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

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

012286

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reviews of Metabolism Study with Technical Propazine and Battery of 6 Acute Studies with Technical Propazine

DP Barcode: D219174 PC Code: 080808
Submission: S493480 Tox Chem No: 184

TO: Jim Tompkins, PM 25
Herbicide Branch
Registration Division (7505C)

FROM: Kit Farwell
Reregistration Branch 1
Health Effects Division (7509C)
Kit Farwell 7-31-97

THRU: Whang Phang, Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)
Whang Phang 7/31/97

REGISTRANT: Griffin Corporation, Valdosta, GA

CONCLUSIONS: The metabolism study with propazine is Unacceptable and does not satisfy the 85-1 guideline requirement for a metabolism study. The Executive Summary follows and tells what data is needed to upgrade the study. The complete DER is attached.

The six acute studies with propazine technical are all Acceptable/Guideline and satisfy the respective 81-1 through 81-6 guideline requirements. Following are tables summarizing the acute studies. The complete DERs are attached.

ACTION REQUESTED: Review and evaluate the following studies:

Krautter, G. (1995) ^{14}C-Propazine: disposition and metabolism in the rat. PTRL East, Inc. PTRL Project No. 821, June 16, 1995. MRID 43689801.

Acute Studies with Propazine Technical:

Kuhn, J. (1994) Acute oral toxicity study in rats. Stillmeadow, Inc. Study Number 1318-94. October 27, 1994. MRID 43474101.

Kuhn, J. (1994) Acute dermal toxicity study in rabbits. Stillmeadow, Inc. Study Number 1319-94. September 1, 1994. MRID 43474102.

Holbert, M. (1994) Acute inhalation toxicity study in rats. Stillmeadow, Inc. Study Number 1320-94. November 9, 1994. MRID 43474103.

Kuhn, J. (1994) Primary eye irritation study in rabbits. Stillmeadow, Inc. Study Number 1321-94. August 30, 1994. MRID 43474104.

Kuhn, J. (1994) Primary dermal irritation study in rabbits. Stillmeadow, Inc. Study Number 1322-94. August 31, 1994. MRID 43474105.

Kuhn, J. (1994) Dermal sensitization study in guinea pigs. Stillmeadow, Inc. Study Number 1323-94. October 27, 1994. MRID 43474106.

Executive Summary for Metabolism Study with Propazine: In a metabolism study (MRID 43689801), Propazine (2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine, unlabeled 98.2% a.i. or as [ring-UL-^{14}C]-Propazine, 99.6% a.i.) was administered to Sprague Dawley rats (5/sex/dose group) as a single gavage dose of 1.0 or 100 mg/kg labeled Propazine or as 14-daily doses of unlabeled 1.0 mg/kg Propazine followed by a single 1.0 mg/kg labeled dose. Corn oil was the vehicle for all treatments.

None of the animals died during the study and overall mass balance for all treatment groups ranged from 97.0-105.7%. Absorption of Propazine from the gastrointestinal tract was rapid and similar for all study groups and no apparent sex-related differences were found. Based on recoveries from urine/cage wash and tissues, absorption was ≥73%. Within 48 hours of treatment, 82-95% of the administered dose was recovered from excreta, predominately the urine. No specific target organs were identified. Labeled Propazine was recovered only in the feces of male and female rats in the single high-dose group and female rats in the single low-dose group. As presented, it cannot be determined if this represents unabsorbed material or material that underwent enterohepatic circulation. Less than 0.1% of the administered dose was detected as CO_2 during a pilot study.

Thirteen metabolites were recovered; three of which were identified. The predominant, G 28273, accounted for 20-30% of the administered dose while the other two contributed <5%. Of 10 unidentified metabolites detected, the combined contribution of six was <15% of the administered dose. Unidentified Metabolite 5 was predominant and contributed 18-24% of the administered dose for all study groups with unidentified Metabolites 4 and 8 next abundant. Although unidentified Metabolite 1 was found at <3% of the administered dose for most treatment groups, it accounted for 11% of the dose from male rats in the single high-dose group. Based on the results and literature review of other 2-chloro-*s*-triazines, the study author proposed that Phase I metabolism proceeded by dealkylation at the 4 and 6 amino positions to ultimately form G 28273 while Phase II metabolism involved glutathione conjugation. Although glucuronidation could not be ruled out, the author suggested that unidentified Metabolites 4 and 5 were glutathione conjugates. While these assumptions are likely correct, definitive studies need to be done for confirmation.

This metabolism study in the rat is classified **supplementary** and does **not** satisfy the guideline requirement for a metabolism study (85-1) in rats. The study can be upgraded upon submission of data identifying the nature of conjugation and the identification of metabolites identified by the study author as 1, 4, 5, and 8. In addition, the registrant should provide a metabolic scheme for the test chemical.

Acute Toxicity of Propazine Technical

Study Type (MRID #)	Results	Tox Category	TB Evaluation
81-1 Acute Oral (43474101)	LD_{50} > 5050 mg/kg	IV	Acceptable
81-2 Acute Dermal (43474102)	LD_{50} > 5050 mg/kg	IV	Acceptable
81-3 Acute Inhalation (43474103)	LC_{50} > 1.22 mg/L	III	Acceptable
81-4 Primary Eye Irritation (43474104)	Slight irritant	IV	Acceptable
81-5 Primary Skin Irritation (43474105)	Negative	IV	Acceptable
81-6 Dermal Sensitization (43474106)	Negative	N/A	Acceptable

cc Catherine Eiden, RCAB

ATTACHMENTS: DERs

DATA EVALUATION REPORT

012286

Propazine

STUDY TYPE: Metabolism Study - Rat (85-1)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 96-02

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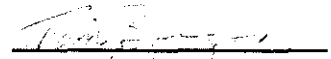
Signature: 
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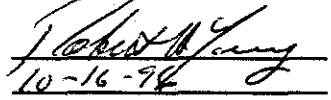
Signature: 
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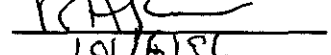
Signature: 
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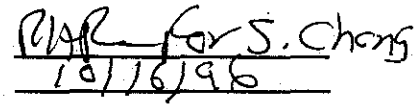
Signature: 
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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy under contract number DE-AC05-96OR22464.

EPA Reviewer: Paul Chin, Ph.D. Paul Chin, Date 11/1/96
Review Section II, Toxicology Branch I (7509C)
EPA Secondary Reviewer: Marion Copley, D.V.M., D.A.B.T. Marion Copley, Date 11/12/96
Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat
OPPTS 870.7485 [§85-1)]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.: 184

TEST MATERIAL (PURITY): Propazine, (nonradiolabeled purity = 98.2%, radiolabeled purity = 99.6%)

SYNONYMS: 2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine; 6-chloro-N,N'-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine

CITATION: Krautter, G. (1995) ^{14}C-Propazine: disposition and metabolism in the rat. PTRL East, Inc., Richmond, KY. PTRL Project No. 821, June 16, 1995. MRID 43689801.

SPONSOR: Griffin Corporation, Valdosta, GA

EXECUTIVE SUMMARY: In a metabolism study (MRID 43689801), Propazine (2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine, unlabeled 98.2% a.i. or as [ring-UL-^{14}C]-Propazine, 99.6% a.i.) was administered to Sprague Dawley rats (5/sex/dose group) as a single gavage dose of 1.0 or 100 mg/kg labeled Propazine or as 14-daily doses of unlabeled 1.0 mg/kg Propazine followed by a single 1.0 mg/kg labeled dose. Corn oil was the vehicle for all treatments.

None of the animals died during the study and overall mass balance for all treatment groups ranged from 97.0-105.7%. Absorption of Propazine from the gastrointestinal tract was rapid and similar for all study groups and no apparent sex-related differences were found. Based on recoveries from urine/cage wash and tissues, absorption was ≥73%. Within 48 hours of treatment, 82-95% of the administered dose was recovered from excreta, predominately the urine. No specific target organs were identified. Labeled Propazine was recovered only in the feces of male and female rats in the single high-dose group and female rats in the single low-dose group. As presented, it cannot be determined if this represents unabsorbed material or material that underwent enterohepatic circulation. Less than 0.1% of the administered dose was detected as CO_2 during a pilot study.

Thirteen metabolites were recovered; three of which were identified. The predominant, G 28273, accounted for 20-30% of the administered dose while the other two contributed <5%. Of 10 unidentified metabolites detected, the combined contribution of six was <15% of the administered dose. Unidentified Metabolite 5 was predominant and contributed 18-24% of the administered dose for all study groups with unidentified Metabolites 4 and 8 next abundant. Although unidentified Metabolite 1 was found at <3% of the administered dose for most treatment groups, it accounted for 11% of the dose from male rats in the single high-dose group. Based on the results and literature review of other 2-chloro-*s*-triazines, the study author proposed that Phase I metabolism proceeded by dealkylation at the 4 and 6 amino positions to ultimately form G 28273 while Phase II metabolism involved glutathione conjugation. Although glucuronidation could not be ruled out, the author suggested that unidentified Metabolites 4 and 5 were glutathione conjugates. While these assumptions are likely correct, definitive studies need to be done for confirmation.

This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (85-1) in rats. The study can be upgraded upon submission of data identifying the nature of conjugation and the identification of metabolites identified by the study author as 1, 4, 5, and 8. In addition, the registrant should provide a metabolic scheme for the test chemical.

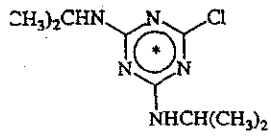
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound

[ring-UL-^{14}C]-2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine, (^{14}C-Propazine)
Radiochemical purity: 99.6% [determined by HPLC-RAM]
Specific activity: 49.42 mCi/mM
Lot/Batch: 812B-4-1
Non radioactive Compound - Propazine
Purity: 98.2% [determined by GC-MS, HPLC]
Lot/Batch No.: 177-19-1
Description: white solid
Contaminants: not reported
CAS No.: 139-40-2



* Denotes site of radiolabel

2. Vehicle

Corn oil.

3. Test animals

Species: rat
Strain: Sprague-Dawley CD (Crl:CDBR)
Age and weight at study initiation: young adult ≈ 200 g
Source: Charles River Laboratories, Portage, MI
Housing: during acclimation period - polycarbonate shoebox cages; after dosing - glass metabolism cages
Diet: Certified Purina Laboratory Rodent Chow 5002, ad libitum
Water: tap water, ad libitum
Environmental conditions:
Temperature: 21-31°C
Humidity: 10-56%
Air changes: 12-18/hour
Photoperiod: 12 hour light/dark
Acclimation period: ≥7 days

4. Preparation of dosing solutions

The test material was solubilized with toluene before dose preparations. When isotopic dilutions were required for the pilot and high dose groups, unlabeled material solubilized in toluene was used. The toluene was evaporated to dryness and the resulting residue suspended in corn oil. Dose preparations were mixed by manual shaking and sonication.

B. STUDY DESIGN AND METHODS

1. Group arrangements

Animals were assigned after randomization to the test groups in Table 1.

TABLE 1. Dosing groups for pharmacokinetic studies of Propazine			
Test Group	**Dose of labeled material (mg/kg)**	**Number/sex**	**Remarks**
Intravenous	not done	not done	not done
Control	0.00	3♂/3♀	single vehicle treatment and used to determine background radioactivity; sacrificed at 7 days
Pilot	100	1♂/1♀	single gavage treatment; sacrificed at 7 days
Low dose	1.0	5♂/5♀	single gavage treatment; sacrificed at 7 days
Low dose with pretreatment	1.0	5♂/5♀	14 daily gavage treatments with 1.0 mg/kg unlabeled Propazine followed by a single dose 1.0 mg/kg of labeled Propazine on day 15; sacrificed at 22 days.
High dose	100	5♂/5♀	single gavage treatment; sacrificed at 7 days

Data taken from p. 18, MRID 43689801

2. Dosing and sample collection

All treatment doses were given by oral intubation at 30-50 μCi/rat. Urine and fecal samples were collected from each animal 8 hours after treatment and daily through study day 7. The samples were collected in containers chilled with wet ice. After material balance for each definitive dose group was determined, individual urine and fecal samples were pooled by sex and treatment group and frozen until time of analysis. After excreta collection, the cages were rinsed with approximately 100 mL distilled water. The wash was collected, its volume recorded, and an aliquot retained for analysis. Seven days after treatment with the radiolabel, the cages were rinsed with 25 mL acetone followed by 75 mL water. Aliquots of the acetone and distilled water washes were retained.

During the pilot study, CO_2 was collected by drawing expired breath into 400 mL of trapping solution (10% sodium hydroxide). Aliquots of the trapping solution were mixed with methanol and scintillation cocktail and the activity determined by direct radioanalysis. Since < 0.1% of the dose was recovered in trapping solutions during the pilot

study, trapping for volatiles was not done during the definitive studies.

Seven days after treatment with the radiolabel, all rats were anesthetized with sodium pentobarbital and exsanguinated. The collected blood samples were heparinized and stored frozen until time of analysis. All or representative sections of the following tissues were removed, rinsed in saline and prepared for radioanalysis: brain, bone, muscle, fat, skin, heart, ovaries, testes, uterus, spleen, thyroid, kidney, liver, lungs, and the entire gastrointestinal tract.

a. Pharmacokinetic studies - For the three definitive study groups, the feces and tissue samples were oxidized to CO_2, water, and inorganic ash using an oxidizer that trapped liberated $^{14}CO_2$ in Carbosorb®. The Carbosorb was combined with liquid scintillation cocktail (Permafluor E®) and the activity determined by liquid scintillation counting. For tissues not entirely excised (e.g. bone, blood, fat, muscle, and skin), a standard percent of body weight conversion was used to calculate radiocarbon recovery as percent of administered dose. Urine samples were pooled and mixed to assure uniformity. Triplicate aliquots were mixed with scintillation cocktail and the activity determined by liquid scintillation counting. Bile was not collected.

b. Metabolite characterization studies - Isolation of metabolites in urine, cage wash, and feces from animals in the three definitive studies was done by HPLC using a Partisphere 5 μm C_{18} reverse-phase column. Pooled fecal samples were doubly extracted with acetonitrile and 1:1 (v/v) acetonitrile/water. The two extracts were combined and concentrated by rotary evaporation. The extraction method used for urine and cage wash samples was not located in the study report. The 60 minute gradient program operating at a flow rate of 1 mL/min began with 100% glacial acetic acid (1%) in HPLC-grade water (Solvent A), progressed to 100% glacial acetic acid (1%) in acetonitrile (Solvent B) and returned to 100% Solvent A. The effluent was monitored by a radiodetector and at 240 nm. The isolated compounds from the excreta were compared to 20 possible metabolic reference standards for identification.

3. Statistics

Statistical analysis was limited to determination of the mean and standard deviation.

II. RESULTS

A. PHARMACOKINETIC STUDIES

1. Preliminary experiment

The pilot study was done to characterize excretion patterns and produce excreta samples for analytical methods development. Within 48 hours of treatment, the male had excreted 95.2% of the dose and the female rat had excreted 81.4% (Table 2). Within three days of treatment, both animals had eliminated >95% of the dose. After 7 days, the cumulative recovery of labeled Propazine was 112.4% and 106% for the male and female rat, respectively. Radiolabeled CO_2 was not detected.

TABLE 2. Cumulative elimination of labeled Propazine expressed as percent of adminstered dose

Day	Animal	Urine and Cage Wash	Feces	CO_2	Tissues	Cumm. Total
0.3	Male	6.1	0.0	0.0	ND	6.1
	Female	6.8	0.1	0.0	ND	6.9
1	Male	40.4	4.2	0.0	ND	44.6
	Female	40.0	0.6	0.0	ND	40.6
2	Male	60.3	34.9	0.0	ND	95.2
	Female	53.7	27.7	0.0	ND	81.4
3	Male	64.1	38.4	0.0	ND	102.5
	Female	57.0	40.8	0.0	ND	97.8
7	Male	67.0	39.5	0.0	5.9	112.4
	Female	59.5	41.1	0.0	5.4	106.0

Data from pp. 104-105, MRID No. 43689801.
ND = Not done

2. Absorption

After 7 days, the cumulative percent of administered dose recovered in the urine/cage wash and tissues of the three definitive study groups was: single low dose - 79.3% males, 79.5% females; single high dose - 76.5% males, 75.4% females; and multiple low dose - 77.8% males, 73.1% females. Sex-related differences in absorption were not found.

3. Tissue distribution

The test material was widely distributed seven days after treatment. However, the tissues and organs of animals in the three treatment groups retained only 5.5-10.7% of the administered dose. The tissues and organs retaining the highest concentrations of radioactivity are shown in Table 3. The highest average concentration of test material was found in the red blood cells of all dose groups. When adjusted for total tissue weight, the muscle of all dose groups contained the highest percent of the dose, ranging from 1.3-3.5%. The other tissues adjusted for weight (bone, fat, and skin) retained <1%.

TABLE 3. Distribution of radioactivity in rat tissues/organs after administration of ^{14}C-labeled Propazine.

Tissue/ organ	Average percent of radioactive dose administered					
	Single low dose		Multiple low dose		Single high dose	
	Male	Female	Male	Female	Male	Female
Carcass	6.28	6.61	4.93	4.68	4.74	4.01
RBC[a]	0.63	0.59	0.58	0.58	0.54	0.64
Liver	1.63	2.09	1.02	0.93	0.34	0.29
Kidney	0.18	0.24	0.10	0.09	0.06	0.05
Muscle[b]	0.17 (2.81)	0.25 (3.53)	0.09 (1.72)	0.10 (1.75)	0.07 (1.26)	0.10 (1.40)

Data extracted from pp. 47, 48, and 144, MRID 43689801.
a = not adjusted for total blood volume.
b = Numbers in parenthesis are calculated total recoveries using estimated tissue weights.

a. Single low dose - As summarized in Tables 3 and 4, much of the labeled Propazine had been excreted within seven days of treatment. The highest remaining concentrations of label were found within the red blood cell and muscle (Table 3).

b. Low dose with pretreatment - As with the single low dose treatment group, much of the labeled Propazine had been eliminated from the body. The highest remaining concentrations of labeled compound were found in the red blood cell and muscle. Long-term administration of Propazine did not appear to influence distribution or elimination.

c. Single high dose - As with the single and multiple low-dose treatment groups, much of the labeled Propazine had been eliminated from the body within seven days of treatment. The remaining labeled compound was found in the red blood cell and muscle. Administration of a single high-dose of Propazine did not appear to influence distribution or elimination.

d. Intravenous dose - An intravenous study was not done. No explanation was provided.

4. Excretion

The excretion of radioactivity following treatment with labeled Propazine was very similar among the single low-dose, multiple low-dose and single high-dose treatment groups. Most of the excretion occurred within 48 hours primarily into the urine but with significant amounts also found in the feces. Excretory data for the three studies are shown in Tables 4 and 5.

TABLE 4. Recovery of radioactivity in tissues and excreta of rats seven days after administration of ^{14}C-labeled Propazine.

	Percent of radioactive dose recovered					
	Single low dose		Multiple low dose		Single high dose	
	Male	Female	Male	Female	Male	Female
Expired air	0.0	0.0	0.0	0.0	0.0	0.0
Tissues	3.5	4.1	2.4	2.2	1.5	1.5
Carcass	6.3	6.6	4.9	4.7	4.7	4.0
Urine and Cage Wash[a]	69.5	68.8	70.5	66.2	70.3	69.9
Feces	19.9	26.2	20.7	21.0	28.6	21.6
Total	99.2	105.7	98.5	94.1	105.1	97.0

Data extracted from pp. 46-48, MRID 43689801.
a = The study author assumed that radiolabel in cage wash was derived from urine and reported the average results combined.

a. Single low dose - As summarized in Table 4 above and Table 5 below, male and female rats excreted the majority of the radioactivity into the urine (68.8-69.5%) with the remainder eliminated in the feces (19.9-26.2%). Approximately 95% of the excretion by either route occurred within 48 hours of treatment. No sex-

administered radiolabel was good (99.2% males, 105.7% females).

b. Low dose with pretreatment - Administration of a single dose of radiolabeled Propazine following 14 days of repeated dosing with unlabeled test material (1 mg/kg/day) gave excretion patterns very similar to those observed seven days after treatment with a single low dose. Most of the recovered radioactivity was found in the urine (70.5% and 66.2% for males and females, respectively) with >95% of excretion occurring within 48 hours of treatment. The remaining excreted radioactivity was recovered in the feces. As with the urine >98% of the radioactivity was recovered within 48 hours of treatment. Repeated treatment with Propazine did not appear to influence the overall excretion pattern of the test material. No sex-related differences in elimination of labeled Propazine were apparent. Overall mass balance recovery of administered radiolabel was good (98.5% males, 94.1% females).

c. Single high dose - The results obtained from this group were very similar to those obtained from the single and multiple low-dose treatment groups. Administration of 100 mg/kg radiolabeled Propazine resulted in 70.3% and 69.9% of the administered dose being recovered in the urine of male and female rats, respectively. The remaining radioactivity was recovered in the feces. As with the other study groups, >95% of the excretion occurred within 48 hours of treatment. A single high-dose of Propazine did not appear to alter the overall excretion pattern by saturating metabolic systems or inducing sex-related differences in excretion. Overall mass balance recovery of administered radiolabel was good (105.1% males, 97.0% females).

d. Intravenous dose - An intravenous study was not done.

TABLE 5. Cumulative recovery of radioactivity in excreta of rats after administration of ^{14}C-labeled Propazine[a]

Day	Cumulative percent of radioactive dose recovered in urine, feces, and cage wash					
	Single Low Dose		Multiple Low Dose		Single High Dose	
	Male	Female	Male	Female	Male	Female
0.3	32.3[a] (32.1/0.2)	25.5 (22.9/2.6)	31.8 (31.2/0.6)	21.2 (20.9/0.3)	25.9 (23.3/2.6)	15.6 (13.8/1.8)
1	74.4 (59.5/14.9)	64.6 (55.3/9.3)	73.0 (60.9/12.1)	66.0 (55.7/10.3)	83.1 (58.8/24.3)	63.7 (53.4/10.3)
2	83.4 (65.8/17.6)	84.5 (63.0/21.5)	86.4 (67.3/19.1)	81.9 (62.4/19.5)	95.0 (67.2/27.8)	85.7 (66.1/19.6)
3	85.5 (67.1/18.4)	88.1 (64.9/23.2)	88.6 (68.8/19.8)	84.6 (64.4/20.2)	96.9 (68.8/28.1)	89.3 (68.2/21.1)
5	87.8 (68.5/19.3)	91.0 (67.0/24.0)	90.3 (69.9/20.4)	86.1 (65.4/20.7)	98.2 (69.8/28.4)	90.8 (69.3/21.5)
7	89.4 (69.5/19.9)	95.0 (68.8/26.2)	91.2 (70.5/20.7)	87.2 (66.2/21.0)	98.9 (70.3/28.6)	91.5 (69.9/21.6)

Data extracted from pp. 149-160, MRID 43689801.
a = Presented as total with urine + cage wash/feces in parenthesis.

B. METABOLITE CHARACTERIZATION STUDIES

The metabolic profile of Propazine in the excreta was similar among the three treatment groups and no major sex-related differences in compound disposition were apparent. The parent compound and 13 metabolites were isolated. Three of the metabolites were identified by HPLC comparison to known reference standards and by TLC. The quantitative data for the parent compound and the various metabolites are shown in Table 6.

Propazine was not recovered in the urine of any treatment group nor was it detected in the feces of rats receiving multiple 1.0 mg/kg/day doses or in feces of male rats receiving a single 1.0 mg/kg dose. The compound was present in the feces of male and female rats (13.8% and 10.5%, respectively) that received 100 mg/kg; likely representing unabsorbed test material. The percent of administered dose recovered in the feces of female rats that received a single 1.0 mg/kg radiolabeled dose of Propazine was 5.2%.

The major identified metabolite was G 28273 (2-chloro-4,6-diamino-1,3,5-triazine) which accounted for 20.1-30.3% of the

administered dose in the three treatment groups. It was found predominately in urine where it accounted for 19.9-28.8% of the administered dose. The remaining amount, 0.2-2.3%, was recovered in the feces. GS 17794 (2-hydroxy-4-amino-6-isopropylamino-1,3,5-triazine) was found primarily in the urine of male rats in the three treatment groups and accounted for 0.9-2.7% of the administered dose. The remaining identified metabolite, G 30033 (2-chloro-4-amino-6-isopropylamino-1,3,5-triazine), was found in the urine and feces of female rats in the single low-dose treatment group and male rats in the single high-dose treatment group. It was also identified in the urine of male rats in the multiple low-dose treatment group. Its contribution to the percent of administered dose was small, accounting for only 1.2-1.8%. The three identified metabolites and Propazine accounted for 28.6-45.5% of the administered dose for the three treatment groups.

Ten additional metabolites were also isolated from the excreta but not identified. Six were minor metabolites found either in the urine, feces, or both and contributed from 7.4-15.2% to the administered dose. The remaining four metabolites were identified by the study author as Metabolites 1, 4, 5, and 8. Metabolite 1 was not identified in the excreta of male or female rats in the multiple low-dose treatment group. It was isolated in the urine of male rats in the single high-dose group and the feces of female rats in the single low-dose and single high-dose treatment groups, but at concentrations of < 2.7% of the administered dose. Metabolite 1 accounted for 11.3% of the administered dose in the excreta of male rats in the single high-dose treatment group. Metabolite 4 was isolated predominately from urine but was also found in the feces of male and female rats in the single low-dose and multiple low-dose treatment groups. This polar metabolite contributed 6.5-11.1% of the administered dose. It was also found in the urine of single high-dose female rats where it accounted for 16.9% of the administered dose. It was not found in the excreta of male rats in the single high-dose treatment group. Metabolite 5, also polar, was the predominant unidentified metabolite in the excreta of the three treatment groups accounting for 18.2-23.6 percent of the administered dose. It was found predominately in the urine of all three groups (15.2-17.0% of dose), but was also identified in the feces (2.5-6.1% of dose). The last of the major unidentified metabolites, Metabolite 8, was found almost exclusively in the urine of male and female rats of all treatment groups where it constituted 7.6-12.2% of the dose. It was also found at ≤1% of the administered dose in the feces of male rats of the multiple low-dose group and all female rat treatment groups.

TABLE 6. Metabolite profile in excreta of rats dosed with ^{14}C-Propazine.

Dose	Percent of administered dose					
	Single low dose		Multiple low dose		Single high dose	
Compound	Male	Female	Male	Female	Male	Female
Propazine	ND	5.2 (ND/5.2)[a]	ND	ND	13.8 (ND/13.8)	10.5 (ND/10.5)
G 28273	30.3 (28.8/1.5)	29.2 (26.9/2.3)	25.4 (23.8/1.6)	28.6 (26.7/1.9)	29.0 (28.2/0.8)	20.1 (19.9/0.2)
GS 17794	2.6 (2.6/ND)	ND	2.7 (2.7/ND)	ND	0.9 (ND/0.9)	ND
G 30033	ND	1.2 (0.7/0.5)	1.3 (1.3/ND)	ND	1.8 (0.9/0.9)	ND
Total identified	32.9 (31.4/1.5)	35.6 (27.6/8.0)	29.4 (27.8/1.6)	28.6 (26.7/1.9)	45.5 (29.1/16.4)	30.6 (19.9/10.7)
Unidentified Metabolite 1	ND	1.2 (ND/1.2)	ND	ND	11.3 (8.6/2.7)	1.7 (ND/1.7)
Unidentified Metabolite 4	6.5 (5.4/1.1)	9.6 (8.6/1.0)	10.0 (8.4/1.6)	11.1 (8.9/2.2)	ND	16.9 (16.9/ND)
Unidentified Metabolite 5	22.3 (16.7/5.6)	23.6 (17.5/6.1)	21.1 (15.2/5.9)	23.0 (17.0/6.0)	19.7 (16.9/2.8)	18.2 (15.7/2.5)
Unidentified Metabolite 8	12.2 (12.2/ND)	11.4 (10.5/0.9)	9.7 (8.9/0.8)	8.1 (7.6/0.5)	9.8 (9.8/ND)	9.9 (9.7/0.2)
6 Additional Unidentified Metabolites	8.0 (3.8/4.2)	7.4 (4.6/2.8)	15.2 (10.2/5.0)	10.0 (6.1/3.9)	8.4 (5.8/2.6)	8.8 (7.6/1.2)
Total unidentif.	49.0	53.2	56.0	52.0	49.2	55.5
Total accounted for[b]	81.9	88.8	85.4	80.8	94.7	86.1
Unaccounted for[c]	18.1	11.2	14.6	19.2	5.3	13.9
Total	100	100	100	100	100	100

ND = Not detected
Data extracted from pp. 49-50, MRID 43689801.
a = Data presented as total urine and feces percent of dose recovered.
Parenthesis contain percent of dose recovered in urine/feces.
b = Total accounted for = (Total identified) + (Total unidentified)
c = 100 - (Total accounted for)

III. DISCUSSION

A. DISCUSSION

A series of studies was done to evaluate the absorption, distribution, metabolism, and excretion of ^{14}C-Propazine using male and female Sprague-Dawley rats. In a pilot study, one male and one female rat were given a single oral 100 mg/kg radiolabeled dose. Two groups of five male and five female rats received a single oral dose of radiolabeled Propazine at concentrations of 1.0 mg/kg (single low-dose) or 100 mg/kg (single high-dose). A fourth group (multiple low-dose) of five male and five female rats received 14 consecutive daily oral doses of 1.0 mg/kg unlabeled Propazine followed by a single oral dose of 1.0 mg/kg labeled test material. All treatments were by gavage with corn oil as the vehicle. For the four studies, urine and feces were collected from each animal eight hours after treatment with labeled Propazine and daily thereafter for seven days. Bile was not collected from any of the study groups. Seven days after treatment with the labeled test material, all rats were killed and blood and tissues collected. Absorption, distribution, metabolism, and excretion following intravenous administration of labeled Propazine were not evaluated.

None of the animals died during the study. The overall recovery of administered radioactivity for the single low-dose, multiple low-dose, and high-dose groups was similar and ranged from 97.0-105.7%, indicating acceptable mass balance. Because <0.1% of the administered dose was detected as CO_2 during the pilot study, expired breath was not collected from animals during the definitive studies.

Propazine was readily absorbed from the gastrointestinal tract following oral administration and its absorption was similar for the three definitive study groups. Based on the percent of administered dose recovered in the urine/cage wash and tissues of animals in the single and multiple low-dose groups and the single high-dose group, absorption was ≥73%. No sex-related differences in absorption were apparent. Seven days after treatment, what test material had not been excreted was widely distributed throughout the body. Although no specific target organs were identified, the red blood cells and muscle contained the highest residual activity (0.54-0.64 and 0.07-0.25% of administered dose, respectively). Within 48 hours of treatment 82-95% of the administered dose was recovered in the excreta suggesting that elimination of the labeled test material was rapid. Seven days after treatment, 87-99% of the administered

dose was recovered in the excreta; the remainder being found in the tissues.

Labeled Propazine was recovered only in the feces. Male and female rats in the single high-dose group excreted 10.5-13.8% and female rats in the single low-dose group excreted 5.2% of the administered dose as parent compound. These results may represent saturation of absorption processes or enterohepatic circulation. Biliary excretion studies could be used to differentiate these two processes. A total of 13 metabolites was recovered primarily in the urine, three of which were identified. The predominant identified metabolite, G 28273 (2-chloro-4,6-diamino-1,3,5-triazine) accounted for 20-30% of the administered dose. The two other identified metabolites were minor and contributed <5% of the administered dose. Of the 10 unidentified metabolites, 6 were minor and accounted for <15% of the administered dose. Of the remaining four, Metabolite 5 was predominant and contributed 18-24% of the administered dose in all groups. Metabolites 4 and 8 were next abundant, independently contributing 6-17% of the administered dose. It is of interest that Metabolite 4 was not recovered from single high-dose male rats. Although Metabolite 1 was found at <3% of the administered dose of male and female rats in the single low-dose and multiple low-dose and female rats in the single high-dose groups, it accounted for 11% of the dose for male rats in the single high-dose group. The amounts of Metabolites 1 and 4 recovered from single high-dose animals suggest a minor difference in metabolic disposition between the sexes at high doses of Propazine.

Based on the study results and literature review of the metabolic disposition of other 2-chloro-*s*-triazines, the study author proposed that the primary Phase I metabolic route proceeds by dealkylation at the 4 and 6 amino positions to ultimately form metabolite G 28273. Phase II metabolism then proceeds by glutathione conjugation of the parent and dealkylated metabolites. The study author speculated that Metabolites 4 and 5 were glutathione conjugates of products from primary Phase I metabolism because of their polarity and being found predominately in urine. Glucuronidation, however, cannot be ruled out. While the study author's assumptions are likely correct, relatively simple studies to determine the nature of the conjugation reaction should be done for confirmation. Metabolite 8 should also be identified.

B. STUDY DEFICIENCIES

In general, the study was conducted consistent with guideline requirements for a metabolism study (85-1) in the rat. However,

the study is considered supplementary until the identity of Metabolites 1, 4, 5, and 8 are determined. These four metabolites constituted 41-47% of the administered dose for the three treatment groups. The identity of Metabolites 4 and 5 as either glutathione or glucuronide conjugates of Phase I metabolism while likely correct, is speculative. Simple deconjugation studies would help to determine their identity. The study can be upgraded to acceptable upon submission of results identifying Metabolites 1, 4, 5, and 8.

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OFFICE OF PESTICIDES/HED/SACB/TOX
ONELINERS

TOXCHEM NO.:184 chemical name: propazine

CITATION	MATERIAL	MRID No.	RESULTS	TOX. CAT.	CORE GRADE
Metabolism Species (strain): rat Lab. Name: PTRL East, Inc. PTRL Project No: 821 Date: 6/16/95	propazine (99.6%)--ring-UL-^{14}C-labeled	43689801	In a metabolism study (MRID 43689801), Propazine (2-chloro-4,6-bis(isopropylamino)-1,3,5-s-triazine, unlabeled 98.2% a.i. or as [ring-UL-^{14}C]-Propazine, 99.6% a.i.) was administered to Sprague Dawley rats (5/sex/dose group) as a single gavage dose of 1.0 or 100 mg/kg labeled Propazine or as 14-daily doses of unlabeled 1.0 mg/kg Propazine followed by a single 1.0 mg/kg labeled dose. Corn oil was the vehicle for all treatments. None of the animals died during the study and overall mass balance for all treatment groups ranged from 97.0-105.7%. Absorption of Propazine from the gastrointestinal tract was rapid and similar for all study groups and no apparent sex-related differences were found. Based on recoveries from urine/cage wash and tissues, absorption was ≥73%. Within 48 hours of treatment, 82-95% of the administered dose was recovered from excreta, predominately the urine. No specific target organs were identified. Labeled Propazine was recovered only in the feces of male and female rats in the single high-dose group and female rats in the single low-dose group. As presented, it cannot be determined if this represents unabsorbed material or material that underwent enterohepatic circulation. Less than 0.1% of the administered dose was detected as CO_2 during a pilot study. Thirteen metabolites were recovered; three of which were identified. The predominant, G 28273, accounted for 20-30% of the administered dose while the other two contributed <5%. Of 10 unidentified metabolites detected, the combined contribution of six was <15% of the administered dose. Unidentified Metabolite 5 was predominant and contributed 18-24% of the administered dose for all study groups with unidentified Metabolites 4 and 8 next abundant. Although unidentified Metabolite 1 was found at <3% of the administered dose for most treatment groups, it accounted for 11% of the dose from male rats in the single high-dose group. Based on the results and literature review of other 2-chloro-s-triazines, the study author proposed that Phase I metabolism proceeded by dealkylation at the 4 and 6 amino positions to ultimately form G 28273 while Phase II metabolism involved glutathione conjugation. Although glucuronidation could not be ruled out, the author suggested that unidentified Metabolites 4 and 5 were glutathione conjugates. While these assumptions are likely correct, definitive studies need to be done for confirmation. This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (85-1) in rats. The study can be upgraded upon submission of data identifying the nature of conjugation and the identification of metabolites identified by the study author as 1, 4, 5, and 8. In addition, the registrant should provide a metabolic scheme for the test chemical.		supplementary

DATA EVALUATION RECORD 012286

Propazine Technical

Study Type: Acute Oral Toxicity (81-1)

Work Assignment No. 2-20A (MRID 43474101)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Christie E. Padova, B.S.

Signature: Christie E. Padova
Date: 8-22-96

Quality Assurance:
Mike Norvell, Ph.D.

Signature: Mike Norvell
Date: 8/24/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 9/10/96

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: W. Greear, MPH, DABT W. Greear, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat
OPPTS 870.1100 [§81-1]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Kuhn, J. (1994) Acute oral toxicity study in rats. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1318-94. October 27, 1994. MRID 43474101. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 43474101), a group of five young adult Sprague-Dawley albino rats/sex was given a single oral dose of Propazine Technical (98.0% purity, Lot# 309027-C) at 5,050 mg/kg (limit concentration). The test substance was administered as a 95% (w:v) concentration in deionized water. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postdosing.

Oral LD_{50} Males = >5,050 mg/kg (observed)
Females = >5,050 mg/kg (observed)

Propazine Technical is classified as **TOXICITY CATEGORY IV** based on the observed LD_{50} values for both sexes.

All animals survived the 14-day observation period. Piloerection was observed in all animals between 1 and 4 hours, and activity decreases were observed in a single male animal at 4 hours and 2 days. All effects subsided by day 3. No treatment-related effects on body weight were observed during the study, and gross necropsies after 14 days revealed no observable abnormalities.

This study is classified **acceptable**, and satisfies the guideline requirements for an acute oral study (81-1) in the rat.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle: Deionized water

3. Test animals: Species: Rat
   Strain: HSD:SD, albino
   Age: Young adult
   Weight: 215-228 g males; 196-210 g females
   Source: Harlan Sprague Dawley, Inc., Houston, TX
   Acclimation period: ≥5 days
   Diet: Purina Formulab Chow (#5008), ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: June 29-July 13, 1994

2. Animal assignment and treatment: Following a fasting period (length not specified), five young adult rats/sex were given a single oral dose of Propazine Technical at 5,050 mg/kg (limit concentration) by gavage; the test material was administered as a 95% (w:v) concentration in deionized water at a constant dosing volume of 5.32 mL/kg. The rats were observed for signs of toxicity and/or mortality at 1, 2, and 4 hours following administration, and at least once daily thereafter for the remainder of the 14-day study. Body weights were recorded at days 0 (prior to dosing), 7, and 14. At 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable for this study.

II. RESULTS AND DISCUSSION:

A. Mortality: All animals survived the 14-day observation period.

Oral LD_{50} Males = >5,050 mg/kg (observed)
Females = >5,050 mg/kg (observed)

B. Clinical observations: Piloerection was observed in 10/10 animals 1 hour following administration and subsided from females by 4 hours and from males by day 1. Activity decreases were observed in a single male animal at 4 hours and 2 days. No effects were observed between 3 and 14 days.

C. Body Weight: No treatment-related effects on body weight were observed during the study, with overall (0-14 days) average increases of 33% for males and 21% for females.

D. Necropsy: Gross necropsies after 14 days revealed no observable abnormalities.

E. Deficiencies: Clinical signs of toxicity should have been recorded on an individual animal basis. However, this deficiency is considered minor and did not alter the results of this study.

DATA EVALUATION RECORD

012286

Propazine Technical

Study Type: Acute Dermal Toxicity (81-2)

Work Assignment No. 2-20B (MRID 43474102)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
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Signature: Christie E. Padova
Date: 8-22-96

Quality Assurance:
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Date: 8/24/96

Project Manager:
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Signature: William J. Spangler
Date: 9/10/96

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: W. Greear, MPH, DABT W. Greear, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT
M Copley, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit
OPPTS 870.1200 [§81-2]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Kuhn, J. (1994) Acute dermal toxicity study in rabbits. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1319-94. September 1, 1994. MRID 43474102. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 43474102), five young adult New Zealand White rabbits/sex were dermally exposed to Propazine Technical (98.0% purity, Lot# 309027-C) at 5,050 mg/kg (>2X limit concentration) for 24 hours. Animals were observed for clinical signs and mortality for up to 14 days postdosing.

Dermal LD_{50} Males = >5,050 mg/kg (observed)
Females = >5,050 mg/kg (observed)

Propazine Technical is classified as **TOXICITY CATEGORY IV** based on the observed LD_{50} values in both sexes.

All animals survived the 14-day observation period. Clinical effects were observed between 1 and 14 days and included decreased defecation, diarrhea, and nasal discharge. The study author reported that no application-site dermal irritation was observed during the study. The body weights of two male animals decreased between 7 and 14 days. Overall, these animals exhibited decreases of 0 and 1.8%. Necropsy of animals sacrificed after 14 days revealed a green slurry in the large intestines of a single male, and dry feces in the large intestines of one animal/sex.

This study is classified **acceptable**, and satisfies the guideline requirements for an acute dermal study (81-2) in the rabbit.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle: Deionized water

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (3-6 months)
   Weight: 2.55-2.90 kg males; 2.75-2.95 kg females
   Source: Ray Nichols Rabbitry, Lumberton, TX
   Acclimation period: ≥5 days
   Diet: Purina Rabbit Chow, unspecified measured amount/animal/day
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: June 23-July 7, 1994

2. Animal assignment and treatment: Fur from the dorsal trunk areas of five young adult animals/sex was clipped 1 day prior to dermal administration of Propazine Technical at 5,050 mg/kg (>2X limit concentration). The test substance was moistened with deionized water and evenly applied to a 4- x 4-inch region of the clipped skin (equivalent to 103.2 cm^2, which is <10% of the total body surface area). Each application site was covered with a 4- x 4-inch surgical gauze patch secured with non-irritating adhesive tape, and the entire trunk of each animal was wrapped with plastic film secured with non-irritating adhesive tape. After 24 hours, the coverings were removed, and the sites were gently washed with tap water and a clean wet cloth. The rabbits were observed for signs of toxicity and/or mortality at 1, 2, and 4 hours following treatment, and at least once daily thereafter for the remainder of the 14-day study. Body weights

were recorded at study days 0 (prior to dosing), 7, and 14. At 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable for this study.

II. RESULTS AND DISCUSSION:

A. Mortality: All animals survived the 14-day observation period.

Dermal LD_{50} Males = >5,050 mg/kg (observed)
Females = >5,050 mg/kg (observed)

B. Clinical observations: Clinical signs of toxicity observed during the study included decreased defecation, diarrhea (males only), and nasal discharges (females only). Effects were observed between 1 and 14 days following administration. Individual observations were not provided.

The study author reported that no application-site dermal irritation was observed during the study.

C. Body Weight: No significant treatment-related effects on body weight were observed in females, who exhibited an overall (0-14 days) average increase of 12%. In contrast, the body weights of two males decreased between 7 and 14 days. Overall, these animals exhibited decreases of 0 and 1.8%. The remaining three male animals exhibited an overall average increase of 11%.

D. Necropsy: Necropsies of animals sacrificed after 14 days revealed a green slurry in the large intestines of a single male, and dry feces in the large intestines of one animal/sex.

E. Deficiencies: Based on information obtained from other acute dermal studies, 190 cm^2 is approximately 10% of the total body surface area of a 2-3 kg rabbit. In this study, the application site was approximately 16 in^2, equivalent to only 103.2 cm^2. However, since the study author described that the test slurry was "applied evenly to each exposure area in a thin, uniform layer" [page 8], suggesting that close to the maximum possible area was covered, and since no mortality occurred at >2X the limit concentration, this deficiency is considered minor.

Clinical findings should have been provided on an individual animal basis. However, this deficiency did not alter the results of this study and is considered minor.

The observation period should have been extended until all test animals appeared normal. However, this deficiency does not alter the results of this study and is considered minor.

DATA EVALUATION RECORD

012286

Propazine Technical

Study Type: Acute Inhalation Toxicity (81-3)

Work Assignment No. 2-20C (MRID 43474103)

Prepared for

Health Effects Division
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U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

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Primary Reviewer:
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Signature: Christie E. Padova
Date: 8-22-96

Quality Assurance:
Mike Norvell, Ph.D.

Signature: Mike Norvell
Date: 8/24/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 9/10/96

Disclaimer

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EPA Reviewer: W. Greear, MPH, DABT, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT, Date 9/18/96
Review Section 4, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat
OPPTS 870.1300 [§81-3]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Holbert, M. (1994) Acute inhalation toxicity study in rats. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1320-94. November 9, 1994. MRID 43474103. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 43474103), groups of five young adult Sprague-Dawley albino rats/sex were exposed by whole-body inhalation to Propazine Technical (98.0% purity, Lot# 309027C) at 0.918 or 1.22 mg/L for 4 hours. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postexposure.

Inhalation LC_{50} Males = >1.22 mg/L (observed)
Females = >1.22 mg/L (observed)

Propazine Technical is classified as **TOXICITY CATEGORY III** based on the observed LC_{50} values for both sexes.

All animals survived the 4-hour exposure and 14-day observation periods. Piloerection, activity decreases, and red crusts on noses were observed in up to all animals between chamber removal and 6 days following exposure. The body weight of one male from the 1.22-mg/L exposure group remained unchanged between 0 and 7 days following exposure. In contrast, the body weights of 9/10 females decreased between 0 and 7 days. Gross necropsies after 14 days revealed no observable abnormalities.

This study is classified **acceptable**, and satisfies the guideline requirements for an acute inhalation study (81-3) in the rat.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rat
   Strain: HSD:SD, albino
   Age: Young adult
   Weight: 206-230 g males; 203-236 g females
   Source: Harlan Sprague Dawley, Inc., Houston, TX
   Acclimation period: ≥5 days
   Diet: Purina Formulab Chow (#5008), ad libitum, except during exposure
   Water: Tap water, ad libitum, except during exposure

B. STUDY DESIGN and METHODS:

1. In-life dates: July 27-August 11, 1994

2. Exposure conditions: A whole-body, dynamic-flow exposure chamber (500 L) constructed of stainless steel and containing individual stainless steel wire mesh cages (New York University design) was utilized in the study.

   Test atmosphere was generated during the first 2.5 hours of the 0.918-mg/L exposure by metering test material via a revolving motorized disc into a Gem T Trost Air Mill. The resultant aerosol was elutriated through a 91-L baffling chamber and diluted with filtered air prior to entering the exposure chamber. The baffling chamber was removed for the last 1.5 hours of the 0.918-mg/L exposure and was not used during the 1.22-mg/L exposure period. The total airflow through the exposure chamber was maintained at 113 L/min (equivalent to 11.5-13.6 chamber turnovers/hour). The time required for 99% equilibration was 24 minutes for the 0.918-mg/L exposure and 20 minutes for the 1.22-mg/L exposure.

The nominal test atmosphere concentration was determined at the end of each exposure period by dividing the total amount of test material delivered to the chamber by the total air volume that passed through the chamber during the exposure time. The actual test atmosphere concentration was determined once per hour for the first 3 hours for the 0.918-mg/L exposure level and during hours 2 and 3 for the 1.22-mg/L exposure level. Samples (18.06 L) obtained from the breathing zone of the animals were drawn through chloroform traps. Samples of the chloroform were analyzed for propazine using a Tracor 560 gas chromatograph in conjunction with flame ionization detection. The nominal and average analytically-determined test concentrations are presented in Table 1.

Particle size was determined twice per exposure period using an Anderson cascade impactor. Samples were collected at a rate of 28.3 L/min for 4 minutes from the breathing zone of the animals at 1.00 and 3.75 hours into exposure for the 0.918-mg/L level and 1.00 and 3.00 hours for the 1.22-mg/L level. The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and the percentage of particles <9, <4.7, and <1.1 μm were calculated; results are presented in Table 1.

TABLE 1. Exposure conditions

Nominal Conc. (mg/L)	Mean Analytical Conc. (mg/L)	MMAD (μm)	GSD (μm)	<9 μm (%)	<4.7 μm (%)	<1.1 μm (%)
99.2	0.918	6.401	2.693	65.90	36.64	4.82
		11.463	4.178	48.94	24.60	5.00
76.8	1.22	6.082	2.673	75.51	21.68	5.23
		25.840	4.399	25.57	11.70	0.80

During the exposure periods, the mean temperature was 73-75 °F, the mean relative humidity was 81-86%, and the oxygen level was reportedly maintained above 19%.

3. Animal assignment and treatment: Five young adult rats/sex were exposed to Propazine Technical at 0.918 or 1.22 mg/L via whole-body inhalation for 4 hours. The animals were observed for signs of toxicity and/or mortality at 0.5, 1.0, 2.5, 4.5, and 6.0 hours following the initiation of exposure, and at least once daily thereafter for the remainder of the 14-day study. Body weights were recorded at

study days 0 (prior to exposure), 7, and 14. After 14 days, surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

4. Statistics: Not applicable for this study.

II. **RESULTS AND DISCUSSION:**

A. Mortality: All animals survived the 4-hour exposure and 14-day observation periods.

Inhalation LC_{50} Males = >1.22 mg/L (observed)
Females = >1.22 mg/L (observed)

B. Clinical observations: Piloerection and activity decreases were observed in 20/20 animals between chamber removal (4.5 hours) and 3 days following exposure. In addition, red crusts on noses were observed in up to 17/20 animals between 1 and 6 days. Effects subsided from all animals by day 7.

C. Body Weight: The body weight of one male from the 1.22-mg/L exposure group remained unchanged between 0 and 7 days following exposure; otherwise, no treatment-related effects were observed in males, with overall (0-14 days) average increases of 20-28%. In contrast, the body weights of 9/10 females decreased between 0 and 7 days. All affected animals then gained weight between 7 and 14 days. Overall, 3/10 exposed females lost up to 3.3% body weight; the remaining seven females gained between 0.5 and 10%.

D. Necropsy: Gross necropsy after 14 days revealed no observable abnormalities.

E. Deficiencies: There were numerous deficiencies in this study: the MMAD values exceeded the ideal respirable range of 1-4 μm and were highly variable; the study was not conducted at the limit concentration of 2 mg/L; particle size was only measured twice per exposure period; concentration determination was only conducted two to three times per exposure period; and the humidity exceeded the 40-60% limits set forth in Subdivision F guidelines. Results of the single preliminary trial (presumably conducted under the conditions described in the study) were more favorable than the definitive study, and no explanation was provided for the differences observed [Refer to Table 6 for preliminary results]. However, since no mortality occurred during the study, and based on data obtained from concurrently-

submitted acute oral and dermal studies (MRIDs 43474101 and 43474102, respectively), Propazine Technical is of low toxicity, and additional testing would most likely not alter the Toxicity Category for acute inhalation. As a result, this study is accepted as a "best effort".

012286

DATA EVALUATION RECORD

Propazine Technical

Study Type: Primary Eye Irritation (81-4)

Work Assignment No. 2-20D (MRID 43474104)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
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Signature: Christie E. Padova
Date: 8-22-96

Quality Assurance:
Mike Norvell, Ph.D.

Signature: Mike Norvell
Date: 8/24/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 9/10/96

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: W. Greear, MPH, DABT W. Greear, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT M Copley, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit
OPPTS 870.2400 [§81-4]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Kuhn, J. (1994) Primary eye irritation study in rabbits. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1321-94. August 30, 1994. MRID 43474104. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 43474104), 56.0 mg (0.1 mL equivalent) of Propazine Technical (98.0% purity, Lot# 309027-C) was instilled into the conjunctival sac of the right eye of nine young adult New Zealand White rabbits (six male and three female). Thirty seconds following instillation, 3/9 treated eyes (all male) were flushed 1 minute with deionized water. All treated eyes were washed after 24 hours. The animals were observed for up to 72 hours following treatment, and eye irritation was scored by the Draize method.

Ocular irritation was most severe 1 hour following instillation and included slight to moderate conjunctival redness, very slight conjunctival chemosis, and slight conjunctival discharge in 6/6 treated unwashed eyes. The average irritation score at 1 hour was 7.3. No corneal opacity or iridial changes were observed during the study, and conjunctival effects subsided from 5/6 eyes by 24 hours and from 6/6 eyes by 48 hours.

Based on the results of this study, **Propazine Technical is a slight ocular irritant**, and is classified as **TOXICITY CATEGORY IV** based on the minimal irritation which subsided from 5/6 treated eyes by 24 hours.

This study is classified **acceptable**, and satisfies the guideline requirements for a primary eye irritation study (81-4) in the rabbit.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (3-6 months)
   Weight: Not provided
   Source: Ray Nichols Rabbitry, Lumberton, TX
   Acclimation period: ≥5 days
   Diet: Purina Rabbit Chow, unspecified measured amount/animal/day
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: June 27-30, 1994

2. Animal assignment and treatment: A 56-mg portion (equivalent to 0.1 mL) of Propazine Technical was instilled into the conjunctival sac of the right eye of nine young adult New Zealand White rabbits (six males and three females). The upper and lower lids were held together for 1 second before releasing to prevent loss of the material. Thirty seconds after instillation, 3/9 treated eyes (all male) were flushed for 1 minute with room temperature deionized water. Twenty-four hours after instillation, all treated eyes were flushed in the same manner. The left eye of each animal served as an untreated control. The animals were observed for ocular irritation at 1, 24 (prior to washing), 48, and 72 hours following instillation. At the 24-hour observation, fluorescein dye was used to confirm the presence or absence of corneal ulceration. Eye irritation was scored by the Draize method.

II. RESULTS AND DISCUSSION:

A. Clinical observations: Ocular irritation was most severe 1 hour following instillation and included slight to moderate conjunctival redness (scores of 1-2), very slight conjunctival chemosis (score of 1), and slight conjunctival discharge (score of 1) in 6/6 treated unwashed eyes. The average irritation score at 1 hour was 7.3. No corneal opacity or iridial changes were observed during the study, and conjunctival effects subsided from 5/6 eyes by 24 hours and from 6/6 eyes by 48 hours. Based on the results of this study, Propazine Technical is a slight ocular irritant.

Effects observed in the treated washed eyes were comparable. At 1 hour, slight conjunctival redness (score of 1) and very slight conjunctival chemosis (score of 1) were observed in 3/3 eyes, and slight conjunctival discharge was observed in 1/3 eyes. No corneal opacity or iridial changes were observed during the study, and all conjunctival effects subsided by 24 hours.

B. Deficiencies: Aside from ocular irritation, individual observations for the entire day of dosing and individual daily observations were not provided. These deficiencies, however, had no effect on the results of the study and are considered minor.

012286

DATA EVALUATION RECORD

Propazine Technical

Study Type: Primary Dermal Irritation (81-5)

Work Assignment No. 2-20E (MRID 43474105)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
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Date: 8-22-96

Quality Assurance:
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Date: 8/24/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 9/10/96

Disclaimer

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EPA Reviewer: W. Greear, MPH, DABT W. Greear, Date 7/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT
Review Section IV, Toxicology Branch I (7509C) M Copley, Date 9/18/96

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS 870.2500 [§81-5]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Kuhn, J. (1994) Primary dermal irritation study in rabbits. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1322-94. August 31, 1994. MRID 43474105. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 43474105), three young adult New Zealand White rabbits/sex were dermally exposed to 500 mg of Propazine Technical (98.0% purity, Lot# 309027-C) for 4 hours; the test substance was moistened with deionized water and applied to a single intact 6.25-cm^2 site/animal. Animals were observed for dermal irritation for up to approximately 70 hours following application, and irritation was scored by the Draize method.

Very slight erythema was observed at 1/6 sites 0.5 hours following patch removal; otherwise, no dermal irritation was observed during the 70-hour observation period. Based on the results of this study, **Propazine Technical is not a dermal irritant**, and is classified as **TOXICITY CATEGORY IV** for primary dermal irritation.

This study is classified as **acceptable**, and satisfies the guideline requirements for a primary dermal irritation study (81-5) in the rabbit.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (3-6 months)
   Weight: Not provided
   Source: Ray Nichols Rabbitry, Lumberton, TX
   Acclimation period: ≥5 days
   Diet: Purina Rabbit Chow, unspecified measured amount/animal/day
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: June 21-24, 1994

2. Animal assignment and treatment: Fur from the dorsal trunk area (approximately 8 x 8 cm/animal) of three young adult animals/sex was clipped 1 day prior to dermal administration with 500 mg of Propazine Technical. The test substance was moistened with 0.25 mL of deionized water, applied to a single intact application site/animal, and covered with a two-ply 6.25-cm^2 surgical gauze patch secured with non-irritating tape. The trunk of each animal was then loosely wrapped with an orthopedic stockinette secured with adhesive tape. Following a 4-hour exposure period, the coverings were removed, and the test sites were gently washed with tap water and a clean cloth. The rabbits were observed for dermal irritation at 0.5, 24, 48, and approximately 70 hours following patch removal. Erythema and edema were scored separately using the Draize method.

II. RESULTS AND DISCUSSION:

A. Clinical observations: Very slight erythema (score of 1) was observed at 1/6 sites 0.5 hours following patch removal; otherwise, no dermal irritation was observed during the 70-hour observation period. Based on the

results of this study, Propazine Technical is not a dermal irritant.

B. Deficiencies: Aside from dermal irritation, individual observations for the entire day of dosing and individual daily observations were not provided. These deficiencies, however, had no effect on the results of the study and are considered minor.

012286

DATA EVALUATION RECORD

Propazine Technical

Study Type: Dermal Sensitization (81-6)

Work Assignment No. 2-20F (MRID 43474106)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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Date: 8-22-96

Quality Assurance:
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Signature: Mike Norvell
Date: 8/24/96

Project Manager:
William Spangler, Ph.D.

Signature: William J. Spangler
Date: 9/10/96

Disclaimer

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EPA Reviewer: W. Greear, MPH, DABT W. Greear, Date 9/18/96
Review Section IV, Toxicology Branch I (7509C)
EPA Secondary Reviewer: M. Copley, DVM, DABT
Review Section IV, Toxicology Branch I (7509C) M. Copley, Date 9/18/96

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea pig
OPPTS 870.2600 [§81-6]

DP BARCODE: D219174 SUBMISSION CODE: S493480
P.C. CODE: 080808 TOX. CHEM. NO.:
EPA REG. NO.:

TEST MATERIAL (PURITY): Propazine Technical (98.0% purity)

SYNONYMS: None specified

CITATION: Kuhn, J. (1994) Dermal sensitization study in guinea pigs. Stillmeadow, Inc., Sugar Land, TX. Laboratory Study Number 1323-94. October 27, 1994. MRID 43474106. Unpublished.

SPONSOR: Griffin Corporation, Rocky Ford Road, Valdosta, GA.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 43474106) conducted with Propazine Technical (98.0% purity, Lot# 309027-C), five guinea pigs/sex were tested using methods based on those derived by Buehler.

No dermal irritation was observed 24 or 48 hours following a single challenge application to either previously-induced or naive control animals. Acceptable positive control data were provided to validate the test methodology. Based on the results of this study, **Propazine Technical is not a dermal sensitizer.**

This study is classified as **acceptable**, and satisfies the guideline requirements for a dermal sensitization study (81-6) in the guinea pig.

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: Off-white powder
   Lot/Batch #: 309027-C
   Purity: 98.0%
   CAS #: 139-40-2

2. Vehicle and positive control: Deionized water was used as a test substance vehicle.

   Summarized positive control data were provided (Stillmeadow Study Number 1372-94; July 8-September 16, 1994) using 1.0 and 0.15% (w:v) 1-chloro-2,4-dinitrobenzene (DNCB; approximately 95% purity) in ethanol for the induction and challenge phase treatments, respectively.

3. Test animals: Species: Guinea pig
   Strain: Hartley-Albino
   Age: Not specified
   Weight: 456-497 g males; 399-462 g females
   Source: SASCO Inc., Madison, WI
   Acclimation period: ≥5 days
   Diet: Purina Guinea Pig Chow, ad libitum
   Water: Tap water, ad libitum
   Housing: 1-4/cage, separated by sex

B. STUDY DESIGN and METHODS:

1. In-life dates: July 6-August 5, 1994

2. Animal assignment and treatment: The study was conducted using methods based on those derived by Buehler [Ritz, H., and E. Buehler, Current Concepts in Cutaneous Toxicity, p. 28 (1980)]. Based on the results of preliminary testing using two animals/sex and 400 mg of Propazine Technical moistened with deionized water (100%) or diluted to 25, 50, or 75% concentrations (w:v) in deionized water, the test substance was administered at 100% in both phases of the definitive study.

   For the induction phase, fur from the dorsal trunk area (at least 8 x 10 cm) of five animals/sex was clipped 1 day prior to dermal administration of 400 mg of Propazine Technical. The test substance was moistened with 0.25 mL of deionized water/application and applied using a Coverlet adhesive dressing (1.6- x 2.8-cm gauze patch

attached to a 3.8- x 5-cm piece of adhesive). One patch was attached to the left front quadrant of each animal, the entire trunk was wrapped in polyethylene film, and the animals were placed in restrainers for a 6-hour exposure period. Removal of the test substance from the skin was not described. Application of the test substance was repeated once weekly to the same site for 2 consecutive weeks (three total applications).

For the challenge phase, a single Propazine Technical treatment was administered in the same manner as described, to the previously untreated right rear quadrant 2 weeks following the final induction treatment. To serve as naive controls, an additional five animals/sex were included for the challenge treatment. The guinea pigs were observed for dermal irritation 24 hours following each induction and challenge exposure; in addition, observations were recorded 48 hours following the first induction and challenge treatments. Erythema was scored according to the following scale:

0 - No reaction
0.5 - Very faint, usually nonconfluent
1 - Faint, usually confluent
2 - Moderate
3 - Strong, with or without edema

Body weights of each animal were recorded on days 0 (1 day prior to the first induction treatment) and 28 (1 day prior to the challenge treatment).

Although many details concerning the induction and challenge phases of the positive control study were not provided, the test animals were obtained from the same supplier as in the definitive study, and the study was conducted according to the Buehler method. In addition, vehicle control tests were conducted.

II. **RESULTS AND DISCUSSION:**

A. Induction reactions and duration: No dermal irritation was observed during the induction phase.

B. Challenge reactions and duration: No dermal irritation was observed 24 or 48 hours following a single challenge application to either previously-induced or naive control animals. Based on the results of this study, Propazine Technical is not a dermal sensitizer.

An apparent treatment-related effect on body weight was observed between animals from the treated and naive control groups. Control males gained an average of 40%, compared to only 29% for test males, and control females gained an average 36%, compared to 26% for test females.

C. Positive control: Twenty-four hours following the first induction application, very faint erythema (score of 0.5) was observed at 1/10 sites; after 48 hours, very faint to moderate erythema (scores of 0.5-2) was observed at 5/10 sites. Twenty-four hours following the second and third induction applications, severe erythema (score of 3) was observed at 10/10 sites.

Twenty-four hours following a single challenge treatment to previously-induced animals, very faint to severe erythema (scores of 0.5-3) was observed at 10/10 sites and persisted or worsened at all sites after 48 hours. In contrast, no dermal irritation was observed 24 or 48 hours following application to naive control sites. These data confirm the adequacy of the test species and method employed.

D. Deficiencies: Although the age of the test animals was not specified, based on the body weights provided, they were probably young adult animals at study initiation, and this deficiency is considered minor.

13544

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Chemical:	**Propazine (ANSI)**
PC Code:	**080808**
HED File Code	**13000 Tox Reviews**
Memo Date:	**08/01/1997**
File ID:	**TX012286**
Accession Number:	**412-01-0120**

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