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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

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

SUBJECT: PROPAZINE - Submission of a 21-Day Dermal Study in Rats and a Developmental Toxicity Study In Rabbits for Review (EPA ID 001812-GAG)

TOX Chem No.:	184
PC Code No.:	080808
DP Barcode:	D232468,D232469
Submission No.:	S514322

FROM: William B. Greear, M.P.H. William B. Greear 4/22/97
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Deborah McCall
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Marion P. Copley, D.V.M., Section Head Marion Copley 4/25/97
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

CC: Terri Stowe/Robert Taylor
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Registration Division (7505C)

I. CONCLUSIONS:

The 21-day dermal toxicity study in rats and the developmental toxicity study in rabbits are acceptable and satisfy the guideline requirements for series 82-2 and 83-3b toxicity studies, respectively.

II. ACTION REQUESTED:

The Registration Division has requested that TOX I review the following studies:

- Naas, D.J. (1995) A 21-day dermal study of propazine in rats. WIL Research Laboratories, Inc., Ashland, Ohio. Laboratory Study No. WIL-157006, December 1, 1995. MRID

44127401.

- Knapp, J. F. (1995) A developmental toxicity study of propazine technical in rabbits. WIL Research Laboratories, Inc., Ashland, Ohio, 44805. Laboratory Study No. WIL-157005, October 11, 1995. MRID 44153401.

III. RESULTS AND DISCUSSION:

The results of the two studies are summarized in the one-liners that are attached. The DERs are also attached.

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OFFICE OF PESTICIDES/HED/TOX
ONELINERS

P. C. No:080808 TOXCHEM NO.:184 Chemical Name:Propazine

CITATION	MATERIAL	MRID NUMBER	RESULTS	CORE GRADE DOC.#
(82-2)21-day dermal Species:rat Lab. Name:WIL Study No:WIL-157006 Date: 12/1/95	prppazine tech (98.0%)	44127401	In a 21-day subchronic dermal toxicity study, propazine TECHNICAL (98.0%, Lot # 309027C) was dermally applied to 5 rats/sex/dose at dose levels of 0, 10, 100 or 1000 mg/kg/day. There was a slight decrease in body weight gain in males (38.2%) in the 1000 mg/kg/day group. There was a slight decrease in body weight in females (5.2%) in the 1000 mg/kg/day group. There was no effect on clinical signs of toxicity, mortality, dermal irritation, food consumption, hematology, clinical chemistry, organ weights or pathology. The LOEL is 1000 mg/kg/day based on decreased body weight gain. The NOEL is 100 mg/kg/day. The 21-day dermal study is classified ACCEPTABLE and satisfies the guideline requirements for a 21-day dermal toxicity study (82-2) in rats.	acceptable
(83-3b) Developmental Species:rabbit Lab. Name:WIL Study No:WIL-157005 Date: 10/11/95	propazine tech (98%)	44153401	In a developmental toxicity study (MRID 44153401), propazine technical (98% a.i., Lot #309027C) was administered to 20 New Zealand White rabbits/dose level by gavage in corn oil at dose levels of 0, 2, 10 or 50 mg/kg/day from day 6 through 19 of gestation. Decreased defecation was observed in the 50 mg/kg/day group. Body weight gain was decreased by 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased by 28% in the 50 mg/kg/day group during the treatment period. The maternal LOEL is 50 mg/kg/day, based on decreased defecation and decreased body weight gain and food consumption during the treatment period. The NOEL is 10 mg/kg/day. Live litter size, mean fetal weight, fetal sex ratios, mean number of corpora lutea and implantation sites and postimplantation loss were unaffected by treatment. There were no treatment related effects in developmental parameters. The LOEL was not determined. The NOEL is 50 mg/kg/day based on decreased defecation, body weight gain and food consumption. The developmental toxicity study in the rabbit is classified ACCEPTABLE and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; 83-3b) in rabbits.	Acceptable

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Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Review: Marion P. Copley, D.V.M. Marion Copley 4/25/97
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 21-Day Subchronic Dermal Toxicity - Rat
OPPTS 870.3200 (82-2)

DP BARCODE: D232468 SUBMISSION CODE: S514322

P.C. CODE: 080808 TOX. CHEM. No.: 184

TEST MATERIAL (PURITY): Propazine TECHNICAL 98.0%

SYNONYMS: Gesamil, Milogard, Geigy 30,028, Plantulin, Prozinex, Primatol P, G 30028, 2-chloro-4,6-bis(isopropylamine)-S-triazine, CAS # 139-40-2

CITATION: Naas, D.J. (1995) A 21-day dermal study of propazine in rats. WIL Research Laboratories, Inc., Ashland, Ohio. Laboratory Study No. WIL-157006, December 1, 1995. MRID 44127401.

SPONSOR: Griffin Corporation, Valdosta, GA 31603

EXECUTIVE SUMMARY: In a 21-day subchronic dermal toxicity study, propazine TECHNICAL (98.0%, Lot # 309027C) was dermally applied to 5 rats/sex/dose at dose levels of 0, 10, 100 or 1000 mg/kg/day.

There was a slight decrease in body weight gain in males (38.2%) in the 1000 mg/kg/day group. There was a slight decrease in body weight in females (5.2%) in the 1000 mg/kg/day group. There was no effect on clinical signs of toxicity, mortality, dermal irritation, food consumption, hematology, clinical chemistry, organ weights or pathology. **The LOEL is 1000 mg/kg/day based on decreased body weight gain. The NOEL is 100 mg/kg/day.**

The 21-day dermal study is classified **ACCEPTABLE** and satisfies the guideline requirements for a 21-day dermal toxicity study (82-2) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality Statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Propazine Technical
   Description: white powder
   Lot/Batch #: 309027C
   Purity: 98.0% a.i.
   Stability of compound: not provided
   CAS #: 139-40-2
   Structure:

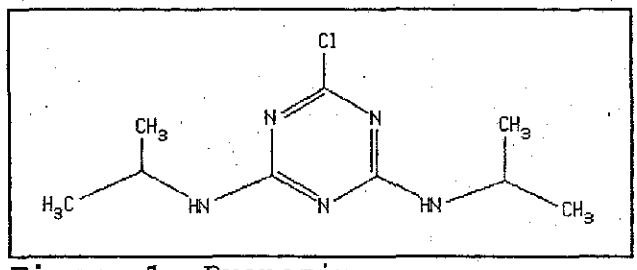

Figure 1 Propazine

2. Vehicle and/or positive control: 0.99% saline
   Lot/Batch #: C275974

3. Test animals: Species: rat
   Strain: Sprague-Dawley Crl:CDBR
   Age and weight at study initiation:
   Males: 58 days old, 264-292g.
   Females: 79 days old, 218-254 g.
   Source: Charles River Breeding Laboratories, Portage, MI.
   Housing: Individually in wire-mesh cages.
   Diet: Purina Certified Rodent Chow # 5002.
   Water: Municipal
   Environmental conditions:
   Temperature: 68-71° F
   Humidity: 28-68%.
   Air changes: not provided
   Photoperiod: 12 hours on/12 hours off
   Acclimation period: 15 days

B. STUDY DESIGN:

1. In life dates: Start: 1/6/95
   End: 1/27/95

2. Animal assignment:

Animals were assigned randomly based on body weight to the test groups in Table 1.

Table 1.

Test Group	Dose to Animals (mg/kg/day)	Male	Female
Control	0	5	5
Low	10	5	5
Mid	100	5	5
High	1000	5	5

3. Treatment:

The test material was applied 5 days per week for 3 consecutive weeks to the shaved intact dorsal skin of each rat for a minimum of 15 applications. The application sites were wrapped for 6 hours with a gauze binder, which was secured with Dermiform tape. A concurrent control group of identical design received 0.99 saline on a comparable regimen. All animals wore Elizabethan collars, which were removed at the end of the 6-hour exposure period. Residual test material was removed from the application site at the end of the 6-hour exposure period. The animals were observed for signs of overt toxicity, dermal irritation, effects on body weight, food consumption, and hematology and clinical chemistry parameters. Complete necropsies were performed on all animals. Selected organs were weighed and a microscopic examination was conducted on selected tissues from all animals.

4. Statistics:

Body weight, body weight change, food consumption, clinical laboratory and absolute and relative organ weight data were subjected to a one-way analysis of variance followed by Dunnett's Test.

C. METHODS:

1. Observations:

Animals were observed twice daily for signs of toxicity and mortality.

2. Dermal irritation:

Application sites were examined for erythema, edema and other dermal findings once daily.

3. Body weight:

Animals were weighed weekly, beginning one week prior to dose administration.

4. Food consumption:

Individual food consumption was recorded weekly, beginning one week prior to dose administration.

5. Blood was collected from all surviving animals at the scheduled necropsy. The animals were fasted overnight prior to the collection of blood samples. The CHECKED (X) parameters were examined.

a. Hematology:

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

*Required for subchronic studies based on Subdivision F Guidelines.

b. Clinical Chemistry:

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total cholesterol
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	ENZYMES	x	Total bilirubin
x	Alkaline phosphatase (ALK)	x	Total serum protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophores
	Lactic acid dehydrogenase (LDH)	x	A/G ratio
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase (also SGOT)*		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* required for subchronic studies based on Subdivision F Guidelines.

6. Urinalysis:

Not performed.

7. Sacrifice and Pathology:

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination.

Kidneys (2)	Skin (treated and untreated)
Liver (sections of 2 lobes)	All gross lesions

The following organs from all animals sacrificed at the scheduled necropsy were weighed.

Brain	Liver
Kidney	Ovaries
	Testes

II. RESULTS

A. OBSERVATIONS:

1. Toxicity: No clinical signs of toxicity were observed that were compound related.

2. Mortality: One male in the 10 mg/kg/day group was found dead on day 3.

B. DERMAL IRRITATION:

Dermal desquamation was observed on 1, 0, 5 and 3 occasions in 1, 0, 1 and 2 animals in the 0, 10, 100 and 1000 mg/kg/day groups, respectively.

C. BODY WEIGHT AND WEIGHT GAIN:

Mean body weight gain was decreased in males and mean body weight loss occurred in females from week 0 to 1 in the 1000 mg/kg/day group. Mean body weight gain was decreased in the 1000 mg/kg/day group males (38.2%) and females (7.5%). Mean body weights were slightly decreased in males and females in the 1000 mg/kg/day group throughout the dosing period (0.8 - 7.5%) (see Table 2).

Table 2. Mean Body Weight and Body Weight Gain[1] and Percent Decrease (%).

Test Group (mg/kg/day)	Body Weight (g) and Weight Gain (g) Week					
	0	1	2	3	0-1	0-3
	Males					
0	280	306	321	348	26	68
10	281	310	333	360	31	71
100	283	309	333	355	26	72
1000	280	293(4.2)	307(4.4)	322(7.5)	13(50)*	42(38.2)
	Females					
0	241	238	242	250	-3	9
10	240(0.4)	244	245	250	1	10
100	240(0.4)	234(1.7)	237(2.1)	239(4.4)	-5	-1
1000	239(0.8)	229(3.8)	231(4.5)	237(5.2)	-10*	-2

1. Data extracted from Tables 3, 4, 5 and 6, pp. 37-42, Study No. WIL-157006, MRID 44127401.
* Significantly different from controls at $p<0.05$.

D. FOOD CONSUMPTION: No treatment related changes occurred.

E. BLOOD WORK:

1. Hematology: No treatment related changes occurred.

2. Clinical Chemistry: No treatment related changes occurred.

F. SACRIFICE AND PATHOLOGY:

1. Organ Weight: No Treatment related changes occurred.

2. Gross Pathology: No treatment related changes occurred.

3. Microscopic Pathology:

a) Non-neoplastic: No treatment related changes occurred.

b) Neoplastic: No treatment related changes occurred.

III. DISCUSSION

A. The test material at 0, 10, 100 and 1000 mg/kg/day was applied 5 days per week for 3 consecutive weeks to the shaved intact dorsal skin of each rat for a minimum of 15 applications. Animals were observed for clinical signs of toxicity, mortality, dermal irritation, effects on body weight, food consumption and hematology and serum chemistry parameters, organ weights and pathology.

There was a slight decrease in body weight gain of male rats (38.2%) in the 1000 mg/kg/day group. Female rats in the 1000 mg/kg/day group lost 2 g in body weight. Male rats appeared to be more affected by treatment than females; however, little body weight gain ocurred in all female groups. No effects were observed with respect to clinical signs of toxicity, mortality, food consumption, hematology, clinical chemistry, organ weight and pathology.

B. Deficiencies

No major deficiencies were noted.

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DATA EVALUATION RECORD 012214/25/97

STUDY TYPE: Prenatal Developmental Study - Rabbit
OPPTS 870.3700 (83-3b)

D.P. BARCODE: D232469 SUBMISSION CODE: S514322

P.C. CODE: 080808 TOX. CHEM. NO.: 184

TEST MATERIAL: Propazine Technical (98% a.i.)

SYNONYMS: Gesamil, Milogard, Geigy 30,028, Plantulin, Prozinex, Primatol P, G30028, 2-chloro-4,6-bio(isopropylamino)-S-triazine, CAS. #129-40-2

CITATION: Knapp, J. F. (1995) A developmental toxicity study of propazine technical in rabbits. WIL Research Laboratories, Inc., Ashland, Ohio, 44805. Laboratory Study No. WIL-157005, October 11, 1995. MRID 44153401.

SPONSOR: Griffin Corporation, Valdosta, Georgia 31603

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44153401), propazine technical (98% a.i., Lot #309027C) was administered to 20 New Zealand White rabbits/dose level by gavage in corn oil at dose levels of 0, 2, 10 or 50 mg/kg/day from day 6 through 19 of gestation.

Decreased defecation was observed in the 50 mg/kg/day group. Body weight gain was decreased by 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased by 28% in the 50 mg/kg/day group during the treatment period. **The maternal LOEL is 50 mg/kg/day, based on decreased defecation and decreased body weight gain and food consumption during the treatment period. The NOEL is 10 mg/kg/day.**

Live litter size, mean fetal weight, fetal sex ratios, mean number of corpora lutea and implantation sites and postimplantation loss were unaffected by treatment. There were no treatment related effects in developmental parameters. **The LOEL was not determined. The NOEL is 50 mg/kg/day based on decreased defecation, body weight gain and food consumption.**

The developmental toxicity study in the rabbit is classified ACCEPTABLE and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; 83-3b) in rabbits.

COMPLIANCE: Signed and dated GLP, quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Propazine Technical
Description: white powder
Lot/Batch #: 309027C
Purity: 98% a.i.
CAS #: 139-40-2

2. Vehicle: 100% Pure Mazola Corn Oil
Description: Clear yellow viscous fluid
Lot/Batch #: Not provided.
Purity: 100% a.i.

3. Test animals: Species: rabbit
Strain: New Zealand White
Age at mating: 26 weeks
Weight at mating: 2990 to 3762g
Source: Hazleton Research Products, Inc., Denver, PA
Housing: individually in stainless steel wire-bottom cages
Diet: Purina Certified Rabbit Chow #5322 ad libitum
Water: municipal water ad libitum
Environmental conditions:
Temperature: 60^0 to 75^0
Humidity: 31 to 56%
Air changes: 10 per hour
Photoperiod: 12 hours light/12 hours dark
Acclimation period (PO) 21 days

B. PROCEDURES AND STUDY DESIGN:

1. In life dates: Start: February 7, 1995
End: March 10, 1995

2. Mating: Semen was collected from 10 resident males. Motility was determined microscopically. Concentration of sperm/ml as determined using a standard dilution in a red blood cell pipette and a hemacytometer. The final concentration of the semen was greater than 3 million mobile sperm/ml after dilution. Diluted semen from one male was used to inseminate 2 females in each group. A 0.25 to 0.50 ml aliquot of diluted semen was placed in the anterior vagina of each female. Immediately after insemination each doe received

an intravenous injection of human chorionic gonadotropin. The day of insemination was designated gestation day 0.

3. Animal Assignment: Animals were assigned to dose group by computer randomization as indicated in Table 1.

Table 1. Animal Assignment[1]

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	20
Low (LDT)	2	20
Mid (MDT)	10	20
High (HDT)	50	20

1. Data extracted from p. 15, Study No. WIL-157005, MRID 44153401

4. Dose selection rationale: Dose selection was based on the results of a preliminary range-finding study (WIL-157004). One animal in the 400 mg/kg/day group died on gestation day 1 and a second animal in the group was sacrificed in extremis on gestation day 17. four animals in each of the 200 and 400 mg/kg/day groups aborted between gestation days 21 and 27. Decreased defecation was noted in the 50, 100, 200 and 400 mg/kg/day groups. Pre-implantation loss was increased and the number of implantations sites and viable fetuses were reduced in 1 female in the 200 mg/kg/day group. Mean fetal body weights were decreased in the 100 and 200 mg/kg/day groups. Postimplantation loss was increased in the 100 mg/kg/day group. Ablepharia in 3 fetuses and a cleft palate in one of the 3 fetuses were observed. These fetuses were from the same litter in the 50 mg/kg/day group. therefore, dose levels selected for administration were 2, 10 and 50 mg/kg/day.

5. Dosage preparation and analyses: An appropriate amount of the test material was placed in a precalibrated storage container. A sufficient amount of vehicle (Mazola corn oil) was added to produce the appropriate concentration. Dosage

formulations were prepared 3 times during the study. The formulations were usually inspected prior to dosing by the study director. The formulations were stated to be acceptable for administration. The following samples were analyzed; control (one aliquot, middle), low dose, mid dose and high dose (2 aliquots, top, middle, bottom). Homogeneity was determined immediately after preparation of the formulation. The other (1) set of samples were combined by dose group for stability analysis. Stability was determined at 5, 7 and 11 day intervals. One set of samples was taken from the middle of each group and was analyzed for concentration.

Prior to start of test material administration, a set of formulations was prepared to evaluate homogeneity and stability. the results of the analyses are as follows:

Homogeneity	
mg/kg/day	**mg/ml (%)**
2	top 1.98 (98.9) mid 2.00 (100) bottom 1.94 (97.2) mean = 1.97 (98.7)
10	top 9.97 (99.7) mid 10.0 (100) bottom 10.1 (101) Mean = 10.0 (100)
50	top 51.9 (104) mid 52.7 (105) bottom 52.3 (105) mean = 52.3 (105)

Stability		
Day	mg/kg/day	mg/ml (%)
5	2 10 50	2.13 (107) 10.3 (103) 49.8 (99.7)
7	2 10 50	1.91 (95.6) 10.3 (103) 50.1 (100)
11	2 10 50	2.15 (108) 10.4 (104) 51.0 (102)

Concentration Analysis		
Date	Dose Group	Actual Concentration mg/ml (%)
2-10-95	2 10 50	1.97 (98.4) 10.5 (105) 50.3 (101)
2-15-95	2 10 50	2.03 (102) 10.5 (105) 49.9 (99.7)
2-22-95	2 10 50	2.08 (104) 9.48 (94.8) 49.7 (99.3)

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. Dosage administration: All doses were administered once daily by gavage on gestation days 6 through 18 in a volume of 1.0 ml/kg of body weight/day. Dosing was based on the most recent body weight determination

C. OBSERVATIONS:

1. Maternal Observations and Evaluations: The animals were observed twice daily for mortality and moribundity except for March 2, 1995.

Detailed clinical observations were recorded from gestation days 0 through 29. Individual body weights were recorded on gestation day 0, 6-19, 24 and 29. Mean body weight change was recorded for each corresponding interval and for gestation days 6-9, 9-12, 12-19, 19-29, 6-19 and 0-29. Individual food consumption was recorded daily from gestation days 0 through 29. Food intake was calculated as g/animal/day and g/kg/day for corresponding body weight change interval. Dams were sacrificed on day 29 of gestation. Examinations at sacrifice consisted of: examination of the thoracic, abdominal and pelvic cavities; the number of corpora lutea, the number and location of all fetuses, early and late resorptions and number of implantation sites were recorded. Maternal tissues were preserved in 10% neutral buffered formalin for possible future histopathological examination. Uteri with macroscopic evidence of implantation were opened and placed in 10% ammonium sulfide solution for detection of early implantation loss.

2. Fetal Evaluations: Each fetus was weighed. Fetal examination included an examination of the eyes, palate and external orifices. Crown-rump measurements were recorded for late resorptions. The sex of each fetus was determined and each fetus was examined viscerally by a modification of the Stuckhardt and Poppe fresh dissection technique to include the heart and major vessels. The brain of each fetus was examined by a mid-coronal slice. All fetuses were eviscerated, skinned and fixed in 100% ethyl alcohol. Each fetus was macerated in potassium hydroxide and stained with Alizared Red S by a method similar to Dawson's. External, visceral and skeletal findings were recorded as developmental malformations or variations.

D. DATA ANALYSIS:

1. Statistical analyses: Fetal sex ratios were analyzed with a Chi-square test with Yates correction factor. Malformations and variations were analyzed with the Fisher's Exact test. Early and late resorptions, dead fetuses and postimplantaion losses were analyzed with the Mann-Whitney U-Test. Corpora lutea, total implantations, viable fetuses, fetal body weights,

maternal body weights and weight changes, maternal net body weight changes, gravid uterine weights and maternal food consumption were analyzed with One-way ANOVA/2 tailed with Dunnett's test. Litter proportions of intrauterine data (the litter, rather than the fetus, as the experimental unit) was analyzed with the Kruskal-Wallis test.

2. Indices: The following indices were calculated from cesarean section records of animals in the study:

a. Group Mean Litter Basis Postimplantation Loss/Litter =	No. Dead Fetuses, Resorptions (Early/Late)/Group No. Gravid Females/Group
b. Proportional Litter Basis Summations per Group(%) =	Postimplantation Loss/Litter(%)[1] No. of Litter/Group
1 = No Dead Fetuses, Resorptions (Late/Early)/Litter x 100 No Implanation Sites/Litter	

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY:

1. Mortality and Clinical Observations: One female in the 10 mg/kg/day group aborted on gestation day 26 and one female in the 50 mg/kg/day group aborted on gestation day 24. The historical control data indicate that in 39 of 79 control groups, 49% had at the minimum one female that aborted. Decreased defecation was observed in the 50 mg/kg/day group. Other clinical signs observed, e.g., hair loss, mucoid feces, soft stool, decreased urination and clear material around the nose, occurred in both control and treated groups at a similar frequency. Decreased defecation occurred 24 times in 9 dams in the 50 mg/kg/day group compared with 8 times in 5 dams in the control group.

2. Body Weight and Gravid Uterine Weight: Mean body weight loss occurred in the 50 /kg/day group during gestation days 6-9. Decreased mean body weight gain was observed in the 50 mg/kg/day group during gestation days 9-12. A significant ($p < 0.05$) increase in body weight gain occurred in the 50 mg/kg/day group during the post-treatment period, gestation days 19-29. The decrease in body weight gain over the treatment period (day 6-19 of gestation) was 65% less than controls in the 50 mg/kg/day group. Mean body weight loss occurred in the 10 mg/kg/day group during gestation days 6-7 and reduced body weight gain was significantly reduced during gestation days 10-11 (see Table 2). Mean body weights were slightly (not significantly) reduced during gestation days 7-29 in the 50 mg/kg/day group. Gravid uterine weights were unaffected by treatment.

Table 2. Mean Body Weight Change in Rabbits[1]

Body Weight Change (g)				
Dose Level				
Day	0	2	10	50
0-6	284	305	251	235
6-7	20	-4	-14*	-61**
10-11	33	24	6*	-1**
18-19	12	4	26	7
24-29	99	67	54	110
6-19	268	262	209	94**
19-29	171	175	165	271*
0-29	722	742	631	600

1. Data extracted from Table 6, pp. 43-45, Study No. WIL-157005, MRID 44153401.
* Significantly different from controls at $p < 0.05$.
** Significantly different from controls at $p < 0.01$.

3. Food Consumption: Food consumption was decreased in animals in the 50 mg/kg/day group throughout the treatment period (see Table 3). Food consumption was decreased 28% in the 50/kg/day group when compared to the control group during the treatment period (gestation days 6-19).

Table 3. Food Consumption in Rabbits during Gestation[1]

Food Consumption (g/animal/day)				
Dose Level				
Day	0	2	10	50
0-6	214	219	207	201
6-9	199	197	183	116**
9-12	210	206	188	130**
6-19	197	199	182	141**
19-29	167	171	163	169
0-29	190	193	180	163*

1. Data extracted from Table 8, pp. 47-49, Study No. WIL-157005, MRID 44153401.
* Significantly different from controls at $p < 0.05$.
** Significantly different from controls at $p < 0.01$.

4. Gross Pathology: No treatment related lesions ere observed. Dark red or brown areas of the lungs were observed in 2, 1 and 3 animals in the control, 10 and 50 mg/kg/day groups, respectively. One animal each in the control, 2 and 50 mg/kg/day groups had cysts on the oviducts. One animal in the 2 mg/kg/day group had a white precipitate in the amniotic fluid at site No. 3. Segmental aplasia of the anterior portion of the left uterine horn was observed in 1 animal in the 10/kg/day group. White purulent material was observed in the right uterine horn of 1 animal in the 50 mg/kg/day group.

5. Cesarean Section Data: Live litter size, mean fetal body weights, fetal sex ratios, mean numbers of corpora lutea and implantation sites and postimplantation loss was unaffected by treatment (see Table 4).

Table 4. Cesarean Section Observations[1]				
Observation	Dose (mg/kg/day)			
	0	2	10	50
No. of Animals Assigned (Mated)	20	20	20	20
No. of Animals Pregnant	19	19	15	15
*Pregnancy Rate (%)	95	95	75	75
No. Non-Pregnant	1	1	5	5
Maternal Wastage				
No. Died	0	0	0	0
Pregnant	0	0	0	0
Non-pregnant	0	0	0	0
No. Aborted	0	0	1	1
No. Premature Delivery	0	0	0	0
Total No. - Corpora Lutea	173	181	133	133
Corpora Lutea/Doe	9.1	9.5	9.5	9.5
Total No. Implantations	129	125	87	97
Implantations/Doe	6.8	6.6	6.2	6.9
Total No. Litters	19	19	14	14
Total No. Live Fetuses	123	116	81	90
Live Fetuses/Doe	6.5	6.1	5.8	6.4
Total No. Dead Fetuses	0	0	0	0
Dead Fetuses/Doe	0	0	0	0
Total No. Resorptions	6	9	6	7
Early	5	7	5	6
Late	1	2	1	1
Resorptions/Doe	0.4	0.5	0.5	0.5
Early	0.3	0.4	0.4	0.4
Late	0.1	0.1	0.1	0.1

Table 4. Cesarean Section Observations[1]				
Observation	Dose (mg/kg/day)			
	0	2	10	50
Litters with Total Resorptions	1	1	1	0
Mean Fetal Weight (g)				
Males	47.1	48.1	47.3	49.7
Females	46.2	47.3	46.6	47.8
Sex Ratio (% Male)	57.5	47.1	46.6	47.8
Preimplantation Loss (%)	24.1	30.0	34.4	24.8
Postimplantation Loss (%)	8.7	9.8	11.9	5.1
1. Data extracted from Tables 1, 10 and 11, pp. 36, 53-56, Study No.WIL-157005, MRID 44153401				

B. DEVELOPMENTAL TOXICITY:

1. External Examination: Carpal flexure was observed in 2 and 1 fetuses in the control and 2 mg/kg/day groups, respectively. One fetus in the control group had a narrow pectoral girdle and a second fetus had a umbilical herniation of the intestine. Gastroschisis, anury, and atresia, body shorter than normal, scoliosis, adactyly, micromelia, sympodia, and brachydactyly was observed in 1 fetus in the 10 mg/kg/day group.

2. Visceral Examination: One fetus in the 10 mg/kg/day group had a kidney, ureter, urinary bladder and testis absent and hypoplasia of the diaphragm. One fetus in the control group had bilateral ventricular and right atrial cardiomegaly, smaller than normal atrium, absent interatrial and interventricular septa and only 1 atrioventricular valve. Accessory spleens were observed in 16, 20, 8 and 5 fetuses and small or absent gallbladders in 1, 1, 2 and 1 fetuses in the control, 2, 10 and 50 mg/kg/day groups, respectively. Major blood vessel variations were observed in 3, 8, 4 and 6 fetuses in the 0, 2, 10 and 50 mg/kg/day groups, respectively. A small spleen was observed in 1 fetus in the 2 mg/kg/day group. One fetus in the 10 mg/kg/day group had a distended ureter. A retrocaval ureter was seen in 2, 1 and 2 fetuses in the control, 2 and 50 mg/kg/day groups, respectively. A hemorrhagic

ring around the iris was observed in 2 fetuses in the 50 mg/kg/day groups.

3. Skeletal Examination: Vertebral anomalies including extra and/or fused ribs, arches and centra, thoracic arches, and centra that were located more anterior or more posterior than normal, ribs that were smaller than normal and forked costal cartilage were observed in 4 fetuses in the 10/mg/kg/day group. Rib anomalies including enlargement of the distal portion of rib No. 8 in 1 control fetus and fusion of rib Nos. 7 and 8 in 1 fetus in the 2 mg/kg/day group were observed. One fetus in each of the 10 and 50 mg/kg/day groups had spherical enlargement of rib nos. 7 or 8. Other skeletal variations occurred in a random pattern and are common in rabbits.

Table 5a. External Examinations[1]

Observations	Dose (mg/kg/day)			
	0	2	10	50
No. Fetuses (litters) examined.	123(18)	116(18)	81(13)	90(14)
No. Fetuses (litters) affected.	3(3)	1(1)	1(1)	0(0)
Findings (Malformations)				
Carpal and/or tarsal flexure.	2(2)	1(1)	0(0)	0(0)
Narrow pectoral girdle.	1(1)	0(0)	0(0)	0(0)
Umbilical herniation of intestine.	1(1)	0(0)	0(0)	0(0)
Multiple Malformations[2]	0(0)	0(0)	1(1)	0(0)

1. Data extracted from Table 12, pp. 57-58, Study No. WIL-157005, MRID 44153401
2. Gastroschisis, anury, and atresia, adactyly, sympodia, scoliosis, etc.

Table 5b. Visceral Examinations[1]				
Observations	Dose (mg/kg/day)			
	0	2	10	50
No. Fetuses (litters) examined	123(18)	116(18)	81(13)	90(14)
No. Fetuses (litters) affected[2]	1(1)	0(0)	1(1)	0(0)
Findings (Malformations)				
Heart and/or great vessel anomaly	1(1)	0(0)	0(0)	0(0)
Multiple malformations[3]	0(0)	0(0)	1(1)	0(0)
Findings (Variations)				
Accessory spleen	16(7)	20(7)	8(4)	5(5)
Gallbladder absent or small	1(1)	1(1)	2(2)	1(1)
Major blood vessel variation	3(2)	8(3)	4(4)	6(3)

1. Data extracted from Tables 12 and 15, pp. 57-58 and 66, Study No. WIL-157005, MRID 44153401
2. Malformations
3. Kidney and ureter absent, urinary bladder absent, testis absent, and diaphragm hypoplasia.

Table 5c. Skeletal Examinations[1]				
Observations	Dose (mg/kb/day)			
	0	2	10	50
No. Fetuses (litters) examined	123(18)	116(18)	81(13)	90(14)
No. Fetuses (litters) affected[2]	1(1)	1(1)	5(2)	1(1)
Findings (Malformations)				
Vertebral anomaly w/wo rib anomaly	1(1)	1(1)	4(2)	0(0)
Rib anomaly	1(1)	1(1)	0(0)	0(0)

Table 5c. Skeletal Examinations[1]				
Observations	Dose (mg/kb/day)			
	0	2	10	50
Ribs w/spherical enlargement	0(0)	0(0)	1(1)	1(1)
Findings (Variations)				
13th rudimentary ribs	28(18)	24(18)	17(13)	18(14)
Hyoid arches bent	13(4)	9(8)	3(3)	6(4)
13th full rib	47(13)	53(15)	31(13)	46(12)
27 presacral vertebrae	20(8)	24(9)	18(9)	22(9)

1. Data extracted from Tables Nos. 12 and 15, pp. 57-58 and 66, Study No. WIL-157005, MRID 44153401.
2. Malformations.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS:

One animal in each of the 10 and 50 mg/kg/day group aborted. These abortions were within the historical control range and, therefore, unrelated to treatment. Decreased defecation was observed in the 50 mg/kg/day group. Mean body weight loss and decreased mean body weight gain were observed in the 50 mg/kg/day group on gestation days 6-9 and 9-12, respectively. Mean body weight gain of animals in the 50 mg/kg/day group was significantly decreased during the treatment period (gestation days 6-19). Food consumption was decreased throughout the treatment period in the 50 mg/kg/day group. Live litter size, mean fetal body weights, fetal sex ratios, postimplantation loss and mean number of corpora lutea and implanation sites were unaffected by treatment. external, visceral and skeletal malformations occurred in 4(4), 2(2), 6(2) and 1(1) fetuses (litters) in the 0, 2, 10 and 50 mg/kg/day groups and were considered to be unrelated to treatment. Fetal variations were also not considered to be treatment related. The LOEL for maternal toxicity 50 mg/kg/day was based as decreased defecation and inhibition of body weight gain and food consumption during the treatment period. The NOAEL is 10 mg/kg/day. The LOEL for developmental toxicity was not determined. The NOAEL is 50 mg/kg/day.

B. REVIEWER'S DISCUSSION:

1. MATERNAL TOXICITY: Decreased defecation was increased in the 50 mg/kg/day group. Body weight gain was decreased 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased 28% in the 50 mg/kg/day group during the treatment period. No treatment related effects were noted at necropsy.

2. DEVELOPMENTAL TOXICITY:

a. No treatment related effects were observed.
b. Altered Growth: No treatment related effect were observed.
c. Developmental Variations: the variations observed fell within the range of historical controls.
d. Malformations: The malformations observed fell within the range of historical controls.

C. STUDY DEFICIENCIES:

There were no major deficiencies.

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Chemical:	**Propazine (ANSI)**
PC Code:	**080808**
HED File Code	***13000 Tox Reviews***
Memo Date:	**05/07/97**
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