

DATA EVALUATION RECORD

7/18/2000

MESOTRIONE

Study Type: §85-1a; Metabolism of [¹⁴C]Mesotrione in Rats

Work Assignment No. 2-01-52KK (MRIDs 44505101 through 44505106)

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MESOTRIONE (ZA1296)

Metabolism (§85-1[a])

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat
OPPTS Number: 870.7485

OPP Guideline Number: §85-1a

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione ($\geq 98.1\%$ radiochemical purity)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; 2-(4-mesyl-2-nitrobenzoyl)-cyclohexane-1,3-dione

CITATIONS: Prescott, E., Bennett, D. (1995) ZA1296: Whole body autoradiography study in the rat following a single oral dose (mg/kg). Central Toxicology Laboratory, Cheshire, UK. Laboratory Report/Study No. CTL/P/4666/PR0990, September 19, 1995. MRID 44505101. Unpublished.

Macpherson, D. (1996) ZA1296: Excretion and tissue retention of a single oral dose (100 mg/kg) in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report/Study No. CTL/P/4927/UR0501, May 17, 1996. MRID 44505102. Unpublished.

Gledhill, A. (1996) ZA1296: Biotransformation in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report/Study No. CTL/P/4930/UR0442, June 3, 1996. MRID 44505103. Unpublished.

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Macpherson, D. (1996) ZA1296: Excretion and tissue retention of a single oral dose (1 mg/kg) in the rat following repeat dosing. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report/Study No. CTL/P/4995/UR0525, May 24, 1996. MRID 44505106. Unpublished.

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EXECUTIVE SUMMARY: In a series of rat metabolism studies (MRIDs 44505101 through 44505106), [¹⁴C-aromatic]mesotrione (≥98.1% radiochemical purity) was administered to Alpk:AP₆SD rats (5/sex/dose) as either a single oral (gavage) dose at 1.00 or 100 mg/kg, a single intravenous (iv) dose at 1.00 mg/kg, or a single oral dose at 1.00 mg/kg following a 14-day pretreatment with mesotrione at 1.00 mg/kg/day. In addition, 2 bile-duct cannulated rats/sex were administered a single oral dose of [¹⁴C-aromatic]mesotrione at 50.0 mg/kg or a single oral dose of [¹⁴C-dione]mesotrione (≥99% radiochemical purity) at 50.0 mg/kg.

The overall recovery of dosed radioactivity in excreta, bile, tissues, cage washes was 92.0-97.1% from rats in the mass balance studies and 62.5-92.9% from rats in the biliary excretion study. Within 72 hours of receiving a single oral dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg, both sexes excreted 54.2-55.9% of the dose in the urine and 23.8-24.5% of the dose in the feces. Radioactivity remaining in the carcass/tissues of both sexes accounted for 11.2-12.5% of the dose. Increasing the dose to 100 mg/kg had little effect on the pattern of excretion with both sexes. Males and females still excreted the majority of the dose in the urine (61.5-63.0% dose), with fecal excretion accounting for 28.8-30.5% dose, although the recovery of radioactivity in the tissues/carcass was lower (0.71-1.1% dose). Repeated dosing at 1.00 mg/kg/day also had little effect on the pattern of excretion; although the levels of urinary (60.8-67.0% dose) and fecal (23.1-30.3% dose) excretion were slightly increased, and recovery of radioactivity in the tissues/carcass was lower (5.1-5.3% dose). The overall pattern of excretion was also generally similar between rats dosed orally or intravenously at 1.00 mg/kg. Radioactivity in urine of the iv-dosed males (79.4% dose) and females (84.1% dose) was somewhat higher (1.5x) than in urine of orally dosed rats, and iv-dosed rats had lower (0.10-0.28x) levels of radioactivity in feces (2.4-6.8% dose). However, intravenous dosing resulted in similar levels of radioactivity being retained in the tissues and carcass (10.0-10.4% dose) after 72 hours.

In the bile-duct cannulated rats administered [¹⁴C-aromatic]mesotrione, a similar pattern of elimination was noted between the sexes with the majority of the administered dose recovered in the urine; further, urinary excretion was slightly higher (1.2x) in females (64.1% dose) than in males (55.2% dose). Radioactivity in the feces accounted for 25.3 and 26.8% of the dose in males and females, respectively, while biliary excretion was a minor route of excretion for males (10.4% dose), but even lower (0.19x) for females (2.0% dose). Altering the position of the ¹⁴C-label within the parent molecule from the aromatic-ring to the dione-ring had only a minor impact on the pattern of excretion in rats. Approximately 46% of the dose was excreted in the urine and approximately 13% of the dose excreted in the feces in both males and females. The recovery of radioactivity decreased (0.4-0.8x) slightly in the urine (44.1-47.5% of dose) and feces (11.2-16.2% dose) of males and females. Biliary excretion of bile-duct cannulated rats was a minor route of excretion for males (14.2% dose), and was even lower (0.27x) for females (3.8% dose).

Concentrations of ^{14}C -residues in tissues were similar between the sexes within each dose group. Although actual ^{14}C -residue concentrations in tissues differed between dose groups, the relative distribution of radioactivity between tissues was the same within each dose group, with ^{14}C -residues being highest in liver and kidney. In each low-dose group, radioactivity in the female kidneys was 3.3-4.4x higher than males; in the high-dose group, the difference was 1.8x. Increasing the dose level from 1.00 to 100 mg/kg increased the concentration of radioactivity in liver (1.9-2.1x) and kidneys (1.5-3.0x) in both sexes. Repeated dosing resulted in reduced accumulation of ^{14}C -residues in tissues, with ^{14}C -residues being 0.44x lower on average in tissues of repeated dose animals. Levels of radioactivity in tissues of iv dosed animals were essentially the same as in orally dosed animals.

With the exception of the bile-duct cannulated group of rats, 62-78% of the dose was identified in urine and fecal extracts of orally dosed rats. Although there were minor differences in levels of metabolites between males and females and between dose groups, the metabolite profile was similar between the sexes in each group and between the single low-dose, single high-dose, and repeated low-dose groups. In rats from each of these groups, free mesotrione was the major metabolite identified in urine, accounting for 47-64% of the dose. In addition, the following minor metabolites were identified: 2-nitro-4-(methylsulphonyl)-benzoic acid (MNBA, 1-4% dose), 4-(methylsulphonyl)-2-aminobenzoic acid (AMBA, 3-12% dose), 5-hydroxy-mesotrione ($\leq 2\%$ dose), and 4-hydroxy-mesotrione (3-6% dose).

In bile cannulated rats administered a 50 mg/kg dose of [^{14}C -aromatic]mesotrione, a total of 74-77% of the dose was identified in excreta and bile, with the major component being parent compound. Analysis of bile identified only two minor components, 4-hydroxy mesotrione (2% dose, males only) and mesotrione (2-8% dose). Although biliary excretion was a minor route of elimination for both sexes, it was more prominent in males (10% dose) than females (2% dose). For both sexes, the majority of the radioactivity was excreted in the urine and was identified as parent (males, 48% dose; females, 60% dose). AMBA was the major component in feces and accounted for 8-10% of the dose.

In bile cannulated rats administered a 50 mg/kg dose of [^{14}C -dione]mesotrione, a total of 55-59% of the dose was identified in excreta and bile. Analysis of bile identified only two components, 4-hydroxy mesotrione (1% dose, males only) and parent (3-11% dose). Biliary excretion was again a more prominent route of excretion for males (12% dose) than females (3% dose). For both sexes, the most prominent route of excretion was in the urine and the major component identified in urine was parent, totaling 43 and 51% of the dose in males and females, respectively. Two minor components were identified in the fecal extracts, 5-hydroxy mesotrione (1% dose, females only) and parent (1% dose, males only).

This study is classified **acceptable (§85-1a)** and does satisfy the guideline requirements for a metabolism study in rats.

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

I. MATERIALS AND METHODS

A. Materials1. Test compounds:[¹⁴C-aromatic]Mesotrione

Radiochemical purity: ≥97% (method unspecified)

Specific activity: 1.42 or 1.12 GBq/mmol

Code: Y06684/159 or Y06684/011

[¹⁴C-dione]Mesotrione

Radiochemical purity: ≥99% (method unspecified)

Specific activity: 1.35 GBq/mmol

Code: Y06684/010

Mesotrione (unlabeled)

Purity: ≥99.3% a.i. (w/w)

Code: Y06684/008 or Y06684/005

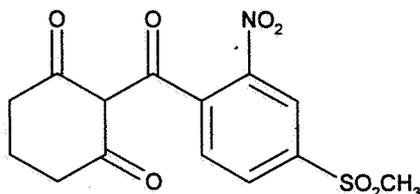
Description: Cream solid or off-white powder

Contaminants: Not specified

Storage: Ambient temperature, in the dark

CAS #: 104206-82-8

Structure:

2. Vehicle: Sodium bicarbonate solution (except for the iv study which used phosphate buffer in injection grade water)3. Test animals: Species: RatStrain: Alpk:AP_rSD

Age: Not specified for the main studies; in the preliminary autoradiography study the rats were 7-9 weeks at dosing

Weight at study initiation: 175-300 g

Source: Biological Services Section or Barriered Animal Breeding Unit, Zeneca Pharmaceuticals, Alderley Park

Housing: During initial acclimation, rats were housed in groups of the same sex in stock rat cages. During the in-life phase, animals were housed individually in stainless steel or all-glass metabolism cages.

Acclimation period: At least 4 days, including 1-2 days in metabolism cages

Diet: Pelleted PCD rat diet (Special Diet Services, Ltd, Stepfield, Wiltham, Essex, UK). ad libitum, except for 10-13 hours prior to dosing and 1-2 hours following dosing. Animals in the biotransformation, preliminary autoradiography, and the repeated oral dose study groups were not fasted.

Water: Tap water, ad libitum

Environmental conditions:

Temperature: $21 \pm 4^\circ\text{C}$

Humidity: 30-70%

Air Changes: At least 12/hour

Photoperiod: 12-hr photoperiod

4. Observations: Observations were not reported.
5. Preparation of dosing solutions: For the low-dose groups, undiluted [^{14}C -aromatic] mesotrione was dissolved in sodium bicarbonate solution. The composition of the final dosing solution was 0.25 mg mesotrione/g and 1.04 MBq/g of dosing solution. For the high-dose groups, [^{14}C -aromatic]mesotrione was dissolved in sodium bicarbonate solution and isotopically diluted by mixing with non-labeled mesotrione. The final specific activity of the dosing solution was 4.19MBq/mg for the low-dose groups and 65.31 KBq/mg for the high-dose groups. Following dosing, the radiochemical purity of the test substance was determined by HPLC analysis; for the biliary study, the purity was determined using TLC and silica gel column chromatography. No results of these analyses were provided.

B. Study Design - These studies were designed to determine the absorption, metabolism, distribution, and excretion of [^{14}C]mesotrione in rats as a function of single or repeated oral dosing, or a single intravenous dose. A preliminary study consisted of two groups of Alpk:AP₁SD rats (2/sex/dose group) that were dosed once with [^{14}C -aromatic]mesotrione or [^{14}C -dione]mesotrione at a target dose of 5 mg/kg. The main mass balance study consisted of four groups of Alpk:AP₁SD rats (5/sex/dose group) that were dosed once with [^{14}C -aromatic]mesotrione either iv at a target dose of 1.00 mg/kg or orally (gavage) at target doses of 1.00 or 100 mg/kg or 1.00 mg/kg following a 14-day pretreatment with nonlabeled mesotrione at 1.00 mg/kg/day. A group composed for bile-duct cannulated rats (2/sex) were also dosed once orally with [^{14}C -aromatic]mesotrione at 50 mg/kg to examine biliary excretion. To assess the effect of ^{14}C -label position within the molecule on metabolism and excretion, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [^{14}C -dione]mesotrione at a target dose of 50 mg/kg.

Animals were randomly assigned to dose groups. Actual average doses for each test group are presented in Table 1 and were within 96-102% of the nominal 1.00 mg/kg dose, 94-99% of the nominal 50.0 mg/kg dose, and 99-111% of the nominal 100 mg/kg dose.

The low-dose level was stated to represent a NOAEL while the high-dose level was stated to exceed the NOAEL by 100 fold.

The in-life portions of these studies were conducted from April 18, 1994 to April 30, 1996.

Table 1. Dose groups for [¹⁴C]mesotrione rat metabolism studies.

Dose Group	Nominal dose (mg/kg)	Actual average ¹⁴ C-dose (mg/kg) ^a	# animals per group	Comments
Preliminary study				
Single oral low dose [¹⁴ C-aromatic] mesotrione	5.0	Male: 5.74 Female: 5.86	2/sex	Mass Balance Study: Urine and feces samples were collected at 6 (urine only), 12, and 24 hours post-dose. At 24 hours post-dose, 1 rat/sex was sacrificed and whole body radiography was performed. Urine and feces samples were also collected from 1 rat/sex at 36 and 48 hours post-dose; these rats were sacrificed at 48 hours post-dose and whole body radiography was performed. Expired air was also collected from 1 rat/sex at 6, 12, and 24 hours post-dose.
Single oral low dose [¹⁴ C-dione] mesotrione	5.0	Male: 5.62 Female: 5.56	2/sex	
Main study				
[¹⁴ C-aromatic]Mesotrione				
Single oral	100.0	Male: 100.11	5/sex	Mass Balance Study: Urine and feces samples were collected at 6 (urine only), 12, 24, 36, 48, and 72 hours post-dose. Organ and tissue samples were collected at sacrifice (72 hours post-dose). Pooled samples of urine and feces from each dose group were used for metabolite identification and characterization.
Single oral	1.00	Male: 1.00	5/sex	
Repeated oral	1.00	Male: 0.99	5/sex	
Single iv	1.00	Male: 0.99	5/sex	
Single oral mid dose	50.00	Male: 49.4 Female: 48.5	2/sex	Biliary excretion study: Bile, feces, and urine were sampled at 6, 12, 24, 36, and 48 hours post-dose. Pooled samples of feces, urine, and bile were also used for metabolite identification/ characterization.
Single oral high dose	100.0	Male: 104.8 Female: 110.7	2/sex	Used solely as a source of fecal and urine samples for isolation of specific metabolites.
[¹⁴ C-dione]Mesotrione				

Dose Group	Nominal dose (mg/kg)	Actual average ¹⁴ C-dose (mg/kg) ^a	# animals per group	Comments
Single oral mid dose	50.00	Male: 47.0 Female: 48.4	2/sex	<u>Biliary excretion study</u> : Bile and urine were sampled at 6, 12, 24, 36, and 48 hours post-dose, and feces were collected at 12, 24, 36, and 48 hours post-dose. Pooled samples of feces, urine, and bile were also used for metabolite identification/characterization.

a Average doses were calculated by reviewers from data obtained in MRID 44505101, Appendix C, page 30; MRID 44505104, Appendix A, page 29; MRID 44505102, Appendix B, page 30; MRID 44505106, Appendix B, page 32; MRID 44505105, Appendix A, page 29; and MRID 44505103, Appendix C, page 65.

1. Dosing - With the exception of the iv dose group, the test animals were dosed orally by gavage at a target dose of 1.00, 50.0, or 100 mg/kg body weight and a target volume of 4 mL/kg body weight. Except for animals in the repeated dose groups and the biliary excretion study, animals were fasted for 10-13 hours prior to dosing with [¹⁴C]mesotrione and for approximately 1-2 hours post-dosing. Animals were weighed prior to ¹⁴C-dosing to determine dose per animal and the actual dose administered was determined by weighing the syringe and catheter assembly prior to and immediately after dosing. For iv dosing, rats were injected in the tail vein at a target dose of 1.00 mg/kg in a volume of 4 mL/100 g body weight. Additionally, cotton wool swabs, used to stop any bleeding following administration were retained for radiochemical analysis.
2. Sampling - In the preliminary mass balance study, exhaled CO₂ (from 1 rat/sex) was trapped in activated charcoal and Nilox columns with aqueous sodium hydroxide for the first 24 hours post-dose. Urine and feces samples were collected from all animals at 6 (urine only), 12, and 24 hours post-dose. At 24 hours post-dose, 1 rat/sex was sacrificed and whole body radiography was performed. Urine and feces samples were also collected from 1 rat/sex at 36 and 48 hours post-dose; these rats were sacrificed at 48 hours post-dose and whole body radiography was performed. Cages were rinsed with water at each sample collection and the rinsate was pooled with the urine; at the end of the study, cages were thoroughly washed with ethanol/water (1:1 v/v).

In the main mass balance study, urine samples were collected over solid carbon dioxide from each animal at 6, 12, 24, 36, 48, and 72 hours post-dose, and feces were collected separately at 12, 24, 36, 48, and 72 hours post-dose. At each collection, cages were rinsed with approximately 10 mL of sodium bicarbonate solution and the rinsate was added to the respective urine sample from that interval. At 72-hours post-dose, animals were sacrificed by exsanguination under halothane Ph Eur anesthesia and the following tissue/organ samples were collected: blood, bone (femur), brain, digestive tract and contents, fat, heart, kidneys, liver, lung, muscle, ovaries, residual carcass, spleen, testes, and tail (iv group only). An aliquot of blood was centrifuged to obtain plasma. The cages

were thoroughly washed with sodium bicarbonate solution followed by 1M hydrochloric acid and the rinsate retained. For the iv study, the kidneys and the tail were collected.

For the biliary excretion studies, male and female rats were anesthetized and their bile ducts were cannulated. Following overnight recovery, bile, urine, and fecal samples were collected at 6, 12, 24, 36, and 48 hours post-dose (feces not collected at 6 hours from [¹⁴C-dione]-dosed rats). Pooled samples of feces, urine, and bile were also used for metabolite identification/characterization.

Samples of tissues, cage wash, and excreta were stored at -20°C until analysis. Blood was stored at approximately 4°C.

3. Radioassay - Samples of urine, plasma, bile, cage wash samples, trapping solutions were analyzed for total radioactivity directly by liquid scintillation counting (LSC). Feces and digestive tract contents were homogenized and radioassayed by LSC following combustion. Samples of tissues, organs, digestive tract, and carcass were digested in tissue solubilizer prior to radioassay by LSC. Bone was cut into pieces and analyzed by combustion. Whole blood was analyzed by combustion. All samples were radioassayed in duplicate (except for the ovaries which were analyzed as a single sample). The reported limit of detection for tissue samples at the low-dose level was 0.0005 µg equivalents of mesotrione/g of tissue and at the high-dose level was 0.032 µg equivalents of mesotrione/g of tissue.
4. Metabolite characterization in excreta - For identification, characterization, and quantitation of metabolites in excreta, aliquots of urine and fecal samples collected 0-48 hours post-dose were pooled by dose group/sex from animals in mass balance study groups.

For analysis, urine and bile samples were injected directly onto an HPLC column and eluted with several solvent systems. For analysis of feces, samples were extracted twice with EtOH/water; for each sample, the resulting extracts were combined, dried, reconstituted in water/acetonitrile (80:20), injected onto an HPLC column, and eluted with several solvent systems. The extraction efficiency for fecal samples was 55-92%. Metabolite identities were confirmed using MS, LC/MS, ¹H-NMR.

5. Statistics - For urine, fecal, and tissue/blood samples, radioactivity in terms of concentration (µg equivalents/g) and the % of administered dose was reported for individual samples and as the mean (with ± S.D.) of five animals/sex/dose group. For urine, fecal, and bile samples from animals in the biliary study, radioactivity in terms of % of administered dose was reported for each animal; the means of the two animals/sex/dose group were calculated by the reviewer.

II. RESULTS

A. Preliminary study

1. Absorption and excretion - Following a single oral dose of [¹⁴C-aromatic]mesotrione at 5.0 mg/kg, excretion in the urine for the males was rapid with 54.1-58.6% of the dose being excreted in the urine within 6 hours of dosing (Table 2), equivalent to 75-88% of the total urinary excretion. In the single male kept to 48 hours, overall excretion in urine and feces, was essentially complete within 24 hours and accounted for 90.2% of the dose, equivalent to 97% of the total excretion. Following oral dosing of [¹⁴C-aromatic]mesotrione at 5.0 mg/kg, excretion in the urine for the females was slower than the males with only 19.3-20.9% of the dose being excreted in the urine within 6 hours of dosing, equivalent to 39-46% of the total urinary excretion. In the single female kept to 48 hours, overall excretion in urine and feces, was essentially complete within 24 hours and accounted for 48.1% of the dose, equivalent to 64% of the total excretion. Recovery of total radioactivity was lower in females when compared to males with only 52.9-75.6% of the total administered dose recovered for the females vs 92.8-100.9% of the dose recovered for the males. Less than 0.1% of the dose was recovered from exhaled air in both sexes.

Inter-animal variability was noted following oral dosing of [¹⁴C-dione]mesotrione (Table 3) at 5.0 mg/kg in both males and females. In the male sacrificed at 24 hours post-dose, only 57.2% of the administered dose was recovered at sacrifice with 53.1% of the total excretion occurring at the 24 hour interval. In the second male sacrificed at 48 hours post-dose, excretion in the urine was rapid with 46.1% of the dose being excreted in the urine within 6 hours of dosing, equivalent to 78% of the total urinary excretion; overall excretion in urine and feces, was essentially complete within 24 hours (86.1% dose, equivalent to 96% of the total excretion). In the female sacrificed at 24 hours post-dose, only 66.4% of the administered dose was recovered at sacrifice. In the remaining female sacrificed at 48 hours post-dose, excretion in the urine was rapid with 42.4% of the dose being excreted in the urine within 6 hours of dosing, equivalent to 67% of the total urinary excretion; overall excretion in urine and feces, was essentially complete within 24 hours and accounted for 82.2% of the dose, equivalent to 90% of the total excretion. Less than 1% of the dose was recovered from exhaled air in both sexes.

Table 2. Recovery over time of radioactivity in excreta and exhaled air of rats following a single oral dose of [¹⁴C-aromatic]mesotrione at 5 mg/kg.^a

Sample	Percent of radioactive dose administered					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
Male 1						
Urine	58.58	5.52	2.86	na	na	66.96
Feces	na	14.76	16.66	na	na	31.42
Carbon dioxide	<0.02	<LOD	<LOD	na	na	<0.04
Charcoal trap	<0.01	<0.01	<0.01	na	na	<0.01
Cage wash	na	na	na	na	na	2.52
Total	58.58	20.28	19.52	na	na	100.90
Male 2						
Urine	54.05	12.68	3.72	0.58	0.66	71.69
Feces	na	9.46	9.77	0.72	0.70	20.65
Carbon dioxide	na	na	na	na	na	na
Charcoal trap	na	na	na	na	na	na
Cage wash	na	na	na	na	na	0.49
Total	54.05	22.14	13.49	1.30	1.36	92.83
Female 1						
Urine	19.32	6.48	16.63	na	na	42.43
Feces	na	0.69	2.31	na	na	3.00
Carbon dioxide	<0.04	<0.03	<LOD	na	na	<0.07
Charcoal trap	<0.01	<0.01	<0.01	na	na	<0.01
Cage wash	na	na	na	na	na	7.50
Total	19.32	7.17	18.94	na	na	52.93
Female 2						
Urine	20.87	10.37	15.64	3.03	3.25	53.16
Feces	na	0.80	0.38	2.02	10.69	13.89
Carbon dioxide	na	na	na	na	na	na
Charcoal trap	na	na	na	na	na	na
Cage wash	na	na	na	na	na	8.58
Total	20.87	11.17	16.02	5.05	13.94	75.63

^a Data were obtained from MRID 44505101, Table 2, page 27 of the study report.
na = not applicable

Table 3. Recovery over time of radioactivity in excreta and exhaled air of rats following a single oral dose of [¹⁴C-dione]mesotrione at 5 mg/kg.^a

Sample	Percent of radioactive dose administered					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
Male 3						
Urine	8.26	6.62	3.88	na	na	18.76
Feces	na	7.52	26.40	na	na	33.92
Carbon dioxide	0.29	0.13	0.05	na	na	0.47
Charcoal trap	0.04	0.02 ^b	0.02	na	na	0.08
Cage wash	na	na	na	na	na	3.98
Total	8.59	14.29	30.35	na	na	57.21
Male 4						
Urine	46.09	7.40	4.94	ns	0.52	58.95
Feces	na	2.90	24.80	1.48	1.11	30.29
Carbon dioxide	na	na	na	na	na	na
Charcoal trap	na	na	na	na	na	na
Cage wash	na	na	na	na	na	0.67
Total	46.09	10.30	29.74	1.48	1.63	89.91
Female 3						
Urine	12.54	8.42	4.33	na	na	25.29
Feces	na	12.39	15.93	na	na	28.32
Carbon dioxide	0.33	0.18	0.05	na	na	0.56
Charcoal trap	0.02	0.02	0.02	na	na	0.06
Cage wash	na	na	na	na	na	12.15
Total	12.89	21.01	20.33	na	na	66.38
Female 4						
Urine	42.40	10.37	8.37	1.00	1.31	63.45
Feces	na	3.41	17.60	1.87	2.74	25.62
Carbon dioxide	na	na	na	na	na	na
Charcoal trap	na	na	na	na	na	na
Cage wash	na	na	na	na	na	2.49
Total	42.40	13.78	25.97	2.87	4.05	91.56

a Data were obtained from MRID 44505101, Table 1, page 26 of the study report.

b Value for one trap only

ns = not sampled

na = not applicable

2. Tissue distribution/whole body autoradiography - After 24 hours, the male dosed with 5 mg/kg of [¹⁴C-aromatic]mesotrione showed labeling in the liver, GI tract, and stomach mucosa, with moderate levels in the renal cortex and very low levels in the renal medulla and stomach contents. The female sacrificed at 24 hours post-dose showed similar labeling in the liver, renal cortex, and GI tract, with a small amount in the renal medulla. By 48 hours post-dose, both sexes showed a similar pattern of labeling in the liver: the intensity of labeling in the renal cortex was lower in the male. A very small amount of labeling was present in the GI tract of the male and a small amount was present in the GI tract contents of the female.

After 24 hours, the animals dosed with 5 mg/kg of [¹⁴C-dione]mesotrione showed the highest levels of radiolabelling in the stomach mucosa and the lumen of the GI tract; the stomach contents were labeled in the male, with very low amounts in the female. A low intensity of labeling was present in the liver and kidney in both sexes. By 48 hours post-dose, the male showed low levels of radioactivity in the liver and very low levels in the stomach contents and the kidney. The female showed labeling in the stomach mucosa, liver, and kidney, with lower levels in the stomach and GI tract contents.

B. Main study

1. Absorption and excretion - Absorption of [¹⁴C]mesotrione from the G.I. tract of rats was evident in both low- and high-dose animals based upon the high level of urinary excretion. In normal rats dosed orally with [¹⁴C]mesotrione at either 1.00 or 100 mg/kg, the pattern of excretion was similar between the sexes and the dose groups; renal excretion accounted for 53.0-64.3% of the dose within 24 hours of dosing, equivalent to 66-71% of the total excretion.

For the bile-cannulated rats dosed with [¹⁴C-aromatic]mesotrione or [¹⁴C-dione]mesotrione at 50 mg/kg, biliary excretion was higher in males (3.8-5.2x) when compared to females, although recovery in bile was low for both labels. By 24 hours post-dose, cumulative biliary excretion accounted for 10.1-14.0 and 1.9-3.5% of the dose for males and females, respectively, and was equivalent to 93-99% of the total biliary excretion. Excretion in the urine was rapid with 39.9-55.5% of the dose being excreted in the urine within 12 hours of dosing, equivalent to 84-91% of the total urinary excretion. Overall excretion was essentially completed within 24 hours, with urinary and fecal excretion together accounting for 54.9-68.6 and 55.7-84.3% of the dose for males and females, respectively, or 74-91% of the total amount of the radioactivity excreted.

- a) [¹⁴C-aromatic] single oral low dose: The pattern of excretion was similar for males and females. Following oral dosing of [¹⁴C-aromatic]mesotrione at 1.0 mg/kg, excretion in the urine was rapid with 44.0-44.5% of the dose being excreted in the urine within 6 hours of dosing (Table 4), equivalent to 80-81% of the total urinary excretion. Overall

excretion, in urine and feces, was essentially complete within 24 hours and accounted for 73.4-74.3% of the dose, equivalent to 92-94% of the total excretion.

Table 4. Recovery over time of radioactivity in excreta of rats following a single oral dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg.^a

Sample	Percent of radioactive dose administered						
	Males						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
Urine	44.02	7.16	1.77	0.51	0.33	0.36	54.15
Feces	ns	12.12	9.23	1.94	0.72	0.50	24.50
Total	44.02	19.28	11.00	2.45	1.05	0.86	78.65
Sample	Females						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
	Urine	44.49	5.63	3.05	0.97	0.84	0.90
Feces	ns	8.92	11.29	2.15	0.82	0.62	23.80
Total	44.49	14.55	14.34	3.12	1.66	1.52	79.68

a Data are the mean of five animals/sex at each sampling interval and were obtained from MRID 44505104, Tables 1 and 2, pages 25 and 26 of the study report.
ns = not sampled

b) [¹⁴C-aromatic] single oral high dose: The pattern of excretion was similar for males and females. Following oral dosing of [¹⁴C-aromatic]mesotrione at 100 mg/kg, excretion in the urine was rapid with 48.3-51.8% of the dose being excreted in the urine within 6 hours of dosing (Table 5), equivalent to 77-84% of the total urinary excretion. Overall excretion, in urine and feces, was essentially complete within 24 hours and accounted for 85.4-85.8% of the dose, equivalent to 93% of the total excretion.

Table 5. Recovery over time of radioactivity in excreta of rats following a single oral dose of [¹⁴C-aromatic]mesotrione at 100 mg/kg.^a

Sample	Percent of radioactive dose administered						
	Males						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
Urine	51.79	6.36	1.93	0.71	0.42	0.34	61.55
Feces	ns	8.77	16.95	2.83	1.29	0.65	30.49
Total	51.79	15.13	18.88	3.54	1.71	0.99	92.04
Sample	Females						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
Urine	48.26	9.25	3.22	1.16	0.61	0.53	63.03
Feces	ns	8.90	15.72	2.52	0.98	0.65	28.77
Total	48.26	18.15	18.94	3.68	1.59	1.18	91.80

a Data are the mean of five animals/sex at each sampling interval and were obtained from MRID 44505102, Tables 1 and 2, pages 25 and 26 of the study report.
ns = not sampled

- c) [¹⁴C-aromatic] repeated oral low dose: The pattern of excretion was similar for males and females. Following oral dosing of [¹⁴C-aromatic]mesotrione at 1.0 mg/kg, excretion in the urine was rapid with 54.5-55.7% of the dose being excreted in the urine within 6 hours of dosing (Table 6), equivalent to 81-91% of the total urinary excretion. Overall excretion, in urine and feces, was essentially complete within 24 hours and accounted for 84.9-87.0% of the dose, equivalent to 94-95% of the total excretion.

Table 6. Recovery over time of radioactivity in excreta of rats following a single oral dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg after a 14-day pretreatment period with mesotrione at 1.00 mg/kg/day.^a

Sample	Percent of radioactive dose administered						
	Males						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
Urine	55.66	3.47	1.07	0.25	0.30	0.10	60.85
Feces	ns	9.38	17.42	2.33	0.81	0.33	30.27
Total	55.66	12.85	18.49	2.58	1.11	0.43	91.12
Sample	Females						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
	Urine	54.54	7.14	2.59	1.13	1.06	0.52
Feces	ns	14.48	6.14	0.89	0.79	0.82	23.12
Total	54.54	21.62	8.73	2.02	1.85	1.34	90.10

a Data are the mean of five animals/sex at each sampling interval and were obtained from MRID 44505106, Tables 1 and 2, pages 27 and 28 of the study report.
ns = not sampled

- d) [¹⁴C-aromatic] single iv low dose: The pattern of excretion was similar for males and females. Following iv dosing of [¹⁴C-aromatic]mesotrione at 1.0 mg/kg, excretion in the urine was rapid with 70.7-75.1% of the dose being excreted in the urine within 6 hours of dosing (Table 7), equivalent to 89% of the total urinary excretion. Overall excretion, in urine and feces, was essentially complete within 24 hours and accounted for 83.8% of the dose, equivalent to 97% of the total excretion. Total fecal excretion was 2.9x higher for the males than the females; however, the relevance of this difference was equivocal because fecal excretion was a minor component of excretion for the iv dosed rats (< 7% of the total dose).

Table 7. Recovery over time of radioactivity in excreta of rats following a single intravenous dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg.^a

Sample	Percent of radioactive dose administered						
	Males						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
Urine	70.68	5.85	1.65	0.62	0.40	0.19	79.39
Feces	ns	2.61	3.05	0.59	0.28	0.24	6.77
Total	70.68	8.46	4.70	1.21	0.68	0.43	86.16
Sample	Females						
	6 hr	12 hr	24 hr	36 hr	48 hr	72 hr	Total
	Urine	75.06	4.75	2.15	1.14	0.59	0.45
Feces	ns	0.71	1.08	0.21	0.19	0.16	2.35
Total	75.06	5.46	3.23	1.35	0.78	0.61	86.49

a Data are the mean of five animals/sex at each sampling interval and were obtained from MRID 44505105, Tables 1 and 2, pages 25 and 26 of the study report.
ns = not sampled

- e) [¹⁴C-aromatic] single oral mid dose (bile-duct cannulated): Within 12 hours of oral dosing with [¹⁴C-aromatic]mesotrione at 50 mg/kg, radioactivity recovered in bile accounted for 9.4% of the dose for males and 1.5% of the dose for females, equivalent to 75-91% of the total biliary excretion (Table 8). By 24 hours post-dose, cumulative biliary excretion accounted for 10.1 and 1.9% of the dose for males and females, respectively, and was equivalent to 95-98% of the total biliary excretion. In males and females, excretion in the urine was rapid with 47.2-55.5% of the dose being excreted in the urine within 12 hours of dosing, equivalent to 86-87% of the total urinary excretion. Fecal excretion peaked at 24 hours post-dose and at this point accounted for 16.0 and 22.4% of the dose for males and females, respectively, and was equivalent to 63-84% of the total fecal excretion. Overall excretion was essentially completed within 24 hours, with urinary and fecal excretion together accounting for 68.6 and 84.3% of the dose for males and females, respectively, or 76-91% of the total amount of the radioactivity excreted. Although urinary excretion was the primary route of excretion for both sexes, biliary excretion was higher (5.2x) in males when compared to females.

Table 8. Recovery over time of radioactivity in excreta of bile-duct cannulated rats following a single oral dose of [¹⁴C-aromatic]mesotrione at 50 mg/kg.^a

Sample	Percent of radioactive dose administered					
	Males					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
Bile	7.6	1.8	0.7	0.2	0.1	10.4
Urine	29.0	18.2	5.4	1.8	0.8	55.2
Feces	4.4	3.4	8.2	6.3	3.0	25.3
Total	41.0	23.4	14.3	8.3	3.9	90.9
Sample	Females					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
	Bile	1.0	0.5	0.4	0.0	0.1
Urine	42.1	13.4	6.4	0.9	1.3	64.1
Feces	0.2 ^b	7.4	14.8	1.0	3.4	26.8
Total	43.3	21.3	21.6	1.9	4.8	92.9

- a Data are the mean of 2 animals/sex at each sampling interval (as calculated by reviewers) unless otherwise noted and were obtained from MRID 44505103, Appendix E, page 68 of the study report.
- b Data for a single animal were provided for this interval.

f) [¹⁴C-dione] single oral mid dose (bile-duct cannulated): Within 12 hours of oral dosing with [¹⁴C-dione]mesotrione at 50 mg/kg, radioactivity recovered in bile accounted for 12.9% of the dose for males and 2.6% of the dose for females, equivalent to 69-91% of the total biliary excretion (Table 9). By 24 hours post-dose, cumulative biliary excretion accounted for 14.1 and 3.5% of the dose for males and females, respectively, and was equivalent to 93-99% of the total biliary excretion. In males and females, absorption and excretion in the urine was rapid with 39.9-40.2% of the dose being excreted in the urine within 12 hours of dosing, equivalent to 84-91% of the total urinary excretion. Fecal excretion peaked at 24 hours post-dose in the males and accounted for 12.6% of the dose and was equivalent to 78% of the total fecal excretion; fecal excretion in females peaked at 12 hours post-dose and accounted for 6.3% of the dose and was equivalent to 56% of the total fecal excretion. Overall excretion was essentially completed within 24 hours, with urinary and fecal excretion together accounting for 54.9 and 55.7% of the dose for males and females, respectively, or 74-89% of the total amount of the radioactivity excreted. Although urinary excretion was the primary route of excretion for both sexes, biliary excretion was higher (3.8x) in males when compared to females.

Table 9. Recovery over time of radioactivity in excreta of bile-duct cannulated rats following a single oral dose of [¹⁴C-dione]mesotrione at 50 mg/kg.^a

Sample	Percent of radioactive dose administered					
	Males					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
Bile	9.2	3.7	1.2	0.1	0.1	14.2
Urine	21.7	18.5	2.1	0.8	1.0	44.1
Feces	ns	2.1	10.5	2.0	1.6	16.2
Total	30.9	24.3	13.8	2.9	2.7	74.5
Sample	Females					
	6 hr	12 hr	24 hr	36 hr	48 hr	Total
	Bile	1.6	1.0	0.9	0.2	0.1
Urine	34.4	5.5	6.1	1.1	0.4	47.5
Feces	ns	6.3	3.4	0.6	0.9	11.2
Total	36.0	12.8	10.4	1.9	1.4	62.5

a Data are the mean of 2 animals/sex at each sampling interval (as calculated by reviewers) unless otherwise noted and were obtained from MRID 44505103, Appendix E, page 67 of the study report.

ns = not sampled

2. Overall excretion and recovery of the administered dose - The overall recovery of dosed radioactivity in excreta, bile, tissues, cage washes was 92.01-97.06% from rats in the mass balance studies and 62.5-92.9% from rats in the biliary excretion study.

Male and female rats excreted approximately equal amounts of the dose in the urine (54.2-55.9% dose) and feces (23.8-24.5% dose) within 72 hours of receiving a single oral dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg (Table 10). Radioactivity remaining in the carcass/tissues of both sexes from the single oral low-dose group accounted for 11.2-12.5% of the dose. Increasing the oral dose to 100 mg/kg had little effect on the pattern of excretion for either males or females. Males and females still excreted an equal percentage of the dose in the urine (61.5-63.0% dose) and feces (28.8-30.5% dose). The recovery of radioactivity in the tissues/carcass was also similar between sexes (0.71-1.1% dose), but much lower when compared to the low dose group. Repeated dosing at 1.00 mg/kg/day also had little effect on the pattern of excretion of [¹⁴C-aromatic]mesotrione. The levels of radioactivity recovered in excreta of males (urine, 60.8% dose; feces, 30.3% dose) and females (urine, 67.0% dose; feces, 23.1% dose) from the repeated oral low-dose group were slightly higher than the levels observed in the single oral low-dose group; recovery of radioactivity in the tissues/carcass were lower (5.1-5.3% dose) than the levels observed in the single oral low-dose group.

The overall pattern of excretion was also generally similar between rats dosed orally or intravenously at 1.00 mg/kg. Radioactivity in urine of the iv-dosed males (79.4% dose) and females (84.1% dose) was somewhat higher (1.5x) than in urine of orally dosed rats: iv-dosed males and females had lower (0.10-0.28x) levels of radioactivity in feces (2.4-6.8% dose) than orally dosed animals. Intravenous dosing resulted in similar levels of radioactivity being retained in the tissues and carcass (10.0-10.4% dose) after 72 hours. In the bile-duct cannulated rats, a similar overall pattern of elimination was exhibited among the sexes following oral dosing of [¹⁴C-aromatic]mesotrione at 50 mg/kg. The majority of the administered dose was recovered in the urine, with urinary excretion being slightly higher (1.2x) in females (64.1% dose) than in males (55.2% dose). Radioactivity in the feces accounted for 25.3 and 26.8% of the dose in males and females, respectively. Biliary excretion of bile-duct cannulated rats was a minor route of excretion for males (10.4% dose), but even lower (0.19x) for females (2.0% dose).

Altering the position of the ¹⁴C-label within the parent molecule from the aromatic-ring to the dione-ring had only a minor impact on the pattern of excretion in rats. In addition, no sex-related differences were apparent in the excretion of radioactivity, with both sexes excreting ~46% of the dose in the urine and ~13% of the dose in the feces. The recovery of radioactivity slightly decreased (0.4-0.8x) in the urine (44.1-47.5% of dose) and feces (11.2-16.2% dose) of males and females. Biliary excretion of bile-duct cannulated rats was a minor route of excretion for males (14.2% dose), but even lower (0.27x) for females (3.8% dose).

Table 10. Recovery of radioactivity in excreta, and tissues/carcass of rats dosed with [¹⁴C]mesotrione at 1.0, 50, or 100 mg/kg.^a

Dose group	Percent of radioactive dose administered					
	[¹⁴ C-aromatic] label					
	Single low oral dose		Single high oral dose		Repeated low oral dose	
Sample	Male	Female	Male	Female	Male	Female
Urine	54.15	55.88	61.54	63.02	60.84	66.97
Feces	24.50	23.80	30.49	28.77	30.27	23.11
Cage Wash	0.90	1.36	0.73	0.97	0.24	0.76
Tissues/Carcass ^b	12.46	11.23	0.71	1.11	5.11	5.34
Total	92.01	92.27	93.47	93.87	96.46	96.18

Dose group	Percent of radioactive dose administered					
	[¹⁴ C-aromatic] label				[¹⁴ C-dione] label	
	Single low iv dose		Single mid oral dose, bile-duct cannulated		Single mid oral dose, bile-duct cannulated	
Sample	Male	Female	Male	Female	Male	Female
Urine	79.39	84.14	55.2	64.1	44.1	47.5
Feces	6.77	2.35	25.3	26.8	16.2	11.2
Cage Wash	0.46	0.53	nr	nr	nr	nr
Bile	na	na	10.4	2.0	14.2	3.8
Tissues/Carcass ^b	10.35	10.03	nr	nr	nr	nr
Total	96.97	97.06	90.9	92.9	74.5	62.5

- a With the exception of the bile-duct cannulated rats, data are the mean of five animals/sex at each sampling interval and were obtained from Tables 1, 2, and 3 in MRIDs 44505104, 44505102, 44505106, and 44505105, pages 25 through 28. Data for bile-duct cannulated rats are the mean of 2 animals/sex at each sampling interval (as calculated by reviewers) unless otherwise noted and were obtained from MRID 44505103, Appendix E, pages 67 and 68 of the study report; bile-duct cannulated rats were terminated within 48 hours of dosing.
- b Includes radioactivity associated with the digestive tract; excised organs and tissue, and the residual carcass.
- na not applicable
- nr not reported

3. Tissue distribution - The concentration of radioactivity in tissues and organs of rats from various dose groups at 72 hours following ¹⁴C-dosing are presented in Table 11. Concentrations of ¹⁴C-residues in tissues were similar between the sexes within each dose group. Although actual ¹⁴C-residue concentrations in tissues differed between dose

groups, the relative distribution of radioactivity between tissues were the same within each dose group. ^{14}C -Residues were highest in liver and kidney. In each low-dose group, radioactivity in the female kidneys was 3.3-4.4x higher than males; in the high-dose group, the difference was 1.8x.

For orally dosed animals, increasing the dose level from 1.00 to 100 mg/kg increased the concentration of radioactivity in liver (1.9-2.1x) and kidneys (1.5-3.0x).

Repeated oral dosing with mesotrione at 1.00 mg/kg/day resulted in reduced accumulation of ^{14}C -residues in tissues. Compared to the single oral low-dose group, ^{14}C -residues were decreased in the liver (0.41-0.43x) and kidneys (0.40-0.51x) of both males and females.

Administering a single low-dose intravenously had no impact on the general distribution of radioactivity among tissues. As in the single oral low-dose group, levels of radioactivity in tissues and organs of rats were similar between sexes and showed the same distribution of radioactivity.

- a) [^{14}C -aromatic] single oral low-dose: Levels of radioactivity in tissues and organs were similar between sexes 72 hours following a single oral dose of [^{14}C -aromatic] mesotrione at 1.00 mg/kg. For both sexes, ^{14}C -residues were highest in liver (male, 1.85 $\mu\text{g/g}$; female, 1.75 $\mu\text{g/g}$) and kidneys (male, 0.28 $\mu\text{g/g}$; female, 0.98 $\mu\text{g/g}$). Tissues with the lowest detectable ^{14}C -residues were the GI tract (male, 0.003 $\mu\text{g/g}$; female, 0.004 $\mu\text{g/g}$) and the residual carcass (male, 0.003 $\mu\text{g/g}$; female, 0.012 $\mu\text{g/g}$). ^{14}C -Residues in the remaining tissues were equal to or less than the LOD.
- b) [^{14}C -aromatic] single oral high-dose: Levels of radioactivity in tissues and organs were similar between sexes 72 hours following a single oral dose of [^{14}C -aromatic] mesotrione at 100 mg/kg. For both sexes, ^{14}C -residues were highest in liver (male, 3.53 $\mu\text{g/g}$; female, 3.66 $\mu\text{g/g}$) and kidneys (male, 0.84 $\mu\text{g/g}$; female, 1.48 $\mu\text{g/g}$), followed by the residual carcass (male, 0.52 $\mu\text{g/g}$; female, 1.07 $\mu\text{g/g}$), GI tract (male, 0.35 $\mu\text{g/g}$; female, 0.28 $\mu\text{g/g}$), spleen (male, 0.09 $\mu\text{g/g}$; female, 0.09 $\mu\text{g/g}$), bone (male, 0.10 $\mu\text{g/g}$; female, 0.09 $\mu\text{g/g}$), and blood (male, 0.08 $\mu\text{g/g}$; female, 0.10 $\mu\text{g/g}$). Tissues with the lowest detectable ^{14}C -residues were the heart (male, 0.05 $\mu\text{g/g}$; female, 0.05 $\mu\text{g/g}$), muscle (male, 0.07 $\mu\text{g/g}$; female, 0.07 $\mu\text{g/g}$), and plasma (male, 0.07 $\mu\text{g/g}$; female, 0.09 $\mu\text{g/g}$). ^{14}C -Residues in the female lung were 0.05 $\mu\text{g/g}$ and in the remaining tissues were equal to or less than the LOD.
- c) [^{14}C -aromatic] repeated oral low-dose: Pretreatment with mesotrione at 1.00 mg/kg/day of 14 days prior to ^{14}C -dosing had little impact on the accumulation and distribution of ^{14}C -residues in tissues and organs. As in the single oral low-dose group, levels of radioactivity in tissues and organs of rats were similar between sexes and showed the same general distribution of radioactivity. For both sexes, ^{14}C -residues were highest in liver (male, 0.80 $\mu\text{g/g}$; female, 0.71 $\mu\text{g/g}$) and kidneys

(male, 0.11 $\mu\text{g/g}$; female, 0.50 $\mu\text{g/g}$). Tissues with the lowest detectable ^{14}C -residues were the GI tract (male, 0.001 $\mu\text{g/g}$; female, 0.003 $\mu\text{g/g}$) and the residual carcass (male, 0.01 $\mu\text{g/g}$; female, 0.02 $\mu\text{g/g}$). ^{14}C -Residues in the remaining tissues were equal to or less than the LOD.

- d) [^{14}C -aromatic] single iv low-dose: Administering a single low-dose intravenously had no impact on the general distribution of radioactivity among tissues. As in the single oral low-dose group, levels of radioactivity in tissues and organs of rats were similar between sexes and showed the same distribution of radioactivity. For both sexes, ^{14}C -residues were highest in liver (male, 1.60 $\mu\text{g/g}$; female, 1.79 $\mu\text{g/g}$) and kidneys (male, 0.28 $\mu\text{g/g}$; female, 0.95 $\mu\text{g/g}$), followed by the tail (male, 0.02 $\mu\text{g/g}$; female, 0.05 $\mu\text{g/g}$) and residual carcass (male, 0.004 $\mu\text{g/g}$; female, 0.002 $\mu\text{g/g}$). ^{14}C -Residues in the remaining tissues were equal to or less than the LOD. Levels of ^{14}C -residues in tissues were comparable for the oral and iv low-dose groups.

Table 11. Distribution of radioactivity in blood, tissues, and organs of rats sacrificed 72 hours following a single oral or iv dose of [¹⁴C-aromatic]mesotrione at 1 or 100 mg/kg. ^a

Dose group	Concentration of radioactivity (µg equivalents/g)							
	[¹⁴ C-aromatic]mesotrione							
	Single oral low dose ^b		Single oral high dose ^c		Repeated oral low dose ^b		Single iv low dose ^b	
Tissue/organ	Male	Female	Male	Female	Male	Female	Male	Female
Heart	<0.002	<0.002	0.049	0.053	<0.001	<0.001	<0.001	<0.001
Lung	<0.002	0.002	<0.038	0.048	<0.001	<0.001	0.001	0.001
Liver	1.846	1.748	3.529	3.655	0.795	0.713	1.596	1.786
Spleen	<0.001	<0.001	0.093	0.085	<LOD	<LOD	<0.001	<0.001
Kidney	0.281	0.979	0.835	1.479	0.112	0.496	0.282	0.953
Muscle	<0.001	<0.001	0.072	0.073	<0.001	<0.001	<0.001	<0.001
Bone	<0.001	<0.002	0.101	0.085	0.002	0.003	0.002	0.002
Brain	<0.001	<0.001	<0.032	<0.042	<0.001	<LOD	<0.001	<0.001
Fat	<0.002	<0.002	<0.033	<0.031	<0.001	<LOD	0.001	0.002
Digestive tract	0.003	0.004	0.350	0.277	0.001	0.003	ne	ne
Testicles	<0.001	na	<0.032	na	0.001	na	<0.001	na
Ovaries/Uterus	na	<0.002	na	<0.073	na	<0.001	na	<0.003
Residual carcass	0.003	0.012	0.517	1.067	0.006	0.016	0.004	0.002
Whole blood	0.002	0.003	0.083	0.104	0.001	0.002	0.002	0.003
Plasma	0.001	0.002	0.070	0.089	0.001	0.001	0.001	0.001
Tail	ne	ne	ne	ne	ne	ne	0.016	0.048

a Data were obtained from MRID 44505104, Table 4, page 28; MRID 44505102, Table 4, page 28; MRID 44505106, Table 4, page 30; and 44505105, Table 4, page 28. Data are the average of 5 animals/sex/dose group.

b LOD = 0.0005 µg equiv/g.

c LOD = 0.032 µg equiv/g.

na not applicable

ne not examined

C. Metabolite Characterization

1. Metabolites in excreta - Quantitative HPLC analyses isolated up to 5 distinct components in urine and bile and up to 5 distinct components in fecal extracts. Results from the analyses of urine and fecal extracts from the single oral low- and high-dose groups and the repeated oral low-dose group treated with [¹⁴C-aromatic]mesotrione are summarized in Table 12; results from the analyses of urine, bile, and fecal extracts from the [¹⁴C-aromatic] and [¹⁴C-dione] bile cannulated groups are summarized in Table 13. The

proposed pathway for biotransformation of mesotrione in rats (as obtained from MRID 44505103, page 37) is presented in Appendix 1.

Mesotrione and its metabolites were isolated and purified from urine, and the identities of parent, 4-hydroxy-mesotrione, 2-nitro-4-(methylsulphonyl)-benzoic acid (MNBA), and 4-(methylsulphonyl)-2-aminobenzoic acid (AMBA) were confirmed by LC-MS and NMR analyses. The metabolite 5-hydroxy-mesotrione was identified by HPLC chromatography with a reference standard.

With the exception of the bile-duct cannulated group of rats, 62-78% of the dose was identified in urine and fecal extracts of orally dosed rats. Although there were minor differences in levels of metabolites between males and females and between dose groups, the metabolite profile was similar between the sexes in each group and between the single oral low-dose, single oral high-dose, and repeated oral low-dose groups. In rats from each of these groups, free mesotrione was the major metabolite identified in urine, accounting for 47-53% of the dose in single oral low-dose group, 56-59% of the dose in the single oral high-dose group, and 54-64% of the dose in repeated oral low-dose group. Mesotrione also accounted for 3-8% of the dose in feces from the single low- and high-dose groups and 1% of the dose in feces from the repeated-dose group. Other minor metabolites identified in excreta included MNBA (1-3% dose), AMBA (3-12% dose), 5-hydroxy-mesotrione ($\leq 2\%$ dose), and 4-hydroxy-mesotrione (3-6% dose). AMBA was detected almost exclusively in feces (3-12% dose) of both sexes; 4-hydroxy-mesotrione was detected only in males and primarily in urine (3-5% dose). No urinary or fecal unknowns were detected which accounted for $>5\%$ of the administered dose.

Analysis of bile from bile-duct cannulated rats administered a 50 mg/kg dose of [^{14}C -aromatic]mesotrione identified only two minor components, 4-hydroxy mesotrione (2% dose, males only) and mesotrione (2-8% dose). Biliary excretion was a more prominent route of excretion for the males (10% dose) than females (2% dose). For both sexes, the majority of the radioactivity was excreted in the urine and was identified as parent and totaled 48 and 60% of the dose in males and females, respectively. AMBA was the major component in feces and accounted for 8-10% of the dose. A total of 74-77% of the dose was identified in excreta and bile, with the major component being parent compound. Only one unknown accounted for $\geq 5\%$ of the dose (unknown E, 5% dose, males only).

Analysis of bile from bile-duct cannulated rats administered a 50 mg/kg dose of [^{14}C -dione]mesotrione identified only two components, 4-hydroxy mesotrione (1% dose, males only) and parent (3-11% dose). Biliary excretion was again a more prominent route of excretion for the males (12% dose) than females (3% dose). For both sexes, the most prominent route of excretion was in the urine and the major component identified in urine was parent, totaling 43 and 51% of the dose in males and females, respectively. Two minor components were identified in the fecal extracts and included 5-hydroxy mesotrione (1% dose, females only) and parent (1% dose, males only). A total of 55-59%

of the dose was identified in excreta and bile. Only one unknown accounted for $\geq 5\%$ of the dose (unknown H, 6% dose, males only).

Table 12. Metabolite profile in excreta of rats following oral dosing with [^{14}C -aromatic] mesotrione at 1.00 or 100 mg/kg.

Dose Group	Percent of administered dose					
	Single oral low dose		Single oral high dose		Repeated oral low dose	
	Male	Female	Male	Female	Male	Female
Identified Urinary Metabolites ^a						
Mesotrione	47	53	56	59	54	64
MNBA	--	1	1	1	1	1
AMBA	1	--	--	--	--	--
5-Hydroxy mesotrione	--	--	--	--	--	--
4-Hydroxy mesotrione	5	--	3	--	4	--
Identified Fecal Metabolites ^a						
Mesotrione	3	7	8	3	1	1
MNBA	1	2	2	1	3	2
AMBA	2	5	5	12	6	7
5-Hydroxy mesotrione	2	--	2	2	--	--
4-Hydroxy mesotrione	1	--	--	--	--	--
Total identified Metabolites	62	68	77	78	69	75
Urinary and Fecal Unknowns ^a						
Unknown A	1	--	1	1	2	2
Unknown B	1	1	1	2	3	2
Unknown C	--	--	--	1	--	--
Unknown D	--	--	--	1	--	--
Unknown E	1	--	--	--	1	2
Unknown F	--	--	1	--	--	1
Unknown G	--	--	1	--	--	--
Total Isolated Unknowns	3	1	4	5	6	7
Unanalyzed Fractions						
Urine (48-72 hr) ^b	0.36	0.90	0.34	0.53	0.10	0.52
Residual fecal solids (0-48 hr) ^c	9.12	7.88	7.76	8.44	13.47	6.24
Feces (48-72 hr) ^b	0.50	0.62	0.65	0.65	0.33	0.82
Cage wash ^d	0.90	1.36	0.73	0.97	0.24	0.76
Tissues/carcass ^d	12.46	11.23	0.71	1.11	5.11	5.34
Total accounted for ^c	88.34	90.99	97.19	94.70	94.25	95.68

a Data are from separate HPLC analyses of pooled urine and fecal extracts (0-48 hour) from 5 rats/sex/dose group and were obtained from MRID 44505103, Tables 8-13, pages 57-62 of study report.

b Data were obtained from Tables 4-6 of this review.

- c Data represent the unextracted radioactivity from pooled 0-72 hour fecal samples and were calculated by reviewers from data obtained in Tables 4-6 of this review and the extraction efficiencies (MRID 44505103, pages 31 and 32 of study report).
- d Data were obtained from Table 10 of this review.
- e Total accounted for = (Total identified) + (Total isolated unknowns) + (Total unanalyzed).
- Not detected

- a) [¹⁴C-aromatic] single oral low dose: A total of 4 components were identified in urine of males and females. For both sexes, the largest single fraction identified in urine was the parent compound that accounted for 47-53% dose. Other components detected in urine extracts included 4-hydroxy mesotrione (5% dose in males), and AMBA and MNBA each at 1% in males and females, respectively.

Parent compound was also the major component in feces, accounting for 3-7% of the dose. Other compounds identified in fecal extracts included AMBA (2-5% dose), MNBA (1-2% dose), 4-hydroxy-mesotrione (1% dose), and 5-hydroxy-mesotrione (2% dose).

A total of 62-68% of the dose was identified in excreta of single oral low-dose rats, with the major component being parent compound. The metabolite profile was quantitatively and qualitatively similar between the sexes. Fecal and urinary unknowns in both sexes accounted for 1-3% of the dose.

- b) [¹⁴C-aromatic] single oral high dose: A total of 3 components were isolated from urine of males and females. For both sexes, the major component identified in urine was parent, accounting for 56 and 59% of the dose in males and females, respectively. Other components detected in urine included 4-hydroxy mesotrione (3% dose in males) and MNBA (1% dose).

In feces, AMBA was identified as the major component accounting for 5-12% of the dose, along with parent (3-8% dose), MNBA (1-2% dose), and 5-hydroxy-mesotrione (2% dose).

A total of 77-78% of the dose was identified in excreta of single oral high-dose rats, with the major component being parent compound. The metabolite profile was quantitatively and qualitatively similar between the sexes and between the low- and high-dose groups. Fecal and urinary unknowns in both sexes accounted for 4-5% of the dose.

- c) [¹⁴C-aromatic] repeated oral low dose: A total of 3 components were isolated from urine of males and females. For both sexes, the major component identified in urine was parent, accounting for 54 and 64% of the dose in males and females, respectively. The only other components detected in urine were 4-hydroxy mesotrione (4% dose in males) and MNBA (1% dose).

AMBA was the major component in feces and accounted for 6-7% of the dose. Another metabolite, MNBA, was identified in the fecal extracts (2-3% dose), while the parent accounted for 1% of the dose in feces of both sexes.

A total of 69-75% of the dose was identified in excreta of repeated oral low-dose rats, with the major component being parent compound. The metabolite profile was quantitatively and qualitatively similar between the sexes and between the single and repeated dose groups. Fecal and urinary unknowns in both sexes accounted for 6-7% of the dose.

Table 13. Metabolite profile in bile and excreta of bile cannulated rats following a single oral dose of [¹⁴C-aromatic]mesotrione or [¹⁴C-dione]mesotrione at 50 mg/kg.^a

Dose Group	[¹⁴ C-aromatic]label		[¹⁴ C-dione]label	
	Single oral mid dose bile-duct cannulated		Single oral mid dose bile-duct cannulated	
	Male	Female	Male	Female
Metabolite/fraction				
Identified Urinary Metabolites ^a				
Mesotrione	48	60	43	51
MNBA	--	1	--	--
AMBA	--	1	--	--
5-Hydroxy mesotrione	5	--	--	--
4-Hydroxy mesotrione	--	--	3	--
Identified Fecal Metabolites ^a				
Mesotrione	2	--	1	--
MNBA	--	1	--	--
AMBA	8	10	--	--
5-Hydroxy mesotrione	1	--	--	1
4-Hydroxy mesotrione	--	2	--	--
Identified Biliary Metabolites ^a				
Mesotrione	8	2	11	3
4-Hydroxy mesotrione	2	--	1	--
Total identified Metabolites	74	77	59	55
Unknown Urinary, Biliary, and Fecal Metabolites ^a				
Unknown A	3	1	4	3
Unknown B	3	1	1	--
Unknown C	2	2	--	--
Unknown D	4	--	--	--
Unknown E	5	1	1	--
Unknown F	--	1	--	--
Unknown G	--	--	1	--
Unknown H	--	--	6	3
Unknown I	--	--	1	2
Unknown J	--	--	1	--
Total Isolated Unknowns	17	6	15	8
Unanalyzed Fractions				
Residual fecal solids (0-48 hr) ^b	5.6	7.5	2.8	0.9
Total accounted for ^c	96.6	90.5	76.8	63.9

a Data are from HPLC analyses of urine, bile, and fecal extracts from 2 rats/sex/dose group and were obtained from MRID 44505103, Tables 4-7, pages 53- 56 of study report.

b Data represent the unextracted radioactivity from pooled 0-48 hour fecal samples and were calculated by reviewers using data obtained from Tables 4-6 of this review and MRID 44505103, pages 31 and 32 of study report.

c Total accounted for = (Total identified) + (Total isolated unknowns) + (Total unanalyzed).

-- Not detected

Note: Cage wash and tissues/carcass were not analyzed and no information was reported as to the levels of radioactivity associated with these fractions.

- d) [¹⁴C-aromatic] single oral mid dose (bile-duct cannulated rats): A total of 4 components were identified in urine of males and females. For both sexes, the major component in urine was parent, accounting for 48 and 60% of the dose in males and females, respectively. Other metabolites detected in urine included: 5-hydroxy mesotrione (5% dose, males only), and MNBA and AMBA (1% dose each, females only).

AMBA was the major component in feces and accounted for 8-10% of the dose. Other metabolites identified in the fecal extracts included: 4-hydroxy mesotrione (2% dose, females only); parent (2% dose, males only); 5-hydroxy mesotrione (1% dose, males only); and MNBA (1% dose, females only).

Analyses of bile identified only two components, 4-hydroxy mesotrione (2% dose, males only) and mesotrione (2-8% dose). Biliary excretion was a more prominent route of excretion for the males (10% dose) than females (2% dose).

A total of 74-77% of the dose was identified in excreta and bile, with the major component being parent compound. With the exception of the differences in biliary excretion, the metabolite profile was quantitatively and qualitatively the same between the sexes. Fecal, biliary, and urinary unknowns in both sexes accounted for 6-17% of the dose, but only one unknown accounted for $\geq 5\%$ of the dose (unknown E, 5% dose, males only).

- e) [¹⁴C-dione] single oral mid dose (bile-duct cannulated rats): Only 2 components were identified in urine of males and females. For both sexes, the major component in urine was parent, accounting for 43 and 51% of the dose in males and females, respectively. The second metabolite detected in urine was 4-hydroxy mesotrione (3% dose, males only).

Two minor components were identified in the fecal extracts: 5-hydroxy mesotrione (1% dose, females only) and parent (1% dose, males only).

Analyses of bile identified only two components, 4-hydroxy mesotrione (1% dose, males only) and mesotrione (3-11% dose). As in the other groups, biliary excretion was a more prominent route of excretion for the males (12% dose) than females (3% dose).

A total of 55-59% of the dose was identified in excreta and bile of [¹⁴C-dione]-dosed rats, with the major component being parent compound. Except for the differences in biliary excretion, the metabolite profile was quantitatively and qualitatively similar between the sexes and to the rats dosed with [¹⁴C-aromatic]mesotrione. Fecal, biliary, and urinary unknowns in both sexes accounted for 8-15% of the dose; only one unknown accounted for $\geq 5\%$ of the dose (unknown H, 6% dose, males only).

III. DISCUSSION

- A. Investigator's Conclusions - The study author concluded that mesotrione was rapidly absorbed by rats following a single oral dose based upon the high levels radioactivity recovered in the urine (54.2-63.0% dose). Seventy two hours after dosing the highest tissue levels were detected in the liver and kidney.

In the repeated dose group, radioactivity was rapidly eliminated in the excreta. Comparison to the single oral low-dose group indicated a slightly increased initial rate of excretion in urine by the repeated dose males. At sacrifice 72 hours post-dose, highest tissue levels of radioactivity were detected in the liver and kidneys, with similar hepatic concentrations between the sexes and much lower renal concentrations in males vs females.

Following a single iv low-dose, radioactivity was eliminated rapidly and primarily in the urine. Males excreted a slightly lower proportion of the administered dose in the urine and a greater proportion in feces when compared to females. At sacrifice, the highest tissue levels of radioactivity were detected in the liver and kidneys with similar hepatic concentrations between the sexes and much lower renal concentrations in males vs females.

At least 60% of the dose was absorbed following oral administration, but the molecule was not extensively metabolized by the rat, since most of the absorbed dose was excreted as parent compound in the urine. In addition, small amounts of minor metabolites including 4-hydroxy mesotrione, 5-hydroxy mesotrione, MNBA, and AMBA were excreted in the urine and feces. In the bile cannulated animals, mesotrione was also eliminated in the bile and this elimination was more pronounced in males. There was evidence of metabolism of mesotrione by the intestinal flora, resulting in an array of fecal metabolites, including cleavage of the aromatic and dione rings to yield MNBA and AMBA; these two metabolites appear to have been reabsorbed and excreted in the urine.

- B. Reviewer's Discussion - Dosed radioactivity was quantitatively recovered from each dose group, with 62.5-97.1% of the dosed radioactivity being recovered in urine, feces, bile, cage washes, and tissues within 72 hours of dosing.

Absorption of [¹⁴C]mesotrione from the G.I. tract of rats was evident in both low- and high-dose animals based upon the high level of urinary excretion. In normal rats dosed once orally with [¹⁴C]mesotrione at either 1.00 or 100 mg/kg, the pattern of excretion was similar between the sexes and the dose groups; renal excretion accounted for 53.0-64.3% of the dose within 24 hours of dosing, equivalent to 66-71% of the total excretion. In the repeated oral low-dose animals, excretion in the urine and feces of both sexes was essentially complete within 24 hours and accounted for 84.9-87.0% of the dose, equivalent to 94-95% of the total excretion. Following iv dosing of [¹⁴C-aromatic]mesotrione at 1.0 mg/kg, excretion in the urine and feces was essentially complete within 24 hours and accounted for 83.8% of the dose, equivalent to 97% of the total excretion. The pattern of excretion was also similar for males and females in the iv dosing group, although total fecal excretion was 2.9x higher for

males than females. However, the relevance of this difference was equivocal because fecal excretion was a minor component of the overall excretion for the iv dosed rats (< 7% of the total dose).

For the bile-cannulated rats dosed with [¹⁴C-aromatic] or [¹⁴C-dione]mesotrione at 50 mg/kg, biliary excretion was higher in males (3.8-5.2x) when compared to females, although recovery in bile was low for both labels. By 24 hours post-dose, cumulative biliary excretion accounted for 10.1-14.0 and 1.9-3.5% of the dose for males and females, respectively. Excretion in the urine was rapid with 39.9-55.5% of the dose being excreted in the urine within 12 hours of dosing, equivalent to 84-91% of the total urinary excretion. Overall excretion was essentially completed within 24 hours, with urinary and fecal excretion together accounting for 54.9-68.6 and 55.7-84.3% of the dose for males and females, respectively.

The overall recovery of dosed radioactivity in excreta, bile, tissues, cage washes was 92.0-97.1% from rats in the mass balance studies and 62.5-92.9% from rats in the biliary excretion study. Within 72 hours of receiving a single oral dose of [¹⁴C-aromatic]mesotrione at 1.00 mg/kg, both sexes excreted 54.2-55.9% of the dose in the urine and 23.8-24.5% of the dose in the feces. Radioactivity remaining in the carcass/tissues of both sexes accounted for 11.2-12.5% of the dose. Increasing the dose to 100 mg/kg had little effect on the pattern of excretion for either males or females. Males and females excreted 61.5-63.0% of the dose in the urine and 28.8-30.5% of the dose in the feces; the recovery of radioactivity in the tissues/carcass was also similar between sexes (0.71-1.1% dose), but much lower when compared to the low-dose group. Repeated dosing at 1.00 mg/kg/day also had little effect on the pattern of excretion of [¹⁴C-aromatic]mesotrione. The levels of radioactivity recovered in excreta of males (urine, 60.8% dose; feces, 30.3% dose) and females (urine, 67.0% dose; feces, 23.1% dose) from the repeated oral low-dose group were slightly higher than the levels observed in the single oral low-dose group, and the recovery of radioactivity in the tissues/carcass were lower (5.1-5.3% dose). The overall pattern of excretion was also generally similar between rats dosed orally or intravenously at 1.00 mg/kg. Radioactivity in urine of the iv-dosed males (79.4% dose) and females (84.1% dose) was somewhat higher (1.5x) than in urine of orally dosed rats, and iv-dosed rats had lower (0.10-0.28x) levels of radioactivity in feces (2.4-6.8% dose) than orally dosed animals. However, intravenous dosing resulted in similar levels of radioactivity being retained in the tissues and carcass (10.0-10.4% dose) after 72 hours.

In the bile-duct cannulated rats, a similar overall pattern of elimination was exhibited among the sexes following oral dosing of [¹⁴C-aromatic]mesotrione at 50 mg/kg. The majority of the administered dose was recovered in the urine, with urinary excretion being slightly higher (1.2x) in females (64.1% dose) than in males (55.2% dose). Radioactivity in the feces accounted for 25.3 and 26.8% of the dose in males and females, respectively. Biliary excretion of bile-duct cannulated rats was a minor route of excretion for males (10.4% dose), but even lower (0.19x) for females (2.0% dose).

Altering the position of the ^{14}C -label within the parent molecule from the aromatic-ring to the dione-ring had only a minor impact on the pattern of excretion in rats. In addition, no sex-related differences were apparent in the excretion of radioactivity, with both sexes excreting ~46% of the dose in the urine and ~13% of the dose in the feces. The recovery of radioactivity slightly decreased (0.4-0.8x) in the urine (44.1-47.5% of dose) and feces (11.2-16.2% dose) of males and females. Biliary excretion of bile-duct cannulated rats was a minor route of excretion for males (14.2% dose), but even lower (0.27x) for females (3.8% dose).

Regarding tissue distribution, concentrations of ^{14}C -residues in tissues were similar between the sexes within each dose group. Although actual ^{14}C -residue concentrations in tissues differed between dose groups, the relative distribution of radioactivity between tissues were the same within each dose group, with ^{14}C -residues being highest in liver and kidney. In each low-dose group, radioactivity in the female kidneys was 3.3-4.4x higher than males; in the high-dose group, the difference was 1.8x. For orally dosed animals, increasing the dose level from 1.00 to 100 mg/kg increased the concentration of radioactivity in liver (1.9-2.1x) and kidneys (1.5-3.0x). Repeated oral dosing with mesotrione at 1.00 mg/kg/day resulted in reduced accumulation of ^{14}C -residues in tissues. Compared to the single oral low-dose group, ^{14}C -residues were on average 0.44x lower in tissues of repeated low-dose animals. Administering a single low-dose intravenously had no impact on the general distribution of radioactivity among tissues. As in the single oral low-dose group, levels of radioactivity in tissues and organs of rats were similar between sexes and showed the same distribution of radioactivity.

With the exception of the bile-duct cannulated group of rats, 62-78% of the dose was identified in urine and fecal extracts of orally dosed rats. Although there were minor differences in levels of metabolites between males and females and between dose groups, the metabolite profile was similar between the sexes in each group and between the single oral low-dose, single oral high-dose, and repeated oral low-dose groups. In rats from each of these groups, free mesotrione was the major metabolite identified in urine, accounting for 47-53% of the dose in single oral low-dose group, 56-59% of the dose in the single oral high-dose group, and 54-64% of the dose in repeated oral low-dose group. Mesotrione also accounted for 3-8% of the dose in feces from the single low- and high-dose groups and 1% of the dose in feces from the repeated-dose group. Other minor metabolites identified in excreta included MNBA (1-4% dose), AMBA (3-12% dose), 5-hydroxy-mesotrione ($\leq 2\%$ dose), and 4-hydroxy-mesotrione (3-6% dose). AMBA was detected almost exclusively in feces (2-12% dose) of both sexes; 4-hydroxy-mesotrione was detected only in males and primarily in urine (3-5% dose). No urinary or fecal unknowns were detected which accounted for $>5\%$ of the administered.

Analysis of bile from bile-duct cannulated rats administered a 50 mg/kg dose of [^{14}C -aromatic]mesotrione identified only two minor components, 4-hydroxy mesotrione (2% dose, males only) and mesotrione (2-8% dose). Biliary excretion was a more prominent route of excretion for the males (10% dose) than females (2% dose). For both sexes, the majority of the radioactivity was excreted in the urine and was identified as parent (males, 48% dose;

females, 60% dose). AMBA was the major component in feces and accounted for 8-10% of the dose. A total of 74-77% of the dose was identified in excreta and bile, with the major component being parent compound. Only one unknown accounted for $\geq 5\%$ of the dose (unknown E, 5% dose, males only).

Analysis of bile from bile-duct cannulated rats administered a 50 mg/kg dose of [^{14}C -dione] mesotrione identified only two components, 4-hydroxy mesotrione (1% dose, males only) and parent (3-11% dose). Biliary excretion was again a more prominent route of excretion for the males (12% dose) than females (3% dose). For both sexes, the most prominent route of excretion was in the urine and the major component identified in urine was parent, totaling 43 and 51% of the dose in males and females, respectively. Two minor components were identified in the fecal extracts and included 5-hydroxy mesotrione (1% dose, females only) and parent (1% dose, males only). A total of 55-59% of the dose was identified in excreta and bile. Only one unknown accounted for $\geq 5\%$ of the dose (unknown H, 6% dose, males only).

This study is classified **acceptable (§85-1a)** and does satisfy the guideline requirements for a metabolism study in rats.

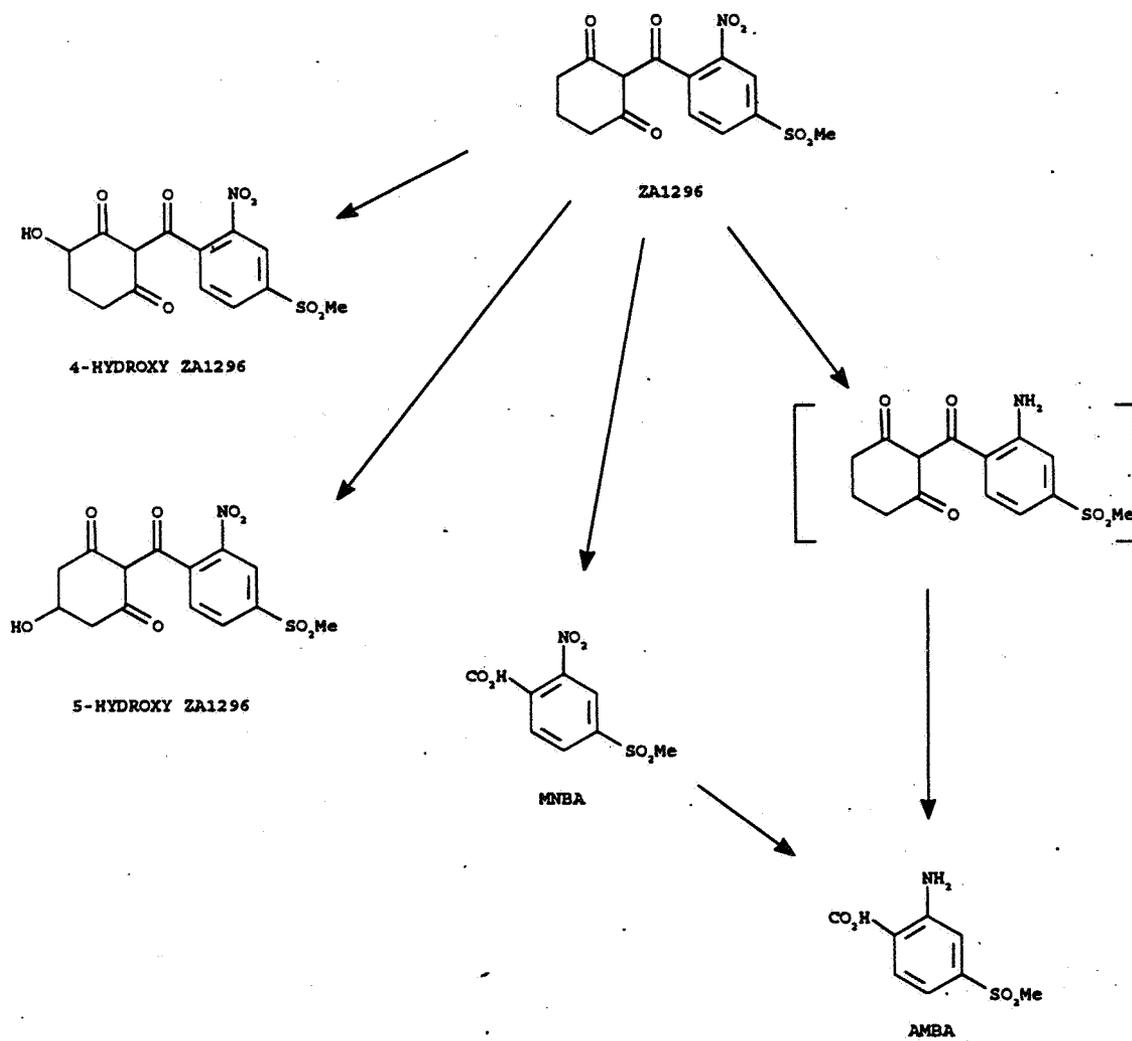
C. Study deficiencies - The following deficiencies were noted, but given the levels of identification achieved for most of the dose groups (62-78% of the dose identified) and the prominence of parent (50-65% dose) in the metabolic profile, these deficiencies will not affect the conclusions and acceptability of this review:

- Compared to [^{14}C -aromatic] mid-dose group, the total amount of radioactivity that was accounted for over the entire 48 hour study period was much lower for the [^{14}C -dione] animals (males, 76.8%; females, 63.9%) vs the [^{14}C -aromatic] animals (males, 96.6%; females, 90.5%). No explanation was provided as to the difference in the accounted radioactivity between the two radiolabels.
- Low extraction efficiencies resulted in residual radioactivity in fecal solids (6.2-13.5% dose unextracted) of normal rats.

Appendix 1

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FIGURE 2 - PROPOSED METABOLIC PATHWAY FOR ZA1296 IN THE RAT



Structures in square brackets indicate postulated intermediates