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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **BROMACIL** - Review of Metabolism Study

TO: Mario F. Fiol
PM Team Reviewer (73)
Reregistration Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 11/18/93
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 11/18/93
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 11/19/93
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant:	DuPont
Chemical:	5-Bromo-3-sec-butyl-6-methyluracil
Synonyms:	Bromacil; INN-976
Caswell No.:	111
Shaughnessy No.	012301
DP Barcode:	D193298
Submission:	S444808
ID #:	012301
Case:	818592

Action Requested: Review the attached DuPont submitted study. "Metabolism of Bromacil by Laboratory Rats.

Comment: In response to the data requirements for the Bromacil Registration Standard, the Registrant has submitted a metabolism study, which has been reviewed. The DER is appended.

Bromacil appears to be readily absorbed from the gastrointestinal tract following single oral low [10 mg/kg] and high [1000 mg/kg] doses and repeat low [10 mg/kg] doses. Urine is the primary route of elimination following all dosing schedules except the preconditioning low dose in males, where urine and fecal elimination were ≈ equal. Additionally, Bromacil is extensively metabolized [primarily by hydroxylation at the 6-methyl position and also on the sec-butyl moiety] and rapidly excreted. The hydroxylated metabolites were eliminated as glucuronide conjugates.

Radiolabel was found in all organs/tissues examined, but there was no evidence of accumulation. The majority of the radiolabel found in the blood at termination was associated with the red blood cells [all dosing schedules]. Proposed metabolic pathways were provided.

This study is classified Core Minimum, and it satisfies the guideline requirement (85-1) for a metabolism study.

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Reviewed by: Linda L. Taylor, Ph.D Linda Lee Taylor 11/18/93
Tox. Branch II, Section II, HED (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 11/18/93
Head Section II, Tox. Branch II, HED (H7509C)

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - rats TOX. CHEM. NO. 111

MRID No.: 428252-01

TEST MATERIAL: [Carbonyl-2-^{14}C] Bromacil

SYNONYMS: 2,4(1H,3H)-pyrimidinedione, 5-bromo-6-methyl-3-(1-methylpropyl)-; 5-bromo-6-methyl-3-(1-methylpropyl)-2,4(1H,3H)-pyrimidinedione; 5-Bromo-3-sec-butyl-6-methyluracil

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

SPONSOR: E.I.du Pont Nemours and Company, Inc.

STUDY NO.: HLR # 104-89; DuPont AMR # 834-87

AUTHOR: KT M^{c} Cooey

TITLE OF REPORT: Metabolism of [Carbonyl-2-^{14}C] Bromacil by the Laboratory Rat

REPORT ISSUED: September 13, 1989

QUALITY ASSURANCE: A quality assurance statement and a Good Laboratory Practice compliance statement were provided.

CONCLUSION: Bromacil appears to be readily absorbed from the gastrointestinal tract following single oral low [10 mg/kg] and high [1000 mg/kg] doses and repeat low [10 mg/kg] doses. Urine is the primary route of elimination following all dosing schedules except the preconditioning low dose in males, where urine and fecal elimination were ≈ equal. Additionally, Bromacil is extensively metabolized [primarily by hydroxylation at the 6-methyl position and also on the sec-butyl moiety] and rapidly excreted. The hydroxylated metabolites were eliminated as glucuronide conjugates. Radiolabel was found in all organs/tissues examined, but there was no evidence of accumulation. The majority of the radiolabel found in the blood at termination was associated with the red blood cells [all dosing schedules]. Proposed metabolic pathways were provided.

Classification: Core Minimum. This study satisfies the guideline requirement (85-1) for a metabolism study.

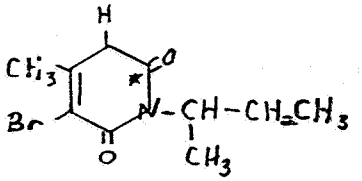
A. MATERIALS

1. Test Compound:

a. Labelled compound - [Carbonyl-2-^{14}C] Bromacil; Purity: >98% [HPLC]; Batch #: Isotopic Compound Inventory # 0238; Specific Activity: 27.2 μCi/mg. Source: Agricultural Products Department, synthesized by DuPont NEN Research Products.

Unlabelled compound - 5-Bromo-3-sec-butyl-6-methyluracil, Bromacil; Batch #: T2D515#19; Purity: ≈98.5%; Description: white to light tan solid; Source: Agricultural Products Department, synthesized by DuPont NEN Research Products.

b. Structure:



2. Test Animals:

Species: Rat
Strain: Crl:CD®BR
Age: between 7 and 9 weeks of age on day of arrival
Weight: ♀ 196-234 grams/♂ 231-365 grams
Source: Charles River Breeding Laboratories, Kingston, NY or Raleigh, NC

B. STUDY DESIGN

1. Dose Administration: There are five phases to this study (described below), which involved 90 rats [18 groups of five rats; 9 groups/sex].

1) **Absorption** - Five rats/sex/group were dosed with 10 or 1000 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight to determine plasma and whole blood kinetics and C_{max} in plasma. These rats were sacrificed at 72- or 96-hours post dose.

2) **Sacrifice at C_{max}** - Five rats/sex/group were dosed with 10 or 1000 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight and sacrificed at the time of average plasma C_{max} for the sex and dosing regimen determined in the **absorption** studies.

3) **Sacrifice at Pre- or Post-C_{max}** - Five rats/sex/group were dosed with (a) 10 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight and sacrificed 24-hours post dose [post-C_{max}]; (b) 1000 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight and sacrificed at the plasma C_{max} of the 10 mg/kg rats for their respective sex (pre-C_{max}).

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4) **90% Excretion** - Five rats/sex/group were dosed with 10 or 1000 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight and sacrificed after ≈ 90% of the dose was excreted or not later than 7 days post dose.

5) **90% Excretion/Preconditioning** - Five rats/sex/group were dosed with 10 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight following dosing for 14 days with nonradiolabeled Bromacil at the same dose level [10 mg/kg]. These rats were sacrificed after ≈90% of the dose was excreted [120 hours].

The rats were quarantined for one week following arrival at the testing facility, and Purina Certified Laboratory Chow® #5002 and water were available ad libitum. The rats were selected for study following the quarantine period, based on weight uniformity; i.e., individual weights were within 10% of the group average weight (sex/dose). Each rat for which excretion data were generated was housed in a "Roth"-type glass metabolism unit [separated urine from feces] immediately after the radiolabeled dose was administered. Rats sacrificed within 24 hours of dosing were housed in wire mesh cages [excreta not monitored for radiolabel]. One rat from each of the low- and high-dose groups [90% excretion studies] was placed into a closed glass metabolism unit designed to trap expired CO_2 and any expired volatile metabolites. Air flow through these units was generated by house vacuum. Incoming air was drawn through sequentially-connected glass columns containing Drierite® and Ascarite® for removal of water and CO_2, respectively. The air exiting the unit passed through two sequential gas-scrubbing bottles, each containing NaOH for trapping expired CO_2. This was followed by an oxidizing furnace housing a quartz-glass tube filled with cupric oxide wire and maintained at ≈600°C. A third gas-scrubbing bottle, also containing NaOH, was connected to the distal end of the oxidizing furnace to trap CO_2 evolved from complete oxidation of any expired volatile metabolites.

2. Dose Preparation and Analysis: There were three dosing regimens [single low, single high, repeat low]. The dosing solutions were prepared in 10% acetone/90% water, v/v, within one hour of dosing. The high doses were suspensions. **Single Low-Dose Phase** - Each rat received a single 10 mg Bromacil/kg body weight dose orally via gavage. [Carbonyl-2-^{14}C] Bromacil was mixed with nonlabeled Bromacil such that each rat received at least 10 μCi ^{14}C radioactivity. One common dosing solution was prepared for each group of 5 rats dosed on a given day, with the concentration being based on the mean body weight of the group [in one case, 10 rats were dosed on a single day and one solution was prepared for the 10 rats]. **Single High-Dose Phase** - Each rat received a single nominal 1000 mg Bromacil/kg body weight dose orally via gavage. [Carbonyl-2-^{14}C] Bromacil

was mixed with nonlabeled Bromacil such that each rat received at least 10 μCi ^{14}C radioactivity. Individual dosing suspensions were prepared for each high-dose rat, which were administered in a volume of 2.0 mL followed by a 1.0 Ml water rinse of the dosing vial. The actual delivered dose to each high-dose rat was determined by subtracting the amount of radioactivity remaining in the dosing vial and syringe from the known amount of radioactivity in each vial. The specific radioactivity of each high dose was known [dpm/mg] and from the calculated amount of radioactivity each rat received, the actual dose was determined. **Repeat Low-Dose Phase** - Each rat was dosed once a day via gavage for 14 consecutive days with 10 mg Bromacil/kg body weight. On the 15th day, each rat received a 10 mg [Carbonyl-2-^{14}C] Bromacil/kg body weight dose via gavage. [Carbonyl-2-^{14}C] Bromacil was mixed with nonlabeled Bromacil such that each rat received at least 10 μCi ^{14}C radioactivity. On each of the dosing days, a common dosing solution was prepared. During the 14-day repeat dosing phase, the volume of solution [≈2.0 mL/rat] was adjusted for individual body weights. Each rat received 2.0 Ml of the radiolabel, which was prepared based on the mean body weight of the five animals.

Test material stability was assessed by analyzing portions of each of the prepared ^{14}C low doses, taken before and after dosing [HPLC using UV detection at 277 nm].

3. Sample Collection: Following dosing, urine and feces were collected at 12, 24, 36, and 48 hours and then every 24 hours thereafter. At each collection, the urine collector was rinsed with water, which was added to the urine sample. The CO_2 trapping solutions were collected and replenished when the urine and fecal samples were collected. Blood samples [0.50 mL] were collected from cannulated rats in the absorption studies at 1, 2, 4, 6, 12, 24, 36, 48, 72, and in one study [♀♀ at high dose] at 96 hours after dosing. Cannulas were surgically inserted into the jugular veins of the rats in the absorption study two days before dosing. At termination for each rat, blood was withdrawn by heart puncture, and portions were separated into plasma and red blood cell fractions. The thyroid, heart, lungs, kidneys, liver, spleen, brain, adrenals, testes or ovaries and uterus, carcass, gastro-intestinal tract with contents, and samples of bone, muscle, fat were excised and weighed. Femurs were excised for bone marrow isolation. Residual feed was weighed and stored until analyzed, and each metabolism unit was thoroughly washed and the washes were stored until analyzed.

4. Sample Analyses: Liquid scintillation counting was conducted with Mark III Model 6882 Liquid Scintillation Counters [Tracor Analytic, Elk Grove, IL.] using Aquasol®-2 scintillation

cocktail. The following samples were assayed directly following the addition of the cocktail: urine, plasma, dose solutions or dilutions, cage washes, CO_2 trapping solutions, fecal extraction samples, liver and kidney extraction samples, and HPLC eluate fractions. Representative samples of blood, lysed red blood cells, tissues, organs, carcasses, feces, contents of the G.I. tract, and residual feed were completely combusted with Packard Model 306 Tissue Oxidizers [Packard Instrument Co., Downers Grove, IL]. Evolved ^{14}C was automatically trapped in Carbo-Sorb® and mixed with Permafluor® V scintillation cocktail for scintillation counting. These samples were thoroughly mixed, minced, or blended before representative portions were removed and weighed for combustion. The sample size did not exceed 0.5 grams; for fat and freeze-dried fecal samples, the sample size did not exceed 0.2 grams. Carcasses were cut into small pieces and blended in water to homogeneity with a Waring blender before combustion. With very small samples [bone marrow, thyroid and adrenals], the entire sample was oxidized. Feces were freeze-dried [VirTis Freezemobile 6] prior to being homogenized, combusted, and analyzed for radioactivity.

(a) Urine and Fecal Pooling: Portions of the urine and fecal samples from rats in the 90% excretion studies were pooled after radioactivity levels were determined for individual samples. Approximately one half of the urine or fecal sample from every rat within a sampling period was pooled per sex for each dosing regimen. The pooled samples were frozen until further analysis for metabolite distribution.

(b) Urine Analysis: The pooled urine samples were thawed and swirled to ensure complete mixing, and portions were prepared for HPLC analysis by filtration through a 0.45 μm Acrodisc® CR disposable filter assembly [Gelman Sciences]. The filtered samples were then added to vials and analyzed for metabolites by HPLC using radiochemical detection.

(c) Enzyme Hydrolysis of Urine from High-Dose Rats: Urine samples were prepared by combining 20% of the male 12-, 24-, 36-, and 48-hour pooled urines and 20% of the female 12-, 24-, 36-, 48-, and 72-hour pooled urines. The two samples were filtered, and portions were incubated with each of the following enzyme preparations:

(1) β-Glucuronidase from Helix pomatia, type H-1 [Sigma # G-0751]. Urine samples were diluted with sodium acetate and adjusted to pH 5.0 with 1.0 N HCl. Approximately 15,000 units of the enzyme were added, and the preparation was incubated for ≈ 18 hours at 37°C in a shaking water bath.

(2) Sulfatase from Abalone entrails, type VIII [Sigma #

S-9754]. Urine samples were diluted as described above under (1). Approximately 400 units of the enzyme were added, and the preparations were incubated as described under (1).

(3) Sulfatase from Aerobacter aerogenes, type VI [Sigma # S-1629]. Urine samples were diluted with Trizma buffer [(tris(hydroxymethyl)aminomethane)] and adjusted to pH 7.1 if necessary. Enzyme was added to give a final concentration of 2.1 units/mL, and the preparation was incubated for ≈18 hours at 37°C.

Control samples without added enzymes were incubated overnight also. Unincubated control samples, as well as the incubated enzyme preparations and their incubated controls were analyzed for metabolite distribution by HPLC using radiochemical detection.

(d) Fecal Extraction: The pooled, freeze-dried fecal samples were thoroughly mixed before weighed portions were transferred to centrifuge tubes for the extraction process. The following sequential extractions were conducted: (1) methylene chloride/methanol, 1/1 [v/v] three times; (2) methylene chloride/methanol/aqueous ammonium carbonate, 3/4/1 [v/v/v] 3 or 4 times; (3) aqueous ammonium carbonate, 2 times. Each extraction solvent/fecal sample was thoroughly mixed by vortexing, sonicated, and centrifuged. The volume of each extract was determined and duplicate portions (0.50 mL) were assayed for radioactivity. The extracts from steps one and two were combined and evaporated to dryness in glass bottles under a gentle nitrogen stream in a warm water bath. The first ammonium carbonate extract was added to the previously evaporated extracts, frozen, and freeze-dried. The second ammonium carbonate extract typically was not pooled with the previous extracts because of low radioactivity levels. Additional extractions with ethanol, acetone, water adjusted to pH 3.4, or ammonium acetate did not remove any appreciable radioactivity from fecal samples in the initial analyses and were, therefore, not continued. To demonstrate exhaustive extraction, the extracted fecal samples were incubated overnight with NaOH in a 37°C water bath, and then the mixture was sonicated, centrifuged, and the NaOH was assayed for radioactivity. The extracted fecal residue was dried, then portions were combusted to determine the total unextracted radioactivity.

(e) Reconstitution of Fecal Extracts: The evaporated, freeze-dried fecal extracts were extracted with methanol [3X] by ultrasonication and separated from particulates by centrifugation. The methanol extracts were pooled, evaporated to dryness, reconstituted in methanol, and filtered through a 0.2 μm Acro LC13 filter assembly before analysis by HPLC/radiomonitoring.

(f) Tissue/Organ Analysis: Plasma, liver, and kidney samples from the following studies were analyzed for metabolite distribution: (1) male low dose 1- and 24-hour sacrifice; (2) female low dose 2- and 24-hour sacrifice; (3) male high dose 1- and 12-hour sacrifice; and (4) female high dose 2- and 12-hour sacrifice. Due to the low levels of radioactivity remaining in the plasma, livers, and kidneys from rats in the 90% excretion studies, further analysis of these samples was not feasible.

[a] Plasma Samples: Samples were thawed and equal fractions [30-50%] were pooled for the 5 rats in a given study. Portions of the pooled plasma samples were added to Centriflo® membrane cones and centrifuged at 4°C. The plasma fraction passing through the cone was collected, the volume recorded, and a portion was assayed for radioactivity. The plasma residue remaining in the cone was washed successively with Dulbecco's phosphate-buffered saline [PBS], K_2HPO_2, and ethanol. After centrifugation, the volume of each wash was recorded and a portion assayed for radioactivity. The ethanol washes were evaporated to dryness and to them were added the remaining washes and filtered plasma. These were then frozen and freeze-dried. Each freeze-dried sample was reconstituted in PBS, most were filtered to remove unsolubilized particulates, and all were assayed by HPLC using radiochemical detection.

[b] Liver and Kidney Samples: Samples were thawed and ≈ half of the sample was pooled for the 5 rats in a given study. About half of each pooled sample was frozen and freeze-dried. All of the freeze-dried kidney samples and 0.5 to 1.5 grams of the freeze-dried liver samples were placed into centrifuge tubes and sequentially extracted with (1) methylene chloride/methanol, 1/1 [v/v] 2-3 times; (2) methanol, zero or one time; (3) methylene chloride/methanol/ammonium carbonate, 3/4/1 [v/v/v] 1 or 2 times.

Each extraction solvent was thoroughly mixed with the liver or kidney sample by vortexing, sonicated, and centrifuged to separate solvent from solid residue. The volume of each extraction was determined and duplicate portions were assayed for radioactivity. Extracts containing appreciable radioactivity were evaporated to dryness. The extracted kidney and liver residues were dried, then portions combusted in order to determine the total unextracted radioactivity. Radioactivity in the evaporated solvent extracts was resolubilized with methanol and filtered before HPLC analysis.

(g) Liquid Chromatographic Analysis/Metabolite Purification: HPLC analyses were conducted with a Hewlett-Packard Model 1090

liquid chromatograph equipped with an autosampler. The column was a Hamilton PRP-1, 305 x 7 mm, 10μm packing equipped with a PRP-1 guard cartridge; radiochemical detection: Ramona-LS radioactivity monitor with a calcium fluoride packed cell for radicactivity monitoring; UV detection: Diode Array Detector at 277 nm; Mobile Phase: There were three systems of varying % of acetonitrile/ammonium acetate [described on page 30 of the report; System A for urine analysis; System B for fecal, liver, and kidney extracts and plasma; and System C for urine and fecal, liver and kidney extracts. A Gibson model 202 fraction collector was used to collect metabolite fractions from multiple injections of a pool of male high dose 36- and 48-hour fecal extracts and from pools of male and female high dose 24- and 36-hour urine. Portions of each collected fraction were analyzed by liquid scintillation counting to clarify the metabolite profile. Contiguous fractions containing the same radiolabeled component were pooled and evaporated to dryness and stored (≈-20°C) until mass spectral analyses were conducted.

(h) Thin Layer Chromatography (TLC) Analysis: Selected urine samples and fecal, liver, and kidney extracts were analyzed by TLC to provide a second chromatographic identification for Bromacil. Portions of each sample were applied to silica gel TLC plates and developed in ethyl acetate. The TLC plates were analyzed with a Berthold LB-2842 automatic TLC-Linear Analyzer to visualize the radiolabeled components.

(i) Mass Spectral Analysis: Mass spectral analyses of reference standards and urinary and fecal metabolites were conducted with a Finnigan Model 4000/4500 or Model 8230 mass spectrometer.Samples were analyzed by one or more of the follcwing methods: (1) electron impact [EI] analysis using an electron energy of 70 eV; (2) desorption chemical ionization [DCI] using a platinum or rhenium probe tip with methane reagent gas and an electron energy of 100 eV; (3) on-line HPLC/MS using a Vestec Series 701 thermospray [TS] interface equipped with a Hitachi HPLC system [conditions defined on page 31 of the report]; (4) continuous flow fast atom bombardment [FAB] using an Ion Tech FAB gun with xenon gas at 8KV anode voltage, 200°C ion source temperature, under liquid chromatographic conditions defined on page 31 of the report.

5. Statistics: Statistical comparisons between means were evaluated using the Student's t distribution [two-tailed], using RS/1 [Release 3.0] from BBN Software Products Corporation.

C. RESULTS

1. Dose Suspensions: No decomposition was observed. Bromacil was reported to have averaged >98% of the non-solvent peak areas

in the chromatograms.

2. Administered Dose: The mean dose [mg/kg] and specific activity of the dose for each of the phases of the study are presented in Table A.

Table A. Administered Dose

DOSE LEVEL Study Group	ABSORPTION STUDY		90% EXCRETION STUDY		2-WK PRECONDITIONING	
	males	females	males	females	males	females
LOW dose(mg/kg) spec. act♦	9.96 19700	10.02 18200	10.02 20700	9.98 19700	10.08 11400	10.06 17400
HIGH dose(mg/kg) spec. act♦	812 180.5	893 190.2	875 184.6	851 190.9	N/A	N/A
DOSE LEVEL Study Group	SACRIFICE at C_{max}		SACRIFICE 24 hrs post dose		SACRIFICE at pre-C_{max}	
	Males	Females	Males	Females	Males	Females
LOW dose(mg/kg) spec. act♦	10.04 16100	10.14 21200	10.10 16100	9.88 21200	N/A	N/A
HIGH dose(mg/kg) spec. act♦	930 148.0	926 181.0	N/A	N/A	921 141.0	922 164.1

♦ specific activity DPM/μG; N/A not applicable

3. Excretion of Radiolabel in Urine: The cumulative percent of the dose excreted in the urine following single low and high doses and repeated dosing at the low dose is shown in Table B. Following the single low dose exposure, ≥ 99% of the amount excreted in the urine was excreted by 72 hours post dose by both sexes. At the single high-dose level, males had excreted ≥ 99% by 96 hours and the females had achieved this value by 120 hours post dose. Following repeat dosing, males excreted ≥ 99% by 72 hours and females by 96 hours. Taking into consideration the fact that ≥ 50% of the administered dose was excreted via the urine and using the cumulative urine data, a rough plot of the urinary data [by this reviewer] suggests an elimination half-life of ≈ 13 hours [both doses and both sexes].

TABLE B. Elimination of Radiolabel via Urine ♦(♣)

Sex/Dose Level/ Phase/ Time (hours)	MALES		FEMALES	
	Low Dose	High Dose	Low Dose	High Dose
Single Dose♦				
12	34.5♣(64)♣	4.5(8)	28.6(51)	2.9(5)
24	49.8(93)	16.3(28)	47.0(84)	9.8(16)
36	51.8(96)	32.7(57)	51.6(92)	19.6(33)
48	52.7(98)	49.7(87)	54.0(96)	32.9(55)
72	53.3(99)	55.2(96)	55.3(99)	54.6(92)
96	53.6(99.8)	56.1(98)	55.7(99)	57.4(96)
120	53.7(100)	56.6(99)	56.0(100)	58.9(99)
144	-	56.9(99)	-	59.5(100)
168	-	57.3(100)	-	-
Repeat Dose♦				
12	23.1(51)		29.4(52)	
24	39.5(87)		48.7(85)	
36	42.6(94)		52.4(92)	
46	44.2(97)		54.8(96)	
72	45.0(99)		56.0(98)	
96	45.3(99.6)		56.6(99)	
120	45.5(100)		57.0(100)	
Single Dose♥				
12	26.2(59)	5.5(13)	36.8(59)	5.2(9)
24	39.5(89)	19.2(46)	54.2(87)	16.7(30)
36	42.0(95)	31.1(74)	58.5(95)	29.3(53)
48	43.5(98)	37.3(89)	60.8(98)	40.8(74)
72	44.4(100)	41.9(100)	61.9(100)	53.6(97)
96	-	-	-	55.3(100)

♦ 90% Excretion study; ♥ Absorption study; ♣ cumulative % of dose excreted in urine; ♣ (% of total amount excreted in urine)

4. Excretion of Radiolabel in the Feces: The cumulative percent of the dose excreted in the feces following the various dosing regimens is listed in Table C. The majority [≥90%] of that eliminated via the feces was excreted by 24 hours post dose by the low-dose males; by 36 hours post dose by low-dose females; and between 72-96 hours post dose by the high-dose rats [both sexes]. Following the multiple low dose exposure, 88-89% was eliminated by 36 hours post dose, 97% by 48 hours post dose [both sexes].

TABLE C. Elimination of Radiolabel in Feces ♦(♣)

Group time interval (hours)	MALES		FEMALES	
	Low Dose	High Dose	Low Dose	High Dose
Single Dose				
12	0.7♦(2)♣	0.8(2)	4.4(12)	1.2(4)
24	37.1(91)	7.1(21)	28.8(80)	4.7(17)
36	39.3(97)	15.5(46)	32.6(90)	10.7(38)
48	40.3(99)	24.6(73)	35.3(98)	16.0(57)
72	40.6(99.8)	31.1(93)	35.9(99)	24.2(86)
96	40.7(100)	32.2(96)	36.1(99.7)	26.7(95)
120	40.7(100)	32.8(98)	36.2(100)	27.6(98)
144	-	33.1(99)	-	28.1(100)
168	-	33.5(100)	-	-
Repeat Dose				
12	0.1(0.2)		1.2(3)	
24	32.8(72)		29.0(78)	
36	40.8(89)		32.8(88)	
48	44.6(97)		36.1(97)	
72	45.5(99)		36.8(99)	
96	45.7(99.8)		37.1(99.5)	
120	45.8(100)		37.2(100)	
144	-		-	
168	-		-	

♦ cumulative % of dose excreted in feces;
♣ (% of total amount excreted in feces)

5. Radiolabel in the Cage Wash: The amount of radiolabel found in the cage washes in the various studies ranged from 0.5% to 4.6% of the dose.

6. Radiolabel in the Tissues: At termination [120-168 hours post dose], the highest levels of Bromacil equivalents were observed in whole blood, red blood cells, liver, and kidney in all six studies in which tissue levels were measured [low- and high-dose 90% excretion studies/both sexes and the preconditioning low-dose studies/both sexes]. Although for the most part the high-dose females displayed higher tissue values than the high-dose males, the differences initially and at termination may be due to the difference in sacrifice times [2 and 144 hours for ♀♀ vs 1 and 168 hours for ♂♂]. With the exception of RBC's in the high-dose groups, the levels of radiolabel declined with time in all tissues in both sexes at both dose levels [Table D]. At termination, the levels of radiolabel in the RBC's in the high-dose rats were greater than the earlier time points. With the exception of the carcass [0.3-1.2%], the amount of radiolabel in the tissues/organs was ≤0.1 % of the administered dose at termination [Table E].

TABLE D. Distribution of Radiolabel in Tissues (µg equivalents/g or mL)

90% Excretion STUDY						
SINGLE LOW DOSE	MALES			FEMALES		
TISSUE/Sacrifice time	1 hour	24 hours	120 hours	2 hours	24 hours	120 hours
Blood	4.3	0.297	0.111	2.8	0.549	0.208
RBC	0.8	0.133	0.098	0.4	0.222	0.193
Plasma	3.7	0.155	0.003	2.5	0.353	0.005
Thyroids	13.6	0.627	<0.2	8.9	0.937	0.106
Adrenals	19.6	0.297	<0.09	12.1	0.623	0.066
Heart	5.1	0.146	0.026	3.8	0.387	0.044
Lungs	4.7	0.168	0.030	3.5	0.419	0.070
Liver	14.6	0.605	0.068	7.1	1.07	0.084
Spleen	4.2	0.116	0.024	3.1	0.317	0.072
Kidneys	19.7	0.617	0.122	5.6	0.943	0.128
GIT	23.1	1.58	0.010	14.8	2.71	0.024
Testes	3.0	0.082	<0.007	3.9	0.394	0.015
Fat	8.2	0.060	<0.008	4.8	0.161	0.009
Skin	3.5	0.130	0.020	2.4	0.368	0.070
Muscle	3.5	0.073	0.004	2.4	0.208	0.007
Bone Marrow	3.1	0.100	<0.04	2.5	0.244	<0.08
Brain	3.5	0.040	0.005	2.2	0.150	0.008
Carcass	3.4	0.135	0.030	2.5	0.471	0.045
SINGLE HIGH DOSE	MALES			FEMALES		
TISSUE/Sacrifice time	1 hour	12 hours	168 hours	2 hours	12 hours	144 hours
Blood	68.3	48.2	13.7	80.6	60.0	22.7
RBC	12.9	9.5	13.4	14.3	10.6	21.2
Plasma	54.6	34.7	<0.4	68.4	48.2	0.7
Thyroids	244	111	17.5	262	171	9.3
Adrenals	305	210	<10	284	195	<8
Heart	95.8	40.4	3.6	107	66.4	4.2
Lungs	84.9	41.7	3.5	115	78.3	6.9
Liver	176	115	4.8	182	132	6.9
Spleen	57.0	33.8	3.7	86.5	68.1	10.7
Kidneys	150	124	6.3	131	91.3	8.7
GIT	1130	1020	1.4	939	678	2.8
Testes/Ovaries/Uterus	47.2	27.4	<0.7	117	66.1	1.5
Fat	142	62.2	<0.8	176	68.8	1.0
Skin	54.2	24.6	1.6	64.9	42.6	6.0
Muscle	58.4	25.1	0.4	74.2	43.8	0.7
Bone Marrow	70.8	26.7	<3	72.4	44.2	7.9
Brain	53.8	18.7	<0.5	66.8	38.1	0.7
Carcass	64.8	31.5	3.6	73.4	46.1	12.4
PRECONDITIONING	MALES			FEMALES		
TISSUE/Sacrifice time	120 hours			120 hours		
Blood	0.120			0.227		
RBC	0.104			0.210		
Plasma	0.007			0.008		
Thyroids	<0.1			<0.2		
Adrenals	<0.1			<0.08		
Heart	0.029			0.056		
Lungs	0.037			0.069		
Liver	0.111			0.076		
Spleen	0.037			0.076		
Kidneys	0.150			0.151		
GIT	0.044			0.025		
Testes/Ovaries/Uterus	<0.01			0.015		
Fat	<0.02			0.009		
Skin	0.089			0.073		
Muscle	0.008			0.008		
Bone Marrow	<0.07			<0.06		
Brain	<0.008			0.007		
Carcass	0.090			0.051		

SPECIFIC RADIOACTIVITY
90% Excretion Study: low dose 207 dpm/µg ♂♂/19700 dpm/µg ♀♀
high dose 182.7-188.2 dpm/µg ♂♂/184.2-199.7 dpm/µg ♀♀
Preconditioning Study: low dose 11400 dpm/µg ♂♂/17400 dpm/µg ♀♀

TABLE E. Distribution of Radiolabel in Tissues (% administered dose)

90% Excretion STUDY						
SINGLE LOW DOSE	MALES			FEMALES		
TISSUE/Sacrifice time	1 hour	24 hours	120 hours	2 hours	24 hours	120 hours
Total in tissues	44.5	2.1	0.3	28.7	5.2	0.4
Contents in GI tract	46.9	6.0	ND	62.1	11.8	ND
TOTAL	91.6	8.1	ND	90.8	17.0	ND
SINGLE HIGH DOSE	MALES			FEMALES		
TISSUE/Sacrifice time	1 hour	12 hours	168 hours	2 hours	12 hours	144 hours
Total in tissues	10.9	7.0	0.5	11.8	7.2	1.2
Contents in GI tract	83.2	88.0	ND	93.5	90.4	ND
TOTAL	94.1	95.1	ND	105.3	97.6	ND

ND = no data

7. Radiolabel in the Blood: In the absorption studies, the average maximum µg equivalents of Bromacil in plasma [C_{max}) and whole blood (C_{max}) were observed at one hour [♂♂]/two hours [♀♀] post dose following low-dose exposure. Following high-dose exposure, plasma C_{max} [♂♂ and ♀♀] and whole blood C_{max} [♂♂] were reached at 12 hours post dose, while whole blood C_{max} was reached at 24 hours in females. Approximately 85% of the radiolabel in the blood during the first 6 hours post dose at the low dose level [both sexes] was found in the plasma, and after 24 hours, less than 50% was found in the plasma. At the high dose, the percent in plasma decreased at a slower rate than at the low dose, with males displaying 49% and females 64% of the radiolabel in the blood at 36 hours post dose. At sacrifice [72 ♂/96 ♀ hours], the average amount of radiolabel in plasma accounted for <10% of the whole blood level at both dose levels. The data were presented graphically [Figures 2-9, appended]. The author stated that at the low dose, both sexes exhibited a non-first-order pattern of decline of equivalents in plasma, while at the high dose a first-order decline was observed. At termination, the majority [88-94%] of the radiolabel in the blood was associated with the RBC's.

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Dose/Sex/ Time (hr)/ Fraction	Table G. Concentration in Blood [µg equivalents/mL of Blood]			
	LOW DOSE		HIGH DOSE	
	males	females	males	females
Plasma				
1	4.23(85)♦	4.40(85)	42.1(77)	75.0(83)
2	2.96(80)	4.51(85)	58.8(86)	97.1(84)
4	1.60(81)	4.23(85)	49.9(73)	98.9(84)
6	1.26(86)	3.64(85)	69.6(83)	91.5(74)
12	0.69(77)	1.52(82)	116(83)	106(83)
24	0.12(48)	0.33(54)	84.1(68)	101(75)
36	0.025(18)	0.085(25)	22.0(49)	57.5(64)
48	0.014(11)	0.041(16)	10.5(35)	24.8(64)
72	0.008(7)	0.015(9)	1.0(6)	7.1(19)
96	-	-	-	1.5(8)
RBC				
1	0.73(15)	0.80(15)	12.5(23)	15.8(17)
2	0.72(20)	0.78(15)	9.9(14)	18.2(16)
4	0.37(19)	0.75(15)	18.4(27)	18.6(16)
6	0.21(14)	0.63(15)	14.2(17)	31.2(25)
12	0.21(23)	0.33(18)	22.3(16)	20.4(16)
24	0.13(52)	0.28(46)	38.5(31)	32.9(25)
36	0.11(82)	0.26(76)	23.1(51)	32.7(36)
48	0.12(92)	0.21(84)	19.3(65)	28.8(53)
72	0.10(91)	0.15(88)	16.8(94)	29.5(81)
96	-	-	-	17.6(92)
Blood				
1	4.96	5.20	54.6	90.8
2	3.68	5.30	68.7	115
4	1.97	4.98	68.3	118
6	1.47	4.27	83.9	123
12	0.90	1.85	139	127
24	0.25	0.61	123	134
36	0.14	0.34	45.2	90.2
48	0.13	0.25	29.8	53.6
72	0.11	0.17	17.8	36.6
96	-	-	-	19.1

♦ % of Bromacil equivalents in blood found in plasma

8. Material Balance: Absorbed Dose: The amount of radiolabel absorbed (calculated as the sum of the percent of the administered dose in urine, cage wash, expired air, and tissues using the single dose 90% excretion data and the preconditioning dose data) ranged from 46.9 to 64.2%. The ratio of radiolabel absorbed at the two dose levels was comparable to the ratio of the dose levels; i.e., ≈ 100 [105-123]. The total amount of radiolabel recovered averaged 93.8% [range of 83.3-100.8%].

TABLE N. Summary of Elimination and Distribution of Radiolabel

Dose Group Study♦	% AD Urine	% AD Feces	% AD Expired Air♦	% AD Tissues/ Carcass	% AD GIT	% AD Cage Wash	% AD Total Excreted	% AD Total Recovered
90% Excretion								
LOW								
♂♂	53.7	40.7	0.1	0.3	<0.1	0.5	94.8	95.2
♀♀	56.0	36.2	0.1	0.4	<0.1	0.8	93.0	93.5
90% Excretion								
HIGH								
♂♂	57.3	33.5	0.4	0.5	0.1	2.2	93.1	93.6
♀♀	59.6	28.0	0.4	1.2	0.1	3.0	90.7	91.9
Preconditioning								
♂♂	45.5	45.8	0.1	0.7	0.1	0.6	91.9	92.7
♀♀	57.0	37.1	0.1	0.5	0.1	1.4	95.6	96.2
Absorption								
LOW			N/A	N/A	N/A			N/A
♂♂	44.4	40.1	-	-	-	2.1	86.6	-
♀♀	61.9	29.8	-	-	-	1.6	93.4	-
Absorption								
HIGH			N/A	N/A	N/A			N/A
♂♂	41.9	28.9	-	-	-	1.1	72.0	-
♀♀	55.3	25.2	-	-	-	4.6	85.0	-

♦ sacrifice times [hrs]: 90% excretion & preconditioning studies-LOW=120; HIGH=168 ♂/144 ♀; absorption studies-LOW ♂&♀, HIGH ♂=72; HIGH ♀=96; ♦ one rat value

10. Body-Weight/Body-Weight Gain: The range of body weights for the various phases of the study are shown in the table below. Only starting weights were provided, so body-weight gains in the preconditioning study could not be calculated.

Table I. Body Weight Data [grams]

Dose Level Study Group	absorption study		90% excretion study		2-wk preconditioning	
	males	females	males	females	males	females
LOW						
range	229-247	216-250	223-239	212-225	351-376	237-260
mean	235	230	231	219	365	251
HIGH						
range	241-255	225-245	236-243	222-241	N/A	N/A
mean	245	234	241	233		
Dose Level Study Group	**sacrifice at C_{max}**		**sacrifice 24 hrs post dose**		**sacrifice at pre-C_{max}♦**	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**
LOW						
range	267-280	209-216	260-280	210-222	N/A	N/A
mean	272	212	270	217		
HIGH						
range	234-246	191-204	N/A	N/A	239-261	207-242
mean	240	196			252	217

♦ ♂♂ sacrificed one hour post dose; ♀♀ sacrificed two hours post dose

11. Metabolite Distribution: **URINE** - Analysis of the pooled urine samples indicated that Bromacil was extensively metabolized after oral administration to rats of both sexes at dose levels of 10 and 1000 mg/kg. The major urinary metabolite in the low- and high-dose 90% excretion and low repeat-dose studies for both sexes was the glucuronide conjugate of Metabolite A [14.1-17.6% AD]. Other major identified radiolabel compounds in the urine were Metabolites A, C, D, 6-demethyl bromacil, and the glucuronide conjugates of Metabolites C and D. Unaltered Bromacil accounted for ≤0.4% of the administered dose and was found only in the 12- and 36-hour urine samples. Four other radiolabeled components, three of which did not contain bromine, were tentatively identified, and three had insufficient data for tentative identification (see Table J).

TABLE J. Distribution of Radiolabeled Components in Urine (% AD)

90% Excretion STUDY				
SINGLE DOSE	MALES		FEMALES	
Radioactive Component	Low	High	Low	High
Unknown 1	2.1	2.1	1.3	1.6
Glucuronide of Metabolite D	6.7	7.1	5.7	6.6
Glucuronide of Metabolite C	2.1	1.7	1.8	1.6
5M-6HM-B♦	5.0	7.0	5.6	5.5
6-Demethyl Bromacil	4.0	5.1	3.9	5.0
Glucuronide of Metabolite A	16.1	16.5	16.2	17.6
5MS-6HM-B♦	3.3	4.7	3.0	5.9
Unknown 2	1.1	0.7	0.9	0.5
Metabolite D	3.8	2.4	8.1	4.0
Metabolite C	2.7	2.1	3.1	1.5
6MS-B♦	2.3	1.7	2.3	2.1
5MS-6A-B♦	0.7	0.8	0.8	1.2
Metabolite A	2.1	2.7	1.1	1.2
Bromacil	0.1	<0.1	0.2	<0.1
Unknown 3	0.4	-	-	-
Ave. % AD recovered♥	52.8	55.2	54.0	54.7
PRECONDITIONING STUDY				
REPEAT DOSE	MALES		FEMALES	
Radiolabeled Component	Low		Low	
Unknown 1	2.2		1.3	
Glucuronide of Metabolite D	4.4		6.2	
Glucuronide of Metabolite C	1.6		1.8	
5M-6HM-B♦	5.4		7.0	
6-Demethyl Bromacil	3.3		5.1	
Glucuronide of Metabolite A	14.1		14.6	
5MS-6HM-B♦	2.8		2.8	
Unknown 2	1.4		1.0	
Metabolite D	3.3		7.7	
Metabolite C	1.9		3.0	
6MS-B♦	1.9		2.2	
5MS-6A-B♦	0.5		0.4	
Metabolite A	1.0		1.4	
Bromacil	0.4		0.1	
Unknown 3	-		-	
Ave. % AD Recovered♥	44.2		54.8	

♦ tentative id based on limited mass spectral data only; ♥ value is average % of administered dose [AD] recovered in pooled urine samples for 5 rats

At the low dose in both sexes, the "peak" level for most of the metabolites occurred at 12 hours, the first time point measured [Tables 47 & 48 of report, copy appended]. The other metabolites displayed "peaks" at 24 hours. Following the repeat dosing, "peak" values were observed at either the 12- or 24-hour time point, similar to the single low-dose groups [Tables 51 & 52 of report, appended]. At the high dose in males, the "peak" level was observed after 24, 36, or 48 hours, with the levels declining by 72 hours [Table 49 of report, appended]. In females at the high dose, nearly all of the metabolites showed "peak" values at 72 hours, the last time point measured [Table 50 of report, appended].

FECES - Extraction efficiency of radiolabel from freeze-dried fecal samples was reported as >80%, with the 12-hour samples displaying the highest extraction efficiencies [>94%]. The distribution of radiolabeled compounds in the feces is shown in Table K. The identified radiolabeled compounds in the feces were Metabolites A, C, and D, the glucuronide conjugates of these metabolites, and Bromacil. Some of the de-brominated metabolites tentatively identified in urine were present in the fecal extracts also. Unextracted radiolabel accounted for 3.7 to 7.3% of the administered dose.

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TABLE K. Distribution of Radiolabeled Components in Feces (% AD)

90% Excretion STUDY				
SINGLE DOSE	MALES		FEMALES	
Radioactive Component	Low	High	Low	High
Bromacil	1.8	1.0	1.2	1.2
Metabolite A	4.4	4.3	7.0	5.8
Metabolite C	2.6	0.7	1.5	1.0
Metabolite D	5.6	3.4	4.9	2.8
Glucuronide of Metabolite A	2.7	2.7	2.0	1.7
Glucuronide of Metabolite D	2.7	3.1	2.0	2.6
Glucuronide of Metabolite C	2.3	-	1.3	-
5M-6HM-B♦	5.3	3.4	5.1	2.8
5MS-6HM-B♦	2.5	1.3	1.6	1.2
5MS-6A-B♦	-	0.6	-	0.4
Unknown 4	-	0.5	-	0.3
Unknown 5	1.5	0.4	0.8	0.2
Unknown 6	-	1.1	-	0.6
Unknown 7	-	1.4	0.1	0.5
Unknown 8	2.6	2.1	1.4	1.5
Unknown 9	1.2	-	-	-
Unknown 10	-	0.8	0.8	0.3
Unknown 11	-	-	0.2	-
Unknown 12	-	-	-	-.1
Unknown 13	-	-	-	-
Unknown 14	-	-	-	-
Unextracted	4.0	4.4	5.3	3.7
Ave. % AD recovered▼	39.3	31.2	35.3	25.6

PRECONDITIONING STUDY		
REPEAT DOSE	MALES	FEMALES
Radiolabeled Component	Low	Low
Bromacil	1.2	1.2
Metabolite A	3.1	4.2
Metabolite C	2.0	1.6
Metabolite D	2.9	4.4
Glucuronide of Metabolite A	3.2	1.3
Glucuronide of Metabolite D	4.3	3.8
Glucuronide of Metabolite C	-	-
5M-6HM-B♦	8.8	6.4
5MS-6HM-B♦	2.0	2.4
Unknown 4	-	1.0
Unknown 5	1.5	0.8
Unknown 6	1.8	-
Unknown 7	1.1	1.2
Unknown 8	2.7	1.8
Unknown 9	-	-
Unknown 10	-	-
Unknown 11	-	-
Unknown 12	-	-
Unknown 13	1.9	-
Unknown 14	9.9	-
Unextracted	7.3	6.2
Ave. % AD recovered▼	44.6	36.0

♦ tentative id based on limited mass spectral data only;
▼ value is average % of AD recovered in pooled urine samples for 5 rats [36/72/48/96/48/48 hours]

PLASMA - In the pooled plasma samples, Bromacil was detected only in the low-dose animals at the 1 hour [♂♂]/2 hour [♀♀] sacrifices. Additionally, the glucuronide of Metabolites A and D and Metabolites A and D were detected in the low-dose males [1 hour sample] and in the low- and high-dose females [2-hour

sample] and at other time points, as shown in Table L.

TABLE L. Distribution of Radiolabeled Components in Plasma (% RD♦)

ABSORPTION STUDY				
SINGLE DOSE	MALES		FEMALES	
Radioactive Component/time of sacrifice	1-hour	24/12-hour	2-hour	24/12-hour
10 mg/kg				
Bromacil	48.5	-	39.8	-
Metabolite A	20.7	-	30.7	90.3
Metabolite D	8.4	-	11.5	-
Glucuronide of Metabolite A	11.0	-	10.7	7.9
Glucuronide of Metabolite D	6.8	-	3.2	-
1000 mg/kg				
Bromacil	-♦	-	-	-
Metabolite A	99.2	67.4	47.6	94.5
Metabolite D	-	4.2	27.0	-
Glucuronide of Metabolite A	-	25.6	24.3	5.5
Glucuronide of Metabolite D	-	-	1.2	-

♦ % of filtered plasma radioactivity; ♦ levels too low to be meaningful or not observed

LIVER - Solvent extraction of pooled liver samples released >88% of the radiolabel in all but one instance [low-dose male 24-hour sacrifice, 75.8%]. Intact Bromacil and Metabolite A were found in all liver extracts [Table M].

TABLE M. Distribution of Radiolabeled Components in Liver Samples (% RE♦)

SINGLE DOSE	MALES		FEMALES	
Radioactive Component/time of sacrifice	1-hour	24/12-hour	2-hour	24/12-hour
10 mg/kg				
Bromacil	78.8	15.5	65.1	16.0
Metabolite A	21.2	29.0	29.0	48.8
Metabolite D	-	14.3	6.0	15.3
Glucuronide Conjugate of Metabolite A	-	-	-	8.4
Glucuronide Conjugate of Metabolite D	-	9.4	-	11.5
Glucuronide Conjugate of Metabolite C	-	7.2	-	-
Unknown	-	24.7	-	-
1000 mg/kg				
Bromacil	21.2	70.9	77.2	51.6
Metabolite A	39.0	29.1	22.8	48.4
Metabolite D	-	-	-	-
Glucuronide Conjugate of Metabolite A	7.3	-	-	-
Glucuronide Conjugate of Metabolite D	19.6	-	-	-
Glucuronide Conjugate of Metabolite C	7.5	-	-	-
Unknown	5.4	-	-	-

♦ % extracted liver radioactivity; ♦ not observed

KIDNEY - Similar extraction efficiencies [>82%] for pooled freeze-dried kidney samples were observed as those for the liver, with the low-dose male 24-hour sacrifice again displaying the lowest efficiency [68.5%]. Bromacil and Metabolite A were the major radiolabeled compounds found in the kidney extracts [Table N].

TABLE II. Distribution of Radiolabeled Components in Kidney Samples (% RE♦)

SINGLE DOSE	MALES		FEMALES	
Radioactive Component/time of sacrifice	1-hour	24/12-hour	2-hour	24/12-hour
10 mg/kg				
Bromacil	79.4	-♦	48.6	77.8
Metabolite A	5.9	-	20.6	22.2
Metabolite D	3.4	-	7.4	ND
Metabolite C	ND	-	1.2	ND
Glucuronide Conjugate of Metabolite A	4.5	-	9.7	ND
Glucuronide Conjugate of Metabolite D	3.7	-	5.4	ND
5M-6HM-B	3.1	-	7.1	ND
1000 mg/kg				
Bromacil	71.1	53.0	ND	37.0
Metabolite A	13.3	47.0	64.9	63.0
Metabolite D	7.5	ND	ND	ND
Metabolite C	ND	ND	ND	ND
Glucuronide Conjugate of Metabolite A	ND	ND	35.1	ND
Glucuronide Conjugate of Metabolite D	8.1	ND	ND	ND
5M-6HN-B	ND	ND	ND	ND

♦ % extracted kidney radioactivity; ♦ too low to provide meaningful data; ND not detected

D. DISCUSSION

Absorption of radiolabel [^{14}C] into plasma and whole blood following oral administration [single dose] of ^{14}C-Bromacil at dose levels of 10 [low] and 1000 [high] mg/kg was investigated to determine the time to peak level; i.e., maximum Bromacil equivalents in the plasma [plasma C_{max}]. The maximum levels of radiolabel [absorption studies] in the plasma and whole blood were observed at 1 hour post dose in low-dose males and at 2 hours post dose in the low-dose females. At the high-dose level [both sexes], plasma C_{max} was reached at 12-hours post dose and whole blood C_{max} was attained at 12 hours in males and at 24 hours post dose in females. Initially [first 6 hours post dose], ≈85% of the ^{14}C in the blood was found in the plasma [low dose]. At sacrifice [72♂/96♀ hours], the average amount of radiolabel in plasma accounted for <10% of the amount in blood [both doses]. Excretion routes and rates of elimination in the urine and feces were determined for both dose levels following single doses [90% excretion studies] and for the low dose following a 14-day preconditioning period (preconditioning studies]. Radiolabel was absorbed from the gastrointestinal tract and eliminated via the urine [primary route of excretion (53.7-59.6%) for all groups except the low-dose males (45.5%) in the preconditioning study]. Fecal elimination accounted for 28.0-40.7% in all groups, except the preconditioning study males (45.8%). Expired air was a minor route of excretion, accounting for ≤ 0.4% AD. Tissue/organ levels were assessed after three time intervals: (1) after ≈ 90% AD was excreted via urine and feces; (2) at time of plasma C_{max}; and (3) within 24 hours of time of plasma C_{max}. Radiolabel was found in all tissues/ organs assessed. At termination [120/144/168 hours], ^{14}C was still detectable in nearly all tissues at both dose levels and in both sexes,

although the percent of the dose detected was ≤0.1 [except in the carcass (0.3-1.2%]. The majority of the radiolabel found in the blood at termination was associated with the RBC's. The ratio between the high- and low-dose with respect to the amount of ^{14}C absorbed was comparable to the ratio of the dose levels. The authors stated that the time to eliminate one-half of the administered dose was 16-18 hours at the low dose [single and repeat doses] and 37 [males] /48 [females] hours at the high dose [Figures 10-15, copies appended]. TB II points out that this is not an elimination $T_{1/2}$. Bromacil appears to be extensively metabolized in the rat following both low and high single doses and repeat low doses. The glucuronide conjugate of Metabolite A [5-bromo-3-sec-butyl-6-hydroxymethyluracil] was the major radiolabeled urinary excretion component. Other identified urinary components were Bromacil, Metabolites A, C [5-bromo-3-(1-hydroxymethylpropyl)-6-methyluracil], and D [5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil], the glucuronide conjugates of Metabolites C and D and 6-demethyl bromacil [5-bromo-3-sec-butyl-uracil]. The metabolic profiles in fecal extracts were similar to those in urine, except that Metabolites A, C, and D were reported as excreted as aglycones to a greater extent than as conjugates. Bromacil and Metabolites A and D were the major ^{14}C-labeled components found in the kidney and liver extracts and filtered plasma from rats sacrificed at 24 hours post dose.

E. CONCLUSION

Bromacil appears to be readily absorbed from the gastrointestinal tract following single oral low [10 mg/kg] and high [1000 mg/kg] doses and repeat low [10 mg/kg] doses. Urine is the primary route of elimination following all dosing schedules except the preconditioning low dose in males, where urine and fecal elimination were ≈ equal. Additionally, Bromacil is extensively metabolized [primarily by hydroxylation at the 6-methyl position and also on the sec-butyl moiety] and rapidly excreted. The hydroxylated metabolites were eliminated mainly as glucuronide conjugates. Radiolabel was found in all organs/tissues examined, but there was no evidence of accumulation. The majority of the radiolabel found in the blood at termination was associated with the red blood cells [all dosing schedules]. Proposed metabolic pathways were provided [copy appended].

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