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FINAL

DATA EVALUATION REPORT

PROMETRYN

Study Type: Metabolism

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
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GUIDELINE 85-1: Metabolism

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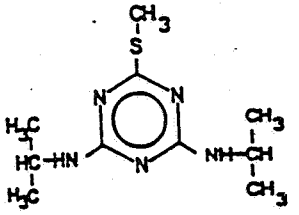
DATA EVALUATION REPORT

STUDY TYPE: Metabolism

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 097
PC Number: 080805
MRID Number: 412559-01

TEST MATERIAL: 2,4-Bis(isopropylamino)-6-(methylthio)-S-triazine is the active ingredient of Caparol® 4L herbicide



Radiolabel is on the triazine ring

SYNONYMS: Prometryn

SPONSOR: CIBA-GEIGY Corporation, Agricultural Division, 410 Swing Road, P.O. Box 18300, Greensboro, NC

TESTING FACILITIES: CIBA-GEIGY Corporation, Greensboro, NC, and WIL Research Laboratories, Ashland, OH

AUTHOR: M. Maynard

DATE: September 29, 1989

TITLE OF REPORT: ^{14}C-Prometryn Distribution, Elimination and Disposition in Rats Following Oral Administration

STUDY NUMBERS: M22-104-7A, M22-104-8A, M22-104-9A, M22-104-10A

CONCLUSIONS: Following oral administration of ^{14}C-prometryn, the predominant routes of excretion were both the urine and the feces, with slightly higher recoveries in the urine. At the end of 7 days, 47.06-53.3% of the administered dose was excreted in the urine and 33.13-45.48% of the administered dose was excreted in the feces. After 24 hours urinary and fecal excretion was greater than 90% complete for animals in the low-dose groups. After 72 hours urinary and fecal excretion was greater than 90% complete for animals in the high-dose group. The 7-day recoveries averaged 95% for all dosing groups. There was a wide but low-level distribution of radioactivity (<2% of the administered dose) in the tissues in all dose groups. The highest radioactivity levels were in the blood, spleen, and lungs. The metabolism of prometryn is extensive. Prometryn and twenty-eight metabolites were identified in urine and feces. Prometryn accounted for <5% of the radioactivity of the urine and feces. Twenty-eight metabolites were identified in the urine. The 10 metabolites identified in the feces were also identified in the urine. Refer to the DER for chemical identification of the metabolites.

STUDY CLASSIFICATION: ~~Minimum~~ Acceptable

The study met the minimum requirements set forth under Guideline 85-1 and Addendum 7 for a metabolism study in rats. Although there were a number of deficiencies in the study (see Section E), they did not affect the integrity of the test results.

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A. MATERIALS

1. Test Substance

Four test materials were used in this study. The first test material, prometryn (GAN-XIV-66), labeled with ^{14}C in the triazine ring, was used for the two low-dose groups (Groups 1 and 3). The specific activity was 20.1 µCi/mg. The radiopurity was 98.6% (determined by the Sponsor). The chemical purity was >95% by gas chromatographic analysis. The second test material, ^{14}C-prometryn (CL-XV-42), was used for the high-dose group (Group 2). The specific activity was 1.0 µCi/mg. The radiopurity was 98.4% (as determined by the Sponsor). The third test material was unlabeled prometryn (Batch FL-870991) with a purity of 98.1% (obtained from the Sponsor). This material was used for pre-conditioning the rats in Group 3. The fourth test material, ^{14}C-prometryn (GAN-XIV-64) was used for the Group 4 rats. Samples from these rats were used for metabolite isolation and identification purposes only. The ^{14}C-prometryn contained a specific activity of 1.0 µCi/mg, a radiochemical purity of 98.4%, and a chemical purity of >95%. The purity values were determined before dosing.

2. Test Animals

Two shipments of Crl:CD BR rats (26/sex and 13/sex) were received from Charles River Breeding Laboratories, Portage, MI. The males were 5 weeks old and the females were 8 weeks old. The animals were assigned to the study by weight using a computer-generated randomization program. The weight variation in both sexes did not exceed ±20% of the mean weight for each sex. Three groups of rats, 5 males and 5 females, were given a single oral dose of ^{14}C-prometryn. Group 1 received a single oral dose of 0.46-0.47 mg/kg. Group 2 received a single oral dose averaging 467 mg/kg. Group 3 received 0.5 mg/kg unlabeled prometryn repeatedly for 14 days followed by a single dose of 0.46 mg/kg ^{14}C-prometryn on day 15. An additional group, Group 4, was used for metabolite isolation and identification purposes. This group, consisting of 5 males and 5 females, received 540 mg/kg of ^{14}C-prometryn. Because of its low water solubility, the test material was administered in an aqueous suspension (0.5% carboxymethylcellulose). The actual doses received by each group were as follows:

Group	Sex	Dose level (mg/kg)
1	M	low, 0.46
1	F	low, 0.47
2	M	high, 494
2	F	high, 440
3	M/F	low, 0.46
4	M/F	high, 540

B. METHODS

1. Acclimation

The rats were held in quarantine for 10 days. They were housed individually in stainless steel wire-mesh cages suspended above cage-board except when placed in metabolism units to collect excreta. Animals were placed in individual Nalgene® type metabolism units at least 1 day prior to dosing with radioactive test material until sacrifice to allow for the separate collection of urine and feces. The diet was Purina® Certified Rodent Chow® (No. 5002). Feed and water were provided ad libitum. Tap water was delivered by an automatic watering system except when animals were in metabolism units where they received deionized water from bottles. Analysis of tap water is performed twice a year according to Standard Operating Procedures.

2. Dosing Solution Preparation and Administration

The oral dosing solutions were prepared in aqueous suspensions of 0.5% carboxymethylcellulose. The specific activities were 20.1 µCi/mg and 1 µCi/mg for the low-dose and high-dose groups, respectively. The dose concentrations were 1.52, 71.44, and 1.68 µCi/g for Groups 1, 2, and 3, respectively. The suspensions were homogenous with respect to ^{14}C-prometryn. Analysis of the suspensions used for preconditioning indicated stability of the suspension throughout the preconditioning period. On day 1, the concentration was 85.4%, and, on day -14, the concentration was 89.6%.

The average amounts of ^{14}C-prometryn delivered (by syringe/cannula) to the rats of Groups 1 and 3 were 0.47 mg/kg and 0.46 mg/kg, respectively. The average amount delivered to the rats in the high-dose group, Group 2, was 467 mg/kg. The low water solubility of prometryn prohibited a intravenous administration.

3. Sample Collection and Analysis

The urine and feces were collected from animals at 4, 8, 12, and 24 hours and daily thereafter for 7 days postexposure. Each urine collection was analyzed for ^{14}C individually. The feces of each collection were extracted with methanol and the residual insoluble fractions were air dried and weighed. Both the methanol extracts and the dry residuals were analyzed for ^{14}C. All urine and feces collections were stored at <-10°C. Following euthanization, whole blood was collected from the inferior vena cava; the plasma and cellular fractions were separated and stored frozen. The following tissues were collected: heart, lungs, spleen, both kidneys, liver, perirenal fat, gonads, uterus, muscle (leg), bone, and brain. The tissues were frozen on crushed dry ice and stored at <-10°C. The metabolism cages were washed with a mixture of water and methanol (50:50) and the washes were analyzed for ^{14}C. All analyses of ^{14}C involved measurement by liquid scintillation techniques. Duplicate samples were analyzed by counting with a Packard TriCarb Model 4430 Liquid Scintillation Counter. Liquids, such as dilutions of the dosing suspensions, urine, extracts, and cage washes, were analyzed by direct count in liquid scintillation systems. Solid materials and blood were analyzed by oxidation in a Harvey BMO (Biological Materials Oxidizer, Model OX300), and the amount of ^{14}C present was measured by scintillation techniques.

4. Characterization and Identification of Metabolites

An additional group (Group 4), comprising 5 male and 5 female rats, were administered 540 mg/kg of ^{14}C-prometryn and sacrificed at 6 and 72 hours after dosing. The initial characterization of the ^{14}C residue was similar in male and female rats, high- and low-dose groups, and with and without preconditioning; therefore, the metabolites were characterized using the high-dose groups (Groups 2 and 4) only. The pooled 24- and 48-hour urine samples were processed to fractionate the ^{14}C residue by application to an XAD-4 column. The XAD H_2O (water soluble), XAD MeOH/H_2O (adsorbed on XAD, partitioned into MeOH/H_2O), and XAD MeOH/CH_2Cl_2 (adsorbed on XAD, partitioned into CH_2Cl_2) from Groups 2 and 4 male and female rats were used for metabolite isolation, purification, and structure identification. Samples were purified by successive thin layer chromatography (TLC) or reversed phase (RP) high pressure liquid chromatography (HPLC). Attempts were made to obtain mass spectra of the major metabolites. Chromatographic comparison against standards (TLC or RP-HPLC) was used for virtually all metabolites.

To characterize the feces, the 12-, 24-, 48-, and/or 72- hour feces for all dosage groups were sequentially extracted with ethanol, acetonitrile/water (ACN/H_2O), and water. The ^{14}C residue was characterized by various TLC systems. The feces extracted with water were incubated with β-glucuronidase or aryl sulfatase to determine the presence of conjugates. The ^{14}C in the control

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and enzyme-treated samples was characterized by a Sephadex A-25 DEAE column with a KBr gradient.

C. REPORTED RESULTS

1. Elimination and Recovery

No major dose-related differences were seen in the elimination of prometryn after 7 days. The mean total recoveries of radioactivity in the urine, feces, tissues, blood, and cage wash ranged from 89.39% to 100.09% of the administered dose (Table 1). The mean total recoveries of radioactivity in the urine and feces ranged from 85.82% to 97.52% of the administered dose after 168 hours (7 days). Both urine and feces were major routes of elimination, with slightly higher recoveries found in urine (47.06-53.3% of the administered dose) than in feces (33.13-45.48% of the administered dose). In the single low-dose group and the high-dose-group, some sex-related differences were seen in the recovery of radiolabel in the urine and feces. Recovery of radiolabel in the urine was slightly greater in females than in males of both groups, whereas the recovery of radiolabel in feces was slightly greater in males than females.

During the first 8 hours after dosing, dose- and sex-related differences were seen in the cumulative urinary excretion of radiolabel, with the animals in the low-dose groups excreting more radiolabel than animals in the high-dose group suggesting the possibility of a slower metabolic rate in the high-dose group than in the low-dose groups. The males in the low-dose and preconditioned low-dose groups excreted 22.84-28.84% of the administered dose (49-54% complete) versus 4.17% of the administered dose (9% complete) excreted by males in the high-dose group. The females in the low-dose and preconditioned low-dose groups excreted 27.91-29.23% of the administered dose (56.2-56.4% complete) versus 3.83% of the administered dose (7.3% complete) excreted by females in the high-dose group. Greater than 90% of the radiolabel in the urine was excreted by both sexes in the low-dose groups by 24 hours. It required 72 hours for urinary excretion to be greater than 90% complete for animals in the high-dose group.

At 12 hours post-dose, dose-related and sex-related differences were seen in the cumulative fecal excretion of radiolabel, with the animals in the low-dose groups excreting more radiolabel than animals in the high-dose group. The males in the low-dose and preconditioned low-dose groups excreted 0.58-14.82% of the administered dose (1.3-33.5% complete), respectively, versus 0.45% of the administered dose (1% complete) excreted by males in the high-dose group. The females in the low-dose and preconditioned low-dose groups excreted 8.45-23.62% of the administered dose (20.3-51.9% complete) versus 2.52% of the administered dose (7.6% complete) excreted by females in the high-dose group. In the

low-dose groups both sexes excreted 80.4%-91.3% of the radiolabel in the feces by 24 hours. It required 72 hours for fecal excretion to be greater than 90% complete for animals in the high-dose group.

Excretion half-lives were estimated by comparison of the natural log (ln) of the excreted dose remaining in the rats versus time. Animals in the low-dose groups appeared to show two phases of excretion with an initial rapid phase followed by a slower second phase. The low-dose groups had elimination half-lives of 7-12 hours and 29-39 hours for the early and late phases, respectively. The high-dose animals appeared to have similar early and late phases of elimination, with elimination half-lives of 15-17 hours. Therefore, elimination was biphasic irrespective of dose levels, but the half-life was slightly longer at the high-dose than at the low-dose. There did not appear to be a significant difference in the elimination kinetics between male and female rats.

2. Tissue Distribution

Mean total recoveries of radioactivity in all the tissues was less than 1% of the administered dose (AD), ranging from 0.35% to 0.63% AD (Table 1). Mean total recoveries of radioactivity in the blood ranged from 1.20% to 1.89% AD (Table 1).

Dose-related differences were seen in residue levels, with concentrations in all tissues in the high-dose group being about 1000 times higher than in the low-dose and preconditioned low-dose groups (Table 2). No major sex-related differences were seen in residue levels in the low-dose groups. Sex-related differences were seen in residue levels in the high-dose group with the residues in female rats being consistently higher than in male rats. The blood cells contained the highest radioactivity. Average radioactivities in the blood cells ranged from 0.196 to 0.271 ppm (1.14-1.40% AD) in the low-dose and preconditioned low-dose groups and from 242.3 to 316.3 ppm (2.07-2.52% AD) in the high-dose group. Of the organs, the spleen and lungs contained the highest radioactivities. In the low-dose and preconditioned low-dose groups, average radioactivities in the spleen ranged from 0.031 to 0.043 ppm (0.02-0.14% AD); in the high-dose group, average radioactivity in the spleen ranged from 25.4 to 50.2 ppm (0.02-0.03% AD). In the lungs, the average radioactivities ranged from 0.026 to 0.042 ppm (0.03-0.05% AD) and 35.4 to 53.9 ppm (0.06-0.07% AD) for the low-dose groups and the high-dose group, respectively.

3. Metabolism

The parent compound and twenty-eight metabolites were identified in urine (Table 3). (See Appendices A and B for the chemical names and structures of the metabolites.) Ninety-three percent of

the urinary fraction was identified. The metabolites identified in Table 3 represent male and female rat urines from the high-dose groups. The initial characterization of the ^{14}C residue was similar in male and female rats, high- and low-dose groups, and with and without preconditioning, therefore, the metabolites were characterized using the high-dose groups (Groups 2 and 4) only. The major metabolite identified from all three fractions combined (XAD H2O, XAD MeOH/H2O, and XAD MeOH/CH2Cl2) in the urine was the N-acetyl cysteine conjugate of GS-11354 (16% of urine), followed by the S-S dimer GS-11354 (9.0% urine) and the N-acetyl cysteine conjugate of prometryn (8.2% urine). The remainder of the metabolites made up ≤6.0% of urine, including the parent compound (4.7%) (Table 3).

Ten metabolites in feces were identified by TLC (Table 4). (See Appendices A and B for chemical names and structures of the metabolites.) The metabolites present in the feces were also present in urine. Prometryn was present (in all dose groups) in less than 5% of the fecal radioactivity, averaging 0.45% in the single low-dose group, 0.7% in the repeated low-dose, 3.95% in the high-dose group (Group 3), and 3.9% in Group 4. GS-11354 was the major fecal metabolite averaging 9.5% and 7.4% in the high-dose groups, Groups 2 and 4, respectively. This metabolite averaged only 1.65% and 1.0% in the single and repeated low-dose groups, respectively. The rest of the metabolites accounted for an average of less than 6% of the fecal radioactivity for all dose groups.

The hydrolysis of aqueous soluble conjugates by β-glucuronidase and aryl-sulfatase indicated the presence of glucuronide and sulfate conjugates. A dose-dependent increase in conjugation was observed. As the dose increased from 0.46 to 540 mg/kg, there was a 1.6-1.8-fold increase in glucuronide conjugation for the males and a 3.5-7.0-fold increase in glucuronide conjugation for the females. As the dose increased from 0.46 to 540 mg/kg there was a 3.3-8.5 fold increase in sulfate conjugation for males, and a 2.3-4.9 fold increase in sulfate conjugation for females. There was a greater degree of sulfate conjugation (2.0-25.2%) than glucuronide conjugation (2.1-14.8%). Sex related differences in both sulfate and glucuronide conjugation were also noted. Females exhibited a greater degree of both sulfate (5.1-25.2%) and glucuronide (2.1-14.8%) conjugation than did males (2.0-16.9% for sulfate conjugation and 3.5-6.3% for glucuronide conjugation).

The proposed metabolic pathways for ^{14}C-prometryn in urine and feces are presented in Figures 1 and 2. The study author indicated that metabolism of prometryn involved "N-dealkylation, S-oxidation, S-conjugation with glutathione or glucuronic acid, S-S dimerization, desulfuration, or deamination to hydroxyl compounds, and O-methylation of the hydroxyl compounds."

D. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES

The urine and feces were the predominant routes of excretion following oral administration of ^{14}C-prometryn. At the end of 7 days, approximately one-half of the orally dosed radioactivity in both male and female rats was excreted in the urine (47.06-53.3% of the administered dose) and feces (33.13-45.48% of the administered dose), with slightly higher recoveries in urine than in feces (Table 1). No major dose-related differences were seen in the elimination of prometryn after 7 days. However, there were some sex-related differences in elimination, with recovery in the urine being slightly greater in females than males of the single low-dose and single high-dose groups. The recovery in the feces was slightly greater in males than females. There were dose-related differences in the rate of both urinary and fecal excretion. Greater than 90% of the radiolabel in the urine and feces was excreted by both sexes in the low-dose groups by 24 hours. It required 72 hours for urinary and fecal excretion to be greater than 90% complete for animals in the high-dose group. Animals in the low-dose groups exhibited a biphasic pattern of elimination, with half-lives of 7-12 hours for the early phase and 29-39 hours for the late phase, while animals in the high-dose group had an elimination half-life of 15-17 hours. No sex-related differences in elimination kinetics were seen. The tissue content of ^{14}C-prometryn and possible metabolites 7 days after dosing, was mostly insignificant. Overall, most tissues, including blood, showed low activities (<2% of the administered dose). Dose-related patterns were seen in residue levels, with concentrations in all tissues in the high-dose group being about 1000 times higher than levels in both the single and preconditioned low-dose groups. Prometryn was extensively metabolized. Prometryn and 28 metabolites were identified in the urine. Prometryn and 10 of the metabolites that were present in the urine were also present in the feces. No major sex- or dose-related differences were seen in the metabolite pattern. The metabolic pathways of prometryn were well described.

The quality assurance statement was signed and dated, 10/25/90. The statement of compliance with Good Laboratory Practices was signed on 10/25/90 and 10/26/90.

E. CONCLUSIONS BASED ON REVIEWERS' DISCUSSION AND INTERPRETATION OF DATA

The study author did not determine the amounts and rates of absorption of prometryn at different dose levels. This study adequately described the distribution, metabolism, and excretion of ^{14}C-prometryn in rats following oral exposure to single low, single high, or repeated low doses of the compound. The data indicated that the urine and feces were the major routes of elimination, with slightly higher recoveries found in urine than in feces. The appearance of radioactivity in the feces could be due to biliary excretion and poor absorption from the gastrointestinal tract; however, since I.V. dosing was not performed, it is difficult to determine the origin of the radioactivity in the feces. Although absorption was not determined, it occurred readily as evidenced by the appearance of radioactivity in the urine within the first 8 hours

for both sexes in both dose groups. There were dose-related differences in the rate of both urinary and fecal excretion, with the animals in the low-dose group excreting radioactivity in the urine and feces at a faster rate than the animals in the high-dose group. The slower urinary excretion of radiolabel by the animals in the high-dose group and the biphasic elimination seen in all dose groups could be due to saturation of the metabolic pathway. The reviewers note that the total amounts eliminated over the 7-day period were not affected. The low tissue levels of radioactivity and the rapid elimination demonstrate that bioaccumulation and retention of prometryn and/or its metabolites are low in rats. As the dosage levels increased from 0.47 to 470 mg/kg, the radioactivity levels of each tissue followed a ratio of approximately 1:1000. Recovery of the radioactivity was nearly complete (89.39-100.09%) (Table 1). No statistical methods were used to analyze the data.

The appropriate methods and solvent systems were used for adequate separation and characterization of prometryn and its urinary and fecal metabolites. Metabolism of prometryn was extensive as evidenced by the identifications of prometryn and 28 metabolites (28 in the urine, 10 in the feces). The metabolites found in the feces were also identified in the urine. The metabolite pattern was similar in all dose groups and in both sexes. However, there were differences in the metabolic pathways, which are both sex- and dose-dependent, as indicated by the differences seen in the degree of sulfate and glucuronide conjugation.

The study met the minimum requirements set forth under Guideline 85-1 and Addendum 7 for a metabolism study in rats. Although there were a number of deficiencies in the study, they did not affect the integrity of the test results. The deficiencies included the following: (1) the rationale for choosing the dose levels was not discussed; (2) exhaled radioactivity was not measured; (3) there was no discussion regarding the potential interference of the dosing vehicle, carboxymethylcellulose, to the kinetics of prometryn; (4) urine samples were not collected over dry ice.

TABLE 1. Mean Percent Recovery of Radioactivity 7 Days After Oral Administration of ^{14}C-Prometryn to Rats

Dose Group[b]	Sex	Percentage of Administered Dose[a]					
		Urine	Feces	Tissues	Blood	Cage Wash	Total Recovery
1	Male	47.06	43.61	0.35	1.20	0.97	93.19
	Female	49.61	39.67	0.37	1.31	0.54	91.50
2	Male	46.47	44.55	0.55	1.52	0.82	93.91
	Female	52.69	33.13	0.63	1.89	1.05	89.39
3	Male	53.30	44.22	0.53	1.48	0.43	99.96
	Female	51.80	45.48	0.38	1.46	0.97	100.09

[a]Based on individual means (5 rats/group)
[b]Dosage groups are as follows:
Group 1 Male -- 0.46 mg/kg ^{14}C-prometryn (single oral dose)
Group 1 Female -- 0.47 mg/kg ^{14}C-prometryn (single oral dose)
Group 2 Male -- 494 mg/kg ^{14}C-prometryn (single oral dose)
Group 2 Female -- 440 mg/kg ^{14}C-prometryn (single oral dose)
Group 3 Male -- 0.46 mg/kg ^{14}C-prometryn following 14 oral daily doses of unlabeled prometryn at 0.50 mg/kg
Group 3 Female -- 0.46 mg/kg ^{14}C-prometryn following 14 oral daily doses of unlabeled prometryn at 0.50 mg/kg

Source: Table I, p. 37

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TABLE 2. Distribution of Radioactivity in Tissues of Rats 7 Days After Oral Administration of Prometryn

Tissue/Organ	Average Radioactivity[a] (ppm) in Rat Tissues Dosed at: 0.46-0.47 mg/kg (single) Males	0.46-0.47 mg/kg (single) Females	467 mg/kg (avg) (single) Males	467 mg/kg (avg) (single) Females	0.46 mg/kg (repeated) Males	0.46 mg/kg (repeated) Females
Liver	0.021 (0.24)	0.025 (0.24)	21.045 (0.28)	33.752 (0.30)	0.028 (0.32)	0.037 (0.23)
Kidney	0.011 (0.02)	0.015 (0.03)	10.925 (0.03)	20.285 (0.04)	0.014 (0.03)	0.016 (0.03)
Muscle	0.003 (0.01)	0.004 (0.01)	4.365 (0.01)	7.053 (0.02)	0.004 (0.01)	0.005 (0.01)
Fat	<0.024 (0.53)	<0.026(<0.63)	3.506 (0.09)	3.820 (0.10)	<0.017(<0.43)	<0.017(<0.40)
Heart	0.024 (0.03)	0.029 (0.03)	24.835 (0.03)	34.339 (0.03)	0.029 (0 03)	0.037 (0.03)
Lung	0.026 (0.03)	0.033 (0.05)	35.392 (0.06)	53.851 (0.07)	0.042 (0.05)	0.042 (0.05)
Spleen	0.035 (0.02)	0.043 (0.02)	25.383 (0.02)	50.173 (0.03)	0.031 (0.14)	0.040 (0.02)
Testes	0.001(<0.01)	--	1.689 (0.01)	--	0.002 (0.01)	--
Ovaries	--	<0.017(<0.01)	--	30.214 (0.01)	--	0.014(<0.01)
Uterus	--	<0.006(<0.01)	--	7.363 (0.01)	--	0.006(<0.01)
Brain	0.004(<0.01)	0.005(<0.01)	2.400 (0.01)	3.123 (0.01)	0.003 (<0.01)	0.002 (0.01)
Bone	<0.017(<0.01)	<0.016(<0.01)	5.690 (0.01)	6.956 (0.01)	<0.017 (<0.01)	<0.016(<0.01)
Plasma	0.006 (0.06)	0.009 (0.08)	7.479 (0.07)	10.594 (0.10)	0.006 (0.06)	0.006 (0.06)
Blood Cells	0.196 (1.14)	0.227(1.23)	242.310 (1.45)	316.312 (1.79)	0.260 (1.49)	0.271 (1.40)
Average Total[b]	1.55	1,68	2.07	2.52	2.01	1.84

[a]Each value represents the mean of 5 rats; values in parentheses represent the mean percentage of the administered dose.

[b]"Average total" values are the averages of the individual totals of the percentage of administered dose for all tissues for each individual animal.

Sources: Tables IX-X, pp. 45-46; CBI Appendix A, Tables 10-11, 20-21, 30-31, pp. 255-256, 265-266, 275-276

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TABLE 3. Metabolites Identified in the Urine From Rats Administered ^{14}C-Prometryn[a]

Metabolite	% of Urine
N-acetyl cysteine conjugate of GS-11354	16.4
N-acetyl cysteine conjugate of prometryn	8.2
CGA-10582	6.0
S-S dimer prometryn	6.0
S-S dimer GS-11354	9.0
S-S dimer prometryn/GS11354	3.5
Cysteine conjugate of GS-11354	1.1
Cysteine conjugate of prometryn	1.9
Glutathione conjugate of prometryn	2.7
Glutathione conjugate of GS-26831	0.5
GS-11354	3.5
GS-26831	3.1
GS-16141	1.4
GS-14129	1.2
Sulfoxide of GS-26831	0.1
GS-16158	1.5
NH2 of prometryn	3.4
NH2 of GS-11354	0.1
Melamine	6.5
GS-17794	3.7
GS-17791	2.5
GS-11526	1.0
GS-11957	0.6
GS-35713	0.8
GS-11955	0.2
Prometon	0.8
GS-14626	1.8
Prometryn	4.7
S-Glucuronic acid of prometryn	0.9
Total	92%

[a]Male and female rat urines were similar. These values represent the high-dose groups.

See Appendices A and B for chemical names and/or structures which correspond to chemical numbers of the metabolites.

Source: Table XXIII, p. 55

TABLE 4. Distribution of Metabolites in Feces After Oral Administration of ^{14}C-Prometryn

	(Values Given As Percentage of ^{14}C in Feces)							
	0.47 mg/kg (single oral)		0.46 mg/kg (repeated oral)		467 mg/kg (single oral)		540 mg/kg (single oral)	
	Male	Female	Male	Female	Male	Female	Male	Female
Metabolites	Feces	Feces	Feces	Feces	Feces	Feces	Feces	Feces
Parent compound	0.4	0.5	1.0	0.4	4.4	3.5	3.2	4.6
GS 11354	1.4	1.9	0.8	1.2	6.8	12.1	6.9	7.8
GS 16141	0.2	0.5	0.8	1.0	1.7	2.2	1.4	2.4
GS 26831	0.1	0.5	0.4	0.4	1.1	1.2	1.2	1.4
GS 16158	1.4	1.8	1.3	1.5	0.8	0.7	0.7	0.7
GS 11955	1.9	2.2	1.5	2.1	3.9	6.3	3.4	3.4
CGA 10582	3.3	4.6	1.9	2.6	3.1	3.7	5.1	5.4
GS 11526	1.7	2.6	3.6	4.9	3.1	2.0	3.3	3.9
GS 11957	4.8	5.6	2.6	3.2	2.4	3.0	2.1	2.2
GS 17794	2.1	4.0	4.7	7.1	1.4	1.0	5.1	5.0
Glutathione conjugate of Diamino Triazine	1.3	3.1	1.8	4.4	1.1	1.2	1.6	1.6

See Appendices A and B for chemical names and/or structures which correspond to chemical numbers of metabolites.

Source: Table VIII, p. 24.

0107239

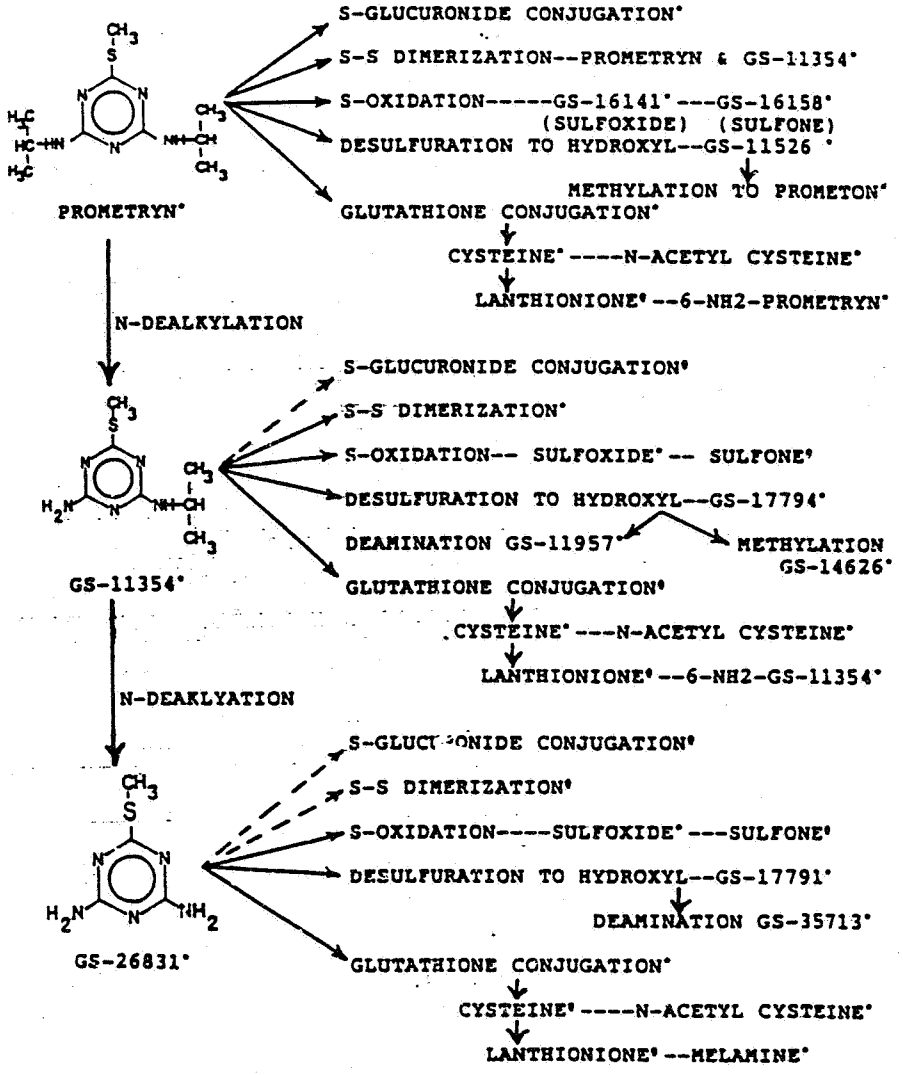


FIGURE 1: Metabolic Pathway of Prometryn in Rats from Urine Data
(Source: Figure 52, p. 117)

37 16

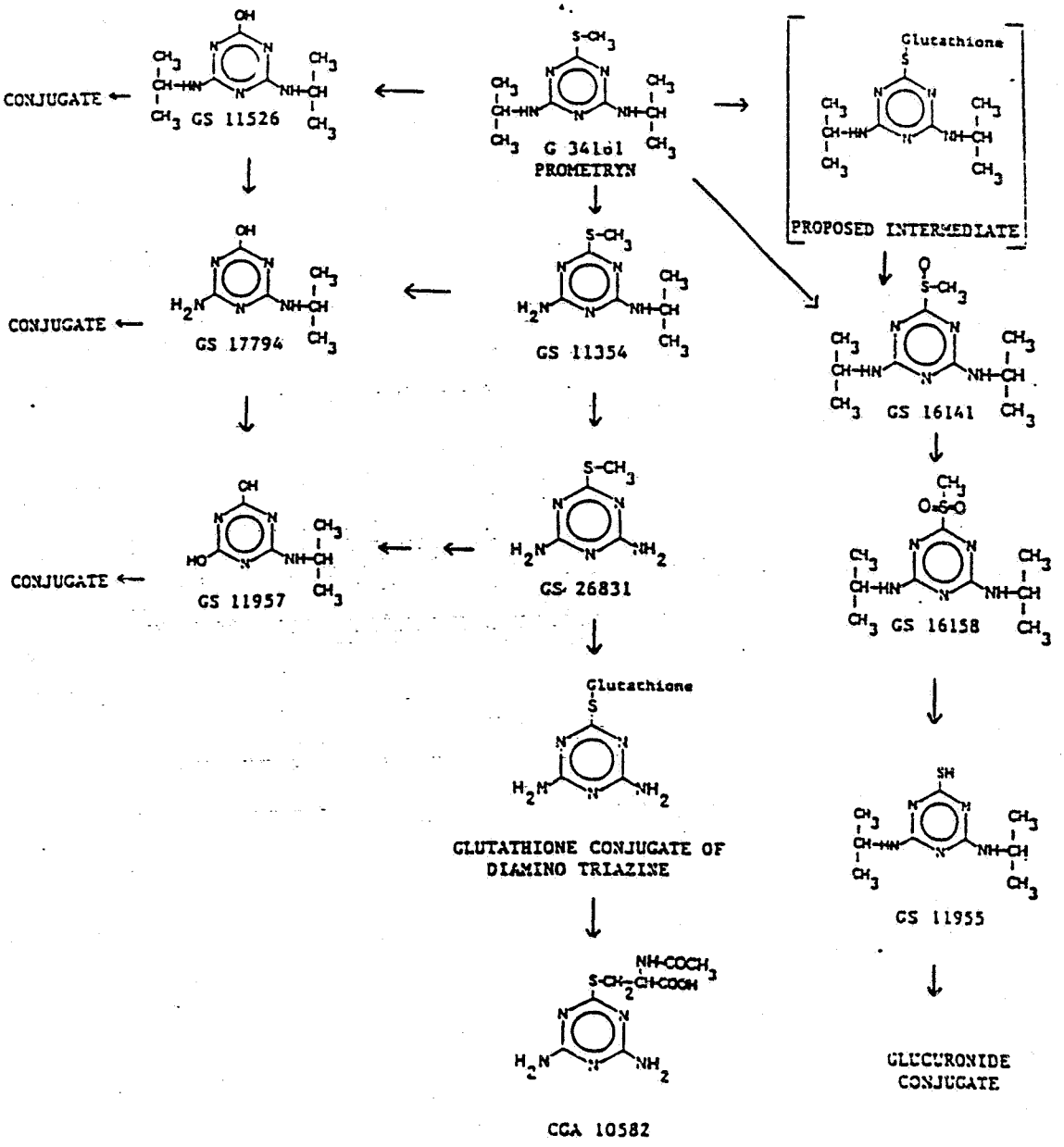


FIGURE 2: Metabolic Pathway of Prometryn in Rats from Feces Data
(Source Figure 7, p. 36)

28 11

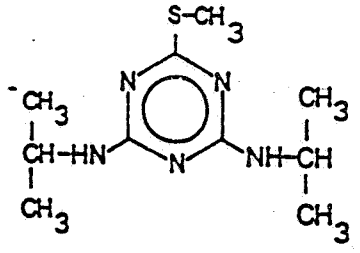
010759

APPENDIX A
Metabolite Numbers and Names
(pp. 27-30)

Metabolite #	Name
GS-11354	2-amino-4-(isopropyl)-6-(methylthio)-s-triazine
GS-26831	2,4-diamino-6-(methylthio)-s-triazine
GS-11526	2-hydroxy-4,6-bis(isopropylamino)-s-triazine
GS-17794	2-amino-4-hydroxy-6-(isopropylamino)-s-triazine
GS-11957	2,4-dihydroxy-6-(isopropylamino)-s-triazine
GS-16158	2,4-bis(isopropylamino)-6-methylsulfonyl-s-triazine
GS-16141	2,4-bis(isopropylamino)-6-methylsulfinyl-s-triazine
GS-11955	2,4-bis(isopropylamino)-6-thio-s-triazine
CGA-10582	2,4-diamino-6-S-(N-acetylcysteine)-s-triazine
Glutathione conjugate of diamino triazine	2,4-diamino-6-S-(glutathione)-s-triazine

APPENDIX B
Chemical Names and Structures
(pp. 27-30, 56-66)

20



PROMETRYN G-34161
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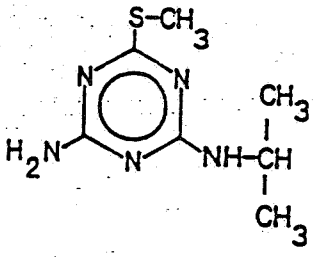
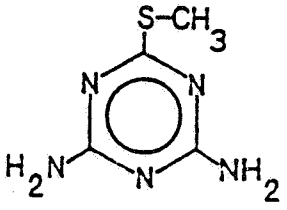
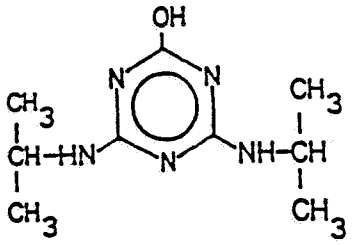
6-(methylthio)-s-triazine



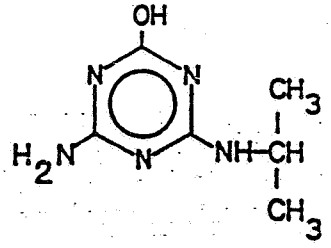
GS 11354
2-amino-4-(isopropyl)-
6-(methylthio)-s-triazine



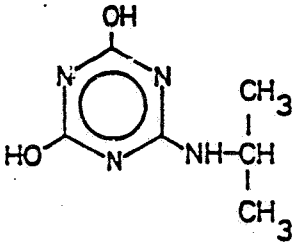
GS 26831
2,4-diamino-6-(methylthio)-
s-triazine



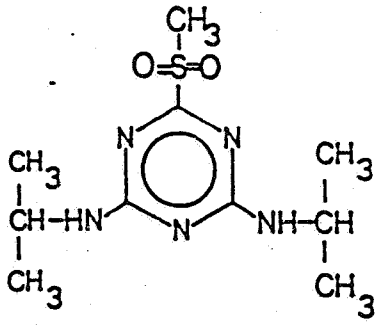
GS 11526
2-hydroxy-4,6-bis(isopropyl amino)-s-triazine



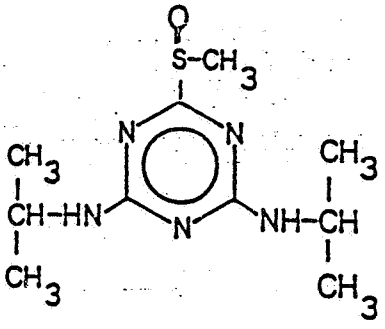
GS 17794
2-amino-4-hydroxy-6-(isopropylamino)-s-triazine



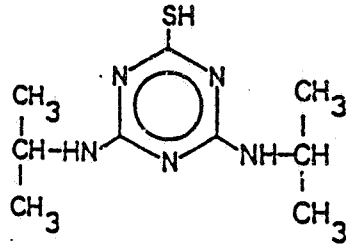
GS 11957
2,4,dihydroxy-6-(isopropylamino)-s-triazine



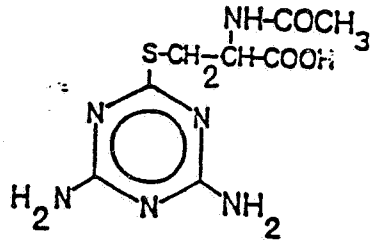
GS 16158
2,4-bis(isopropylamino)-6-methylsulfonyl-s-triazine



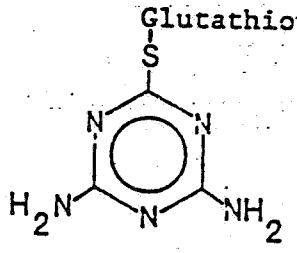
GS 16141
2,4-bis(isopropylamino)-6-methylsulfinyl-s-triazine



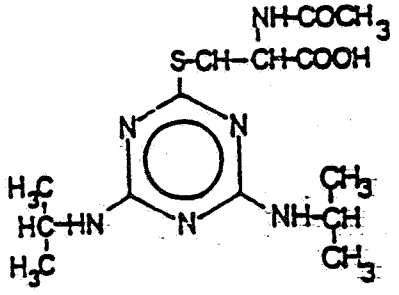
GS 11955
2,4-bis(isopropylamino)-6-thio-s-triazine



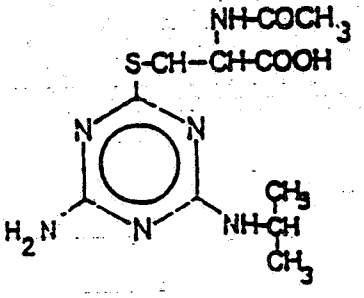
CGA 10582
2,4-diamino-6-S-(N-acetyl cysteine)-s-triazine



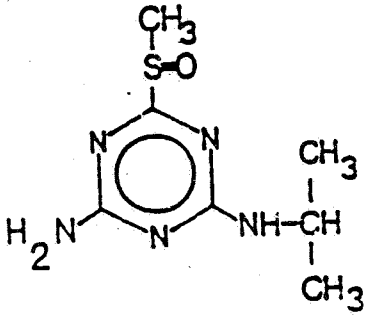
GLUTATHIONE CONJUGATE OF DIAMINO TRIAZINE
2,4-diamino-6-S-(glutathione)-s-triazine



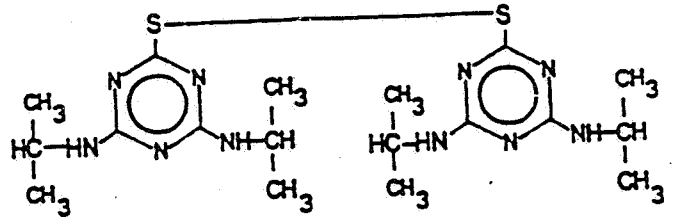
N-ACETYL-CYSTEINE
CONJUGATE
OF PROMETRYN



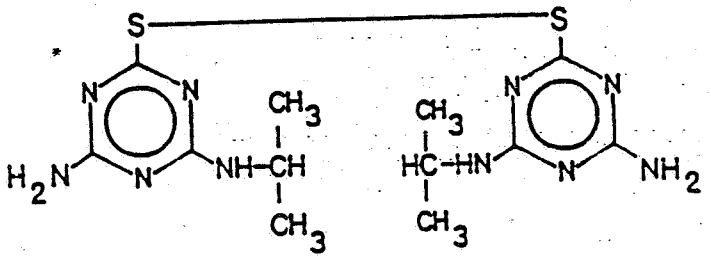
N-ACETYL-CYSTEINE
CONJUGATE
OF GS-11354



GS-14129



S-S DIMER
OF PROMETRYN



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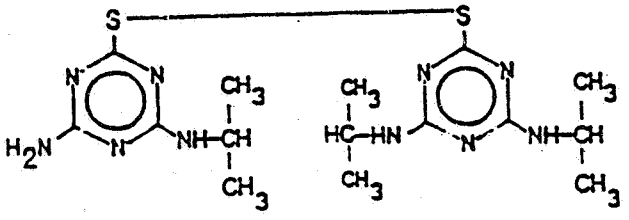

S-S DIMER
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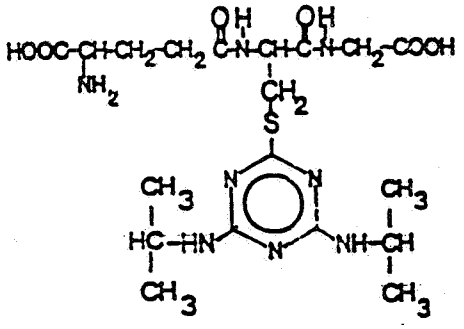
AND GS-11354



GLUTATHIONE
CONJUGATE
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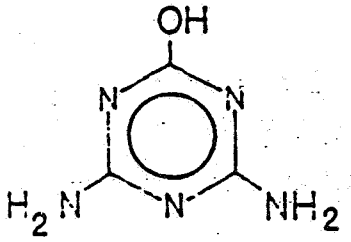
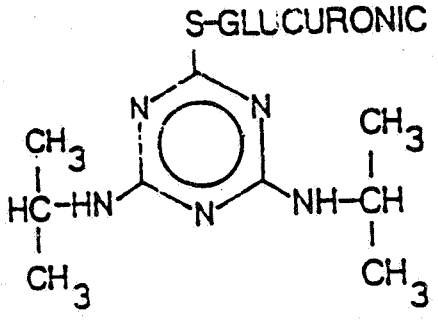
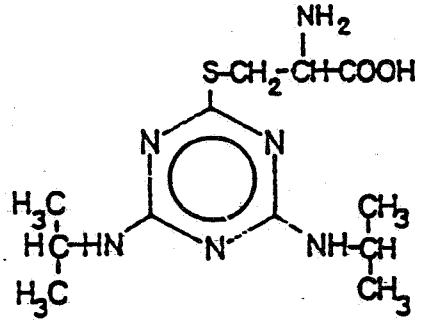


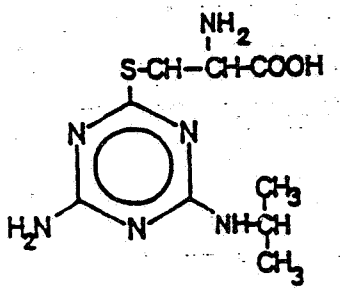
GS-17791



- GLUCURONIC ACID
OF PROMETRYN



CYSTEINE CONJUGATE OF PROMETRYN



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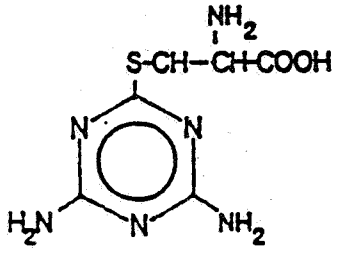
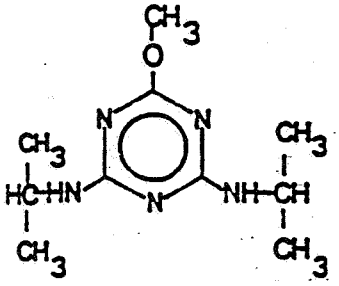


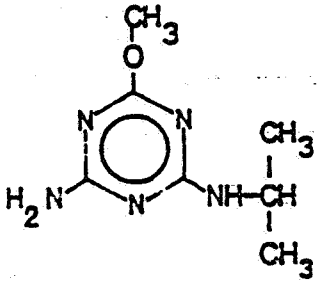
CYSTEINE CONJUGATE OF GS-26831

010759

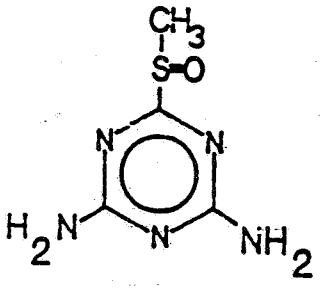


PROMETRON

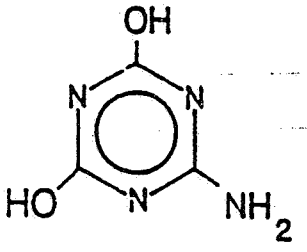
G-31435



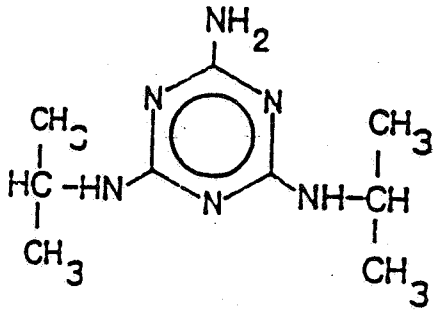
GS-14626



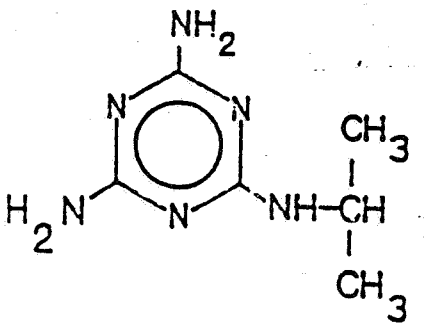
SULFOXIDE
OF GS-26831



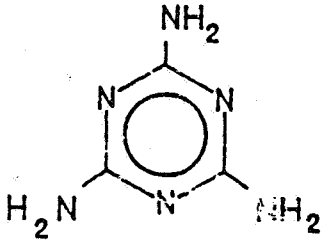
GS-35713



6-NH_2 OF PROMETRYN



6-NH_2 OF GS-11354



MELAMINE