9)
-- 4 ppm (19)

Solubility in other solvents
-- Difficult to dissolve in organic solvents (20)
-- 6.2 g/kg at 22°C in benzene and toluene (21)
-- 2.5 g/kg in carbon tetrachloride (21)
-- 0.5 g/100 ml at 20° in diethyl ether (6)

Melting point -- 212-214°C (7, 1)
-- 210-212°C (9)

Vapor pressure -- 2.9×10^{-6} mmHg at 20°C (7)
-- 3.4×10^{-6} mmHg at 50°C (20)

pka -- 1.85 (19).

Kow -- log Kow = 2.94 (16)
--785 (8)

Koc -- 154 plus or minus 37% (19)

Kd -- 0.1-20; Class 3 Intermediate (19)
-- 207 (PC) (14)

Chemical Class/Use -- selective triazine herbicide

Exposure Guidelines:

ADI -- 0.0464 mg/kg/day (12)

N.Y. 12/4/87

DISCLAIMER: The information in this profile does not in any way replace or supersede the information on the pesticide product label/ing or other regulatory requirements. Please refer to the pesticide product label/ing.

CHEMICAL: PROPAZINE
PC CODE: 080808

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