DATA EVALUATION REPORT

Propazine

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

Prepared for

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

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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.

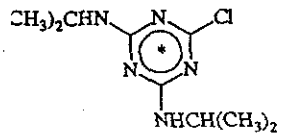
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

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.