6-29-98

DATA EVALUATION RECORD

DIFLUFENZOPYR (SAN 835 H Technical)

Study Type: 85-1; Metabolism of ^{14}C-Diflufenzopyr in Rats

Work Assignment No. 3-50H (MRID 44307406)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat
OPPTS Number: 870.7485; OPP Guideline Number: §85-1

EPA ID Numbers:

P.C. CODE: ~~007703~~ 005107
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SUBMISSION CODE: S509228

TEST MATERIAL (PURITY): Diflufenzopyr (>98% a.i.)

SYNONYMS: 2-(Methyl(((3,5-difluorophenylamino)-carbonyl)hydrazono)methyl)-3-pyridine carboxylic acid; SAN 835 H

CITATION: Yu, C.C., Thorne, R.L., and P.K. Sen (1997) Metabolism of SAN 835 H in rats. Sandoz Agro, Inc. 1300 East Touhy Avenue, Des Plaines, IL. Project No. 414205. Report No. 1. April 17, 1997. MRID 44307406. Unpublished.

SPONSOR: Sandoz Agro, Inc.
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EXECUTIVE SUMMARY: In a rat metabolism study (MRID 44307406), [phenyl-U-^{14}C] or [pyridinyl-4,6-^{14}C]diflufenzopyr was administered to five Wistar rats/sex/dose group as a single intravenous dose at 1 mg/kg/day, a single oral dose (gavage) at 10 or 1000 mg/kg or a single dose at 10 mg/kg following a 14-day pretreatment with unlabeled diflufenzopyr at 10 mg/kg. Bile-duct cannulated rats from each dose group were sacrificed at 48 hours post-dose (Subgroup 2). Non-cannulated rats from each dose group were sacrificed at 72 hours (Subgroup 1) or 24 hours (Subgroup 3) post-dose.

[^{14}C]Diflufenzopyr was only partially absorbed from the GI tracts of orally dosed rats as indicated by the levels of excretion in urine and bile. In all orally dosed groups, 20-44% of the dose was excreted in the urine and 3-11% was excreted in the bile. In contrast, intravenously dosed rats excreted 61-89% of the dose in urine and 4-19% of the dose in bile. For all orally dosed groups, the level of absorption was similar between sexes. Dose level and pretreatment had little effect on the proportion of the dose excreted in urine following oral administration.

Enterohepatic circulation plays a role in the elimination of [^{14}C[diflufenzopyr in rats 3-19% of the dose was recovered in the bile of all dose groups.

Within 72 hours of dosing, intravenously-dosed rats excreted the majority of radioactivity in urine (61-89%), whereas orally-dosed rats excreted most of the radioactivity in feces (49-79%), regardless of radiolabel or sex. Pretreatment did not appear to affect the pattern of excretion. Bile-cannulated rats excreted lesser amounts in feces compared to non-cannulated rats; 3-19% of the dose was excreted in bile. The estimated half-lives of radiocarbon eliminated in urine and feces was 5.3-6.9 hours for all single intravenous and oral dose groups, and 7.7-10.8 hours for all repeat oral dose groups.

Total radioactive residues in tissues from rats in all dose groups were <3% of the administered dose. Total tissue residue levels were highest in rats sacrificed at 24 hours post-dose; residue levels were highest in blood, blood cell, and serum for the phenyl label groups, and were highest in liver and kidney for the pyridinyl label groups.

Blood residue levels for all dose groups were <1% of the administered dose at all sampling intervals through 72 hours post-dose.

TLC and HPLC analyses were conducted on 0-72 and 0-48 urine and feces samples, and on 0-48 hour bile samples from each treatment regimen. The structures of the metabolites were confirmed using 2-D TLC, HPLC, LC/MS, DIP/MS, FAB/MS, and proton NMR. For each dose group, the metabolic profile was similar between sexes, except for differences in metabolite levels. Unchanged diflufenzopyr was identified as the major component in urine, feces, and bile from all dose groups using either radiolabel. Urinary metabolites identified in the ^{14}C-phenyl labeled dose groups included: 3,5-difluoroaniline (M2; aniline) and 6-((3,5-difluorophenyl) carbomyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (M5; carbamoyl phthalazinone). Urinary metabolites identified in the ^{14}C-pyridinyl labeled dose groups included: 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (M1; phthalazinone); carbamoyl phthalazinone (M5); 2-acetyl nicotinic acid (M6; 2-acetyl nicotinic acid); 8-methylpyrido[2,3-d]pyridazine-2,5(1H, 6H)-dione (M9; 2-keto-M1); 8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (M10; 8-hydroxymethyl-M1); and, 8-hydroxymethylpyrido[2,3-d]pyridazine-2;5(1H,6H)-dione (M19; 2-keto-8-hydroxymethyl-M1 or Metabolite E). Fecal metabolites identified in the phenyl label groups included: methyl N-(3,5-difluorophenyl)carbamate (M8) and M5. Fecal metabolites identified in the pyridinyl label groups included: M1, M5, M6, M9, and M10. Besides parent, bile samples also contained minor amounts of M5 (both labels) and M1 (pyridinyl label only).

The data indicate that diflufenzopyr is excreted primarily as unchanged parent in urine, feces, and bile. Minor amounts of hydrolysis products (M1, M5, and M6) and hydroxylation products (M9, M10, and M19) were identified in excreta.

This metabolism study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study in the rat (§85-1).

COMPLIANCE:

A signed and dated Statement of No Data Confidentiality Claims, Good Laboratory Practice Compliance Statement, and Quality Assurance Unit Final Report Statement were provided.

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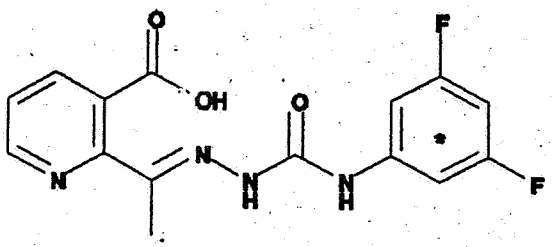
I. MATERIALS AND METHODS

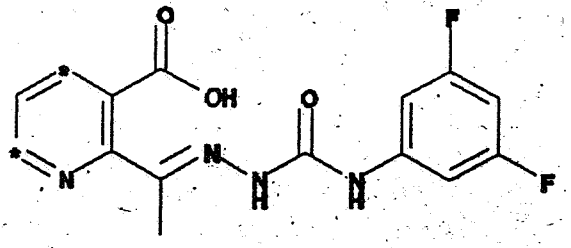
A. MATERIALS:

1. Test Compounds:

[Phenyl-U-^{14}C]diflufenzopyr (SAN 835 H technical)
Radiochemical purity: >98% [determined by TLC and HPLC]
Specific activity: 77 and 56 mCi/mmole
Lot/Batch: CFQ6737, CFQ7939



[Pyridinyl-4,6-^{14}C]diflufenzopyr (SAN 835 H technical)
Radiochemical purity: >98% [determined by TLC and HPLC]
Specific activity: 53 mCi/mmole
Lot/Batch: CFQ7629



Non-radioactive diflufenzopyr
Purity: 99.47%
Lot/Batch No.: RS-835-062392
Contaminants: Not reported
CAS No.: 109293-97-2

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2. Vehicle and/or positive control: Dosing solutions for intravenous dosing were prepared in sodium bicarbonate solution. Dosing solutions for oral dosing were prepared in dimethyl sulfoxide (DMSO).

3. Test animals: Species: Rat
Strain: Wistar
Age at study initiation: 7-9 weeks old
Weight at study initiation: Approximately 200 g
Source: Charles River Laboratory, Portage, MI
Housing: All test animals were individually housed in suspended metabolism cages suitable for the collection of urine and feces.
Diet: During acclimation: Certified Purina rat chow, Product #5002, ad libitum, except during a 16-hour fasting period prior to dosing. During dosing: Certified Purina rat meal, Product #512R (Scientific Animal Feeds, Arlington Hts, IL), ad libitum, except during 16-hour fasting period prior to dosing.
Water: Tap water, ad libitum
Environmental conditions:
Temperature: Not reported
Humidity: Not reported
Air Changes: Not reported
Photoperiod: 12-Hour light/dark cycle
Acclimation period: ≥3 Days

4. Preparation of dosing solutions: For intravenous dosing, the test substance was dissolved in sodium bicarbonate solution. For oral dosing, the test substance was dissolved in DMSO.

B. STUDY DESIGN:

The study was designed to determine the adsorption, metabolism, distribution, and excretion of [phenyl-U-^{14}C] and [pyridinyl-4,6-^{14}C]diflufenzopyr in Wistar rats.

1. Study Dates

The in-life portion of the study was conducted from April 1994 to March 1995, and the analytical phase of the study was conducted from May 1995 to October 1996.

2. Group Arrangements

Animals were randomly assigned to the test groups listed in Table 1. Groups A and E received a single intravenous dose of [^{14}C]diflufenzopyr at 1 mg/kg. Groups B and F received a single oral dose of [^{14}C]diflufenzopyr at

10 mg/kg by gavage. Groups C and G received a single oral dose of [^{14}C]diflufenzopyr at 1000 mg/kg by gavage. Groups D and H received a daily oral dose of unlabeled diflufenzopyr at 10 mg/kg/day for 14 days followed by a single oral dose of [^{14}C]diflufenzopyr at 10 mg/kg.

Table 1. Dosing groups for pharmacokinetics studies for [^{14}C]diflufenzopyr.[a]

Test Group	Dose of labelled material (mg/kg)	Number/sex[a]	Remarks
Single i.v. dose of [phenyl-U-^{14}C]diflufenzopyr (Group A)	1	15/sex	Excretion/distribution studies: Urine and feces were collected from all dose groups at 7 hours post-dose and then at 24-hour intervals until sacrifice. Blood samples were collected at 1, 2, 4, 7, and 24 hours post-dosing (Subgroup 2 rats). Bile samples from bile-duct cannulated rats (Subgroup 3 rats) were collected at 1, 2, 4, 7, 24, and 48 hours post-dose. Following sacrifice, tissues were collected from each test animal. Pooled urine and fecal samples were used for metabolite characterization.
Single low dose of [phenyl-U-^{14}C]diflufenzopyr (Group B)	10	15/sex	
Single high dose of [phenyl-U-^{14}C]diflufenzopyr (Group C)	1000	15/sex	
Single low dose of [phenyl-U-^{14}C]diflufenzopyr following pretreatment (Group D)	10	10/sex	
Single i.v. dose of [pyridinyl-4,6-^{14}C]diflufenzopyr (Group E)	1	15/sex	
Single low dose of [pyridinyl-4,6-^{14}C]diflufenzopyr (Group F)	10	15/sex	
Single high dose of [pyridinyl-4,6-^{14}C]diflufenzopyr (Group G)	1000	15/sex	
Single low dose of [pyridinyl-4,6-^{14}C]diflufenzopyr following pretreatment (Group H)	10	10/sex	

[a] Each dose group except for the repeat dose groups (Groups D and H), consisted of three Subgroups (5 rats/sex/Subgroup): (Subgroup 1) rats were killed 72 hours after ^{14}C dosing; (Subgroup 2) rats for periodic blood sampling that were killed 24 hours after dosing; and (Subgroup 3) bile-duct cannulated rats killed 48 hours after dosing. Groups D and H each consisted of Subgroups 1 and 2 as described above.

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3. Dose selection rationale

The dose level used for intravenous dosing (1 mg/kg) was selected based on the limited solubility of diflufenzopyr in the available intravenous injection vehicle. The oral dose levels of 10 and 1000 mg/kg were selected based upon results from a 90-day feeding study in which the NOEL was 5000 ppm (350 mg/kg/day for males; 430 mg/kg/day for females) and the LOEL was 10000 ppm (629 mg/kg/day for males; 890 mg/kg/day for females). Based upon the above LOEL, the 1000 mg/kg dose level was considered to be high enough to result in some toxic effects but not be lethal to the rats.

4. Dosing and sample collection

Rats in the intravenous groups received a single dose of [^{14}C]diflufenzopyr in 0.05 M sodium bicarbonate (120-175 µl/dose) via the jugular vein. For i.v dosing, Subgroups 1 and 2 Subgroups consisted of jugular vein-cannulated rats, and Subgroup 3 consisted of jugular vein- and bile-duct doubly-cannulated rats. All orally-dosed rats were treated by gavage (125-800 µl DMSO/dose). Single oral dose groups consisted of normal rats (Subgroups 1 and 2) and bile-duct cannulated rats (Subgroup 3). The repeated oral dose groups consisted of normal rats (Subgroups 1 and 2).

a. Pharmacokinetics studies

Excretion/distribution study: Following dosing with [^{14}C]diflufenzopyr, animals were placed in metabolism cages suitable for urine and feces collection. For all groups, urine and feces were collected at 7 hours post-dose and thereafter at 24-hour intervals until sacrifice (24, 48 or 72 hours post-dose). At each sampling interval, the cage was rinsed with water and the washes were combined with the urine sample for that interval. At the last sample collection, the metabolism cages were washed with methanol then water, and the washings were added to the last urine collection. Bile was collected from bile-cannulated rats (Subgroup 3) at 1, 2, 4, 7, 24, and 48 hours post-dose. Blood was collected from the tail Subgroup 2 rats at 1, 2, 4, and 7 hours post-dose, and by cardiac puncture at 24 hours post-dose. The test animals in Subgroups 1, 2 and 3 were killed by cardiac puncture at 72, 24, 48 hours post-dose, respectively. At sacrifice, blood, fat, gonad, muscle, bone, lung, spleen, heart, kidney, liver, and brain were collected from each animal.

b. Metabolite characterization studies

For metabolite characterization, pooled urine and fecal samples from Subgroups 1 and 3, and pooled bile samples from Subgroup 3 animals were analyzed using 1- and 2-D TLC and HPLC. Structural confirmation of [^{14}C]compounds was made using 2-D TLC, HPLC, LC/MS, DIP/MS, FAB/MS, and proton NMR.

Urine samples containing ≥1% of the dosed radioactivity were pooled by dose group/sex for metabolite analysis. Pooled urine samples were acidified to pH ~1 with trifluoroacetic acid (TFA) and diluted with a small amount of methanol (~4% by volume). The acidified samples were loaded onto a 60 RP-18 column and eluted sequentially with 1% TFA and methanol, resulting in a aqueous and organic fraction. Organic fractions were concentrated by rotary evaporation and directly analyzed for metabolites by 2D-TLC or were subjected to preparative 1-D TLC prior to HPLC and MS analyses. The aqueous fractions were analyzed using LSC.

For metabolite analysis, fecal samples containing ≥1% of the dosed radioactivity were pooled by dose group/sex, homogenized, and lyophilized. The dried samples were extracted with methanol on a shaker for 30 minutes, sonicated (^{14}C-Phenyl labeled samples only), centrifuged, and filtered. The extraction process was repeated, and the methanol extracts were combined and concentrated. Metabolites in methanolic extracts were analyzed by 1- and 2-D TLC, or were subjected to preparative 1-D TLC prior to HPLC and MS analyses. Residual solids from the phenyl-labeled samples were air-dried, refluxed in 1 N HCl for 1 hour, and filtered. The filtrate was partitioned three times with ethyl acetate. The ethyl acetate fractions were combined, concentrated, diluted with 1% TFA with 5% acetonitrile and loaded onto a C_{18} SPE column. Residues were eluted sequentially with 1% TFA and acetonitrile. The resulting C_{18}-acetonitrile fraction was analyzed by TLC. Aqueous fractions were analyzed using LSC.

Bile samples containing ≥1% of the dosed radioactivity were also pooled by dose group/sex for metabolite analysis. The pooled samples were acidified to pH ~3 with 1% TFA and purified using a C18 column eluted sequentially with methanol and 1% TFA. The organic fractions were concentrated by rotary evaporation and analyzed directly by 2-D TLC or were subjected to preparative 1-D TLC. Radioactive bands were analyzed for individual metabolites using HPLC and MS. Clusters of polar metabolites in the organic fraction were also refluxed with 1N HCl for 1 hour, and partitioned with ethyl acetate. The acidic ethyl acetate fraction was concentrated and analyzed by TLC. The remaining acidic aqueous fraction was refluxed sequentially with 1N and 3N NaOH for 1 hour each time, and partitioned with ethyl acetate following each base hydrolysis. The resulting basic organic fractions were combined and analyzed by TLC.

Metabolites were identified by cochromatography with diflufenzopyr and the following unlabeled reference

standards: 8-methyl-5-hydroxy-pyrido(2,3-d)-pyridazine (M1; phthalazinone); 3,5-difluoroaniline (M2; aniline); N,N'-bis(3,5-difluorophenyl)-urea (M3; symmetric urea); 6-((3,5-difluorophenyl)carbomyl)-8-methyl-pyrido (2,3-d)-5-pyridazinone (M5; carbamoyl phthalazinone); 2-acetyl nicotinic acid (M6); 4-(3,5-difluorophenyl)semicarbazide (M7; semicarbazide); methyl N-(3,5-difluorophenyl)carbamate (M8; carbamate); 8-methylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M9; 2-keto-M1); 8-hydroxymethyl-5(6H)-pyrido[2,3-d]pyridazinone (M10; 8-hydroxymethyl-M1); and, 8-hydroxymethylpyrido[2,3-d]pyridazine-2,5(1H,6H)-dione (M19; 2-keto-8-hydroxymethyl-M1 or Metabolite E). Structures and TLC and HPLC characteristics of diflufenzopyr and its metabolites are presented as Attachment 1 of this DER.

5. Statistics

Averages of all replicate analyses were obtained.

II. RESULTS

A. Pharmacokinetics Studies

1. Absorption

[^{14}C]Diflufenzopyr was only partially absorbed from the GI tracts of orally dosed rats as indicated by the levels of excretion in urine and bile. In all orally dosed groups, 20-44% of the dose was excreted in the urine (including cage washes) and 3-11% was excreted in the bile. In contrast, intravenously dosed rats excreted 61-89% of the dose in urine and 4-19% of the dose in bile. For all orally dosed groups, the level of absorption was slightly higher for females than males, and slightly higher for rats treated with the [pyridinyl-4,6-^{14}C] label than [phenyl-U-^{14}C] label. Dose level and pretreatment had little effect on the proportion of the dose excreted in urine following oral administration.

a) Intravenous dose with [phenyl-U-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 61.01% of the administered dose for male rats and 72.55% of the administered dose for female rats (Table 2). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 73.22 and 76.54% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 70.58 and 68.01%,

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respectively, was excreted in urine and 18.58 and 11.02%, respectively, was excreted in bile.

Table 2. Recovery over time of radioactivity in excreta of rats intravenously dosed with [phenyl-U-^{14}C]diflufenzopyr at 1 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	58.59	53.15	55.54	59.59	61.38	55.72
7-24 hr	11.40	5.75	10.50	12.92	8.26	8.93
24-48 hr	2.05	--[c]	2.53	2.35	--	3.06
48-72 hr	0.77	--	--	1.15	--	--
SUBTOTAL	72.81	58.90	68.57	76.01	69.64[c]	67.71[d]
Feces						
0-7 hr	0.01	5.65	0.40	0.62	6.19	0.17
7-24 hr	18.88	16.10	0.77	12.27	6.86	0.88
24-48 hr	0.91	--	0.40	0.46	--	0.44
48-72 hr	0.06	--	--	0.10	--	--
SUBTOTAL	19.86	21.75	1.57	13.45	13.05	1.49[d]
Cage wash	0.41	2.11	2.01	0.53	2.91[d]	0.30[d]
Bile						
0-1 hr	--	--	15.78	--	--	8.67
1-2 hr	--	--	2.03	--	--	1.58
2-4 hr	--	--	0.48	--	--	0.45
4-7 hr	--	--	0.13	--	--	0.11
7-24 hr	--	--	0.12	--	--	0.15
24-48 hr	--	--	0.04	--	--	0.06
SUBTOTAL			18.58	--	--	11.02[d]
TOTAL	93.08	82.76	90.73	89.99	85.60	80.60

a Data are the mean of five animals except as noted, and were obtained from Table 4, page 39 of the study report.

b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.

c Not sampled.

d Data are the mean of four animals.

b) Single low oral dose with [phenyl-U-^{14}C] label: In rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 19.63% of the administered dose for male rats and 25.31% of the administered dose for female rats (Table 3). In normal rats sacrificed at 72 hours post-dose (Subgroup 1),

cumulative urinary excretion was 23.20 and 25.17% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 19.60 and 34.95%, respectively, was excreted in urine and 10.54 and 7.59%, respectively, was excreted in bile.

Table 3. Recovery over time of radioactivity in excreta of rats following a single oral dose of [phenyl-U-^{14}C]diflufenzopyr at 10 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	14.02	8.91	5.10	15.48	12.21	14.34
7-24 hr	7.92	9.50	11.07	7.67	11.26	16.19
24-48 hr	0.87	--[c]	2.56	1.54	--	3.93
48-72 hr	0.32	--	--	0.33	--	--
SUBTOTAL	23.13	18.41	18.73	25.02	23.47	34.46
Feces						
0-7 hr	0.90	26.30	0.08	3.52	9.81	0.01
7-24 hr	76.79	39.37	49.78[d]	59.41	54.46	38.73
24-48 hr	1.29	--	4.88[d]	4.39	--	14.50
48-72 hr	0.07	--	--	0.13	--	--
SUBTOTAL	79.05	65.67	54.74	67.45	64.27	53.24[d]
Cage wash	0.07	1.22	0.87	0.15	1.84	1.03
Bile						
0-1 hr	--	--	0.29	--	--	0.15
1-2 hr	--	--	0.28	--	--	1.06
2-4 hr	--	--	0.71	--	--	0.61
4-7 hr	--	--	3.29	--	--	0.85
7-24 hr	--	--	5.64	--	--	4.41
24-48 hr	--	--	0.33	--	--	0.51
SUBTOTAL	--	--	10.54[d]	--	--	7.59
TOTAL	102.25	85.30	84.88	92.62	89.58	96.32

a Data are the mean of five animals except as noted, and were obtained from Table 5, page 40 of the study report.

b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.

c Not sampled.

d Data are the mean of four animals.

c) Single high oral dose with [phenyl-U-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 24.17% of the administered dose for male rats and 26.68% of the administered dose for female rats (Table 4). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 24.55 and 26.17% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 26.39 and 33.58%, respectively, was excreted in urine and 6.36 and 7.48%, respectively, was excreted in bile.

Table 4. Recovery over time of radioactivity in excreta of rats following a single oral dose of [phenyl-U-^{14}C]diflufenzopyr at 1000 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	7.67	6.82	4.47	8.76	8.61	7.48
7-24 hr	14.70	14.77	12.92	14.39	15.57	16.37
24-48 hr	1.94	--[c]	7.40	2.35	--	7.80
48-72 hr	0.24	--	--	0.32	--	--
SUBTOTAL	24.55	21.59	24.79	25.82	24.18	31.65
Feces						
0-7 hr	0.34	9.73	0.18	0.17	1.93	0.01
7-24 hr	61.89	42.50	34.24	55.80	47.30	18.56
24-48 hr	9.43	--	23.14	15.67	--	27.87
48-72 hr	0.18	--	--	0.35	--	--
SUBTOTAL	71.84	52.23	57.56	71.99	49.23	46.44[d]
Cage wash	NR[e]	2.58	1.60	0.35	2.50	1.93
Bile						
0-1 hr	--	--	0.10	--	--	0.02
1-2 hr	--	--	0.20	--	--	0.05
2-4 hr	--	--	0.58	--	--	0.24
4-7 hr	--	--	0.92	--	--	0.93
7-24 hr	--	--	3.37	--	--	4.39
24-48 hr	--	--	1.19	--	--	1.85
SUBTOTAL	--	--	6.36	--	--	7.48
TOTAL	96.39	76.40	90.31	98.16	75.91	87.50

a Data are the mean of five animals except as noted, and were obtained from Table 6, page 41 of the study report.

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b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.
c Not sampled.
d Data are the mean of three animals.

d) Repeat oral dose with [phenyl-U-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 19.79% of the administered dose for male rats and 21.65% of the administered dose for female rats (Table 5). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 19.53 and 26.48% of the dose for males and females, respectively.

Table 5. Recovery over time of radioactivity in excreta of rats treated with a single oral dose of [phenyl-U-^{14}C]diflufenzopyr at 10 mg/kg following a 14-day pretreatment with diflufenzopyr at 10 mg/kg/day.[a]

Sample	Percent of Administered Dose			
	Males			
	Subgroup 1[b]	Subgroup 2	Subgroup 1	Subgroup 2
Urine				
0-7 hr	7.11	6.95	12.01	8.99
7-24 hr	9.22	11.25	10.68	11.15
24-48 hr	2.20	--[c]	2.24	--
48-72 hr	0.58	--	1.06	--
SUBTOTAL	19.11	18.20	26.01	20.14
Feces				
0-7 hr	0.25	14.66	0.00	10.56
7-24 hr	71.90	41.65[d]	68.56	58.32
24-48 hr	3.95	--	0.95	--
48-72 hr	0.19	--	0.13	--
SUBTOTAL	76.29	56.31	69.64	68.88[d]
Cage wash	0.42	1.59	0.47	1.51
TOTAL	95.82	76.27	96.12	90.53

a Data are the mean of five animals except as noted, and were obtained from Table 7, page 42 of the study report.
b Subgroup 1 rats sacrificed at 72 hrs.; Subgroup 2 rats were sacrificed at 24 hrs. post-dose.
c Not sampled.
d Data are the mean of four animals.

e) Intravenous dose with [pyridinyl-4,6-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2),

radioactivity recovered in the urine (including cage washes) accounted for 66.24% of the administered dose for male rats and 86.02% of the administered dose for female rats (Table 6). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 75.62 and 89.38% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 63.71 and 70.21%, respectively, was excreted in urine and 16.37 and 4.05%, respectively, was excreted in bile.

Table 6. Recovery over time of radioactivity in excreta of rats dosed intravenously with [pyridinyl-4,6-^{14}C]diflufenzopyr at 1 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	65.67	57.25	52.26	66.69	77.21	58.62
7-24 hr	5.65	6.38	6.92	17.12	6.99	8.52
24-48 hr	2.46	--[c]	2.84	3.53	--	1.74
48-72 hr	1.33	--	--	1.28	--	--
SUBTOTAL	75.11	63.63	62.02	88.62	84.20	68.88
Feces						
0-7 hr	0.04	13.35	0.41	0.60	2.17	0.13
7-24 hr	12.15	7.97	0.80	5.89	6.23	0.79
24-48 hr	0.53	--	0.42	0.55	--	0.36
48-72 hr	0.05	--	--	0.05	--	--
SUBTOTAL	12.77	21.32	1.63	7.09	8.40	1.28
Cage wash	0.51	2.61	1.69	0.76	1.82	1.33
Bile						
0-1 hr	--	--	13.01	--	--	3.11
1-2 hr	--	--	2.63	--	--	0.46
2-4 hr	--	--	0.39	--	--	0.15
4-7 hr	--	--	0.12	--	--	0.11
7-24 hr	--	--	0.20	--	--	0.18
24-48 hr	--	--	0.02	--	--	0.04
SUBTOTAL	--	--	16.37	--	--	4.05
TOTAL	88.40	87.56	81.70	96.46	94.42	75.54

a Data are the mean of five animals and were obtained from Table 8, page 43 of the study report.
b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.
c Not sampled.

f) Single low oral dose with [pyridinyl-4,6-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 32.38-34.27% of the administered dose for male and female rats (Table 7). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 29.70 and 26.93% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 38.19 and 43.57%, respectively, was excreted in urine and 10.09 and 3.08%, respectively, was excreted in bile.

Table 7. Recovery over time of radioactivity in excreta of rats treated with a single oral dose of [pyridinyl-4,6-^{14}C]diflufenzopyr at 10 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	10.94	11.23	9.05	11.36	12.78	11.01
7-24 hr	15.88	19.57	22.43	13.41	18.56	18.68
24-48 hr	2.49	--[c]	5.04	1.68	--	12.79
48-72 hr	0.32	--	--	0.34	--	--
SUBTOTAL	29.63	30.80	36.52	26.79	31.34	42.48
Feces						
0-7 hr	0.03	15.41	2.09	0.01	7.78	0.04
7-24 hr	61.94	35.55	38.94	60.56	48.29	40.05
24-48 hr	8.09	--	9.10	5.24	--	3.89
48-72 hr	0.13	--	--	0.14	--	--
SUBTOTAL	70.19	50.96	50.13	65.95	56.07	43.98
Cage wash	0.07	1.58	1.67	0.14	2.93	1.09
Bile						
0-1 hr	--	--	0.76	--	--	0.12
1-2 hr	--	--	0.77	--	--	0.10
2-4 hr	--	--	1.15	--	--	0.18
4-7 hr	--	--	1.63	--	--	0.59
7-24 hr	--	--	5.19	--	--	1.78
24-48 hr	--	--	0.59	--	--	0.31
SUBTOTAL	--	--	10.09	--	--	3.08
TOTAL	99.89	83.34	98.41	92.88	90.34	90.63

a Data are the mean of five animals/sex except as noted, and were obtained from Table 9, page 44 of the study report.

b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.
c Not sampled.

g) Single high oral dose with [pyridinyl-4,6-^{14}C] label: In normal rats sacrificed at 24 hours post-dose (Subgroup 2), radioactivity recovered in the urine (including cage washes) accounted for 21.09-23.48% of the administered dose for male and female rats (Table 8). In normal rats sacrificed at 72 hours post-dose (Subgroup 1), cumulative urinary excretion was 32.04 and 34.82% of the dose for males and females, respectively. In bile-cannulated male and female rats sacrificed at 48 hours post-dose (Subgroup 3), a total of 38.14 and 35.80%, respectively, was excreted in urine and 8.11 and 4.58%, respectively, was excreted in bile.

Table 8. Recovery over time of radioactivity in excreta of rats treated with a single oral dose of [pyridinyl-4,6-^{14}C]diflufenzopyr at 1000 mg/kg.[a]

Sample	Percent of Administered Dose					
	Males			Females		
	Subgroup 1[b]	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Urine						
0-7 hr	6.41	3.31	3.21	6.09	4.33	5.33
7-24 hr	17.69	17.16	18.99	16.98	12.42	14.69
24-48 hr	7.02	--[c]	11.94	9.64	--	10.02
48-72 hr	0.69	--	--	1.65	--	--
SUBTOTAL	31.81	20.47	34.14	34.36	16.75	30.04
Feces						
0-7 hr	0.01	1.41	0.00	0.03	3.73	0.09
7-24 hr	46.91	24.71	11.00	19.25	13.43	20.49
24-48 hr	20.98	--	8.97	28.41	--	15.46
48-72 hr	1.04	--	--	1.52	--	--
SUBTOTAL	68.94	26.12	19.97	49.21	17.16	36.04
Cage wash	0.23	3.01	4.00	0.46	4.34	5.76
Bile						
0-1 hr	--	--	0.02	--	--	0.04
1-2 hr	--	--	0.02	--	--	0.05
2-4 hr	--	--	0.08	--	--	0.12
4-7 hr	--	--	0.25	--	--	0.87
7-24 hr	--	--	3.90	--	--	2.05
24-48 hr	--	--	3.84	--	--	1.45
SUBTOTAL	--	--	8.11	--	--	4.58

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	Percent of Administered Dose					
TOTAL	100.98	49.60	66.22	84.03	38.25	76.42

Sample

a Data are the mean of five animals and were obtained from Table 10, page 45 of the study report.
b Subgroup 1 rats were sacrificed at 72 hours post-dose, Subgroup 2 rats were sacrificed at 24 hours post-dose, and Subgroup 3 rats were bile-duct cannulated and sacrificed at 48 hours post-dose.
c Not sampled.

h) Repeat oral dose with [pyridinyl-4,6-^{14}C] label: Within 24 hours of administering diflufenzopyr, radioactivity recovered in the urine accounted for 28.49-29.32% of the administered dose for male and female rats (Table 9; Subgroups 1 and 2). At 72 hours post-dose, cumulative urinary excretion (including cage washes) for Subgroups 1 was 36.94-37.61% of the dose for males and females.

Table 9. Recovery over time of radioactivity in excreta of rats treated with a single oral dose of [pyridinyl-4,6-^{14}C]diflufenzopyr at 10 mg/kg following a 14-day pretreatment with diflufenzopyr at 10 mg/kg/day.[a]

Sample	Percent of Administered Dose			
	Males		Females	
	Subgroup 1[b]	Subgroup 2	Subgroup 1	Subgroup 2
Urine				
0-7 hr	12.61	9.35	11.60	9.16
7-24 hr	18.55	17.96	18.52	17.88
24-48 hr	4.89	--[c]	6.26	--
48-72 hr	0.82	--	1.01	--
SUBTOTAL	36.87	27.32	37.39	27.04
Feces				
0-7 hr	0.03	8.85	0.05	5.40
7-24 hr	57.08	41.60	46.81	45.51
24-48 hr	6.82	--	17.03	--
48-72 hr	0.28	--	0.37	--
SUBTOTAL	64.21	50.45	64.26	50.91
Cage wash	0.07	1.18	0.22	2.28
TOTAL	101.15	78.95	101.87	80.23

a Data are the mean of five animals/sex except as noted, and were obtained from Table 11, page 46 of the study report.
b Subgroup 1 rats sacrificed at 72 hrs; Subgroup 2 rats sacrificed at 24 hrs post-dose.
c Not sampled.

2. Tissue Distribution

Levels of radioactivity determined in tissues and blood sampled in rats sacrificed at 24, 48, and 72 hours post-dose are summarized in Tables 10-15. Total tissue residue levels for all dose groups accounted for <3% of the administered dose at each sampling interval and were highest in rats sacrificed at 24 hours post-dose. Within each dose group, tissue residue concentrations were higher in females than males. In rats sacrificed at 24 hours post-dose, residue concentrations for the phenyl label groups were highest in blood, blood cell, and serum, and for the pyridinyl label groups were highest in liver and kidney.

For orally dosed [phenyl-U-^{14}C] labeled rats, levels of radioactivity in tissues were proportional to the dose level, with residues being generally 100x greater in the high dose (1000 mg/kg) group than the low dose (10 mg/kg) group. Residues in the repeated dose group were also generally twice as high as in the same tissues from the low dose group. For orally dosed [pyridinyl-4,6-^{14}C] labeled rats, levels of radioactivity in tissues of single high dose animals were generally 250-700x higher than in the same tissues in single low dose rats. Residues in tissues from the repeated dose group were also generally 2-3x higher than in tissues the single low dose group.

a) Intravenous dose with [phenyl-U-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in blood (males, 0.0119 mg/kg; females, 0.0114 mg/kg), blood cell (males, 0.0111 mg/kg; females, 0.0094 mg/kg), and serum (males, 0.0130 mg/kg; females, 0.0126 mg/kg). Residue concentrations were also high in kidney (males, 0.0109 mg/kg; females, 0.0116 mg/kg), lung (both sexes, 0.0064-0.0065 mg/kg), and liver (both sexes, 0.0057-0.0059).

b) Single low oral dose with [phenyl-U-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in blood (males, 0.5443 mg/kg; females, 0.6359 mg/kg), blood cell (males, 0.5284 mg/kg; females, 0.5811 mg/kg), and serum (males, 0.5244 mg/kg; females, 0.6975 mg/kg). Residue concentrations were also high in kidney (males, 0.1879 mg/kg; females, 0.2678 mg/kg) and lung (males, 0.1899 mg/kg; females, 0.2646 mg/kg).

c) Single high oral dose with [phenyl-U-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in blood (males, 57.1225 mg/kg; females, 82.7284 mg/kg), blood cell (males, 69.7123 mg/kg; females, 92.5824 mg/kg), and serum (males, 40.8442 mg/kg; females, 44.4136 mg/kg). Residue concentrations were also high in

kidney (males, 28.0293 mg/kg; females, 35.8990 mg/kg) and lung (males, 22.0515 mg/kg; females, 29.0180 mg/kg).

d) Repeated dose with [phenyl-U-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in blood (males, 0.8970 mg/kg; females, 0.7831 mg/kg), blood cell (males, 0.8320 mg/kg; females, 0.7363 mg/kg), and serum (males, 0.9841 mg/kg; females, 0.7831 mg/kg). Residue concentrations were also high in kidney (males, 0.4197 mg/kg; females, 0.3213 mg/kg) and lung (males, 0.4123 mg/kg; females, 0.3543 mg/kg).

Table 10. Radioactivity in blood, tissues, and organs of rats 24 hours after dosing with [phenyl-U-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents							
	Group A Single i.v. dose (1 mg/kg)		Group B Single low dose (10 mg/kg)		Group C Single high dose (1000 mg/kg)		Group D Repeated low dose (10 mg/kg)	
	Male	Female	Male	Female	Male	Female	Male	Female
Blood	0.0119	0.0114	0.5443	0.6359	57.1225	82.7284	0.8970	0.7831
Blood Cell	0.0111	0.0094	0.5284	0.5811	69.7123	92.5824	0.8320	0.7363
Serum	0.0130	0.0126	0.5244	0.6975	40.8442	44.4136	0.9841	0.7831
Liver	0.0057	0.0059	0.1038	0.1322	18.8198	20.3404	0.1967	0.1797
Kidney	0.0109	0.0116	0.1879	0.2678	28.0293	35.8990	0.4197	0.3213
Spleen	0.0028	0.0037	0.0914	0.1337	12.6045	17.6688	0.1903	0.1633
Heart	0.0028	0.0027	0.1123	0.1374	12.4707	14.6073	0.1996	0.1545
Lung	0.0064	0.0065	0.1899	0.2646	22.0515	29.0180	0.4123	0.3543
Brain	0.0003	0.0004	0.0112	0.0156	1.7397	2.4320	0.0293	0.0200
Muscle	0.0013	0.0010	0.0327	0.0831	3.2703	3.9089	0.0586	0.0378
Gonad	0.0016	0.0038	0.0598	0.1887	4.5802	18.2908	0.1105	0.2071
Fat	0.0012	0.0011	0.0617	0.0728	3.7646	6.5160	0.0802	0.0813
Bone	0.0025	0.0021	0.0468	0.0503	5.5242	5.0448	0.0708	0.0554

a Data are from rats in Subgroup 2 and are the mean of five animals/group; data were obtained from Table 16, page 51 of the study report.

Table 11. Radioactivity in blood, tissues, and organs of rats **48 hours** after dosing with [phenyl-U-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents					
	Group A Single i.v. dose (1 mg/kg)		Group B Single low dose (10 mg/kg)		Group C Single high dose (1000 mg/kg)	
	Male	Female	Male[b]	Female	Male	Female
Blood	0.0042	0.0050	0.4628	0.8301	56.8549	76.8235
Blood Cell	0.0054	0.0063	0.5671	0.8993	70.9312	86.5856
Serum	0.0041	0.0037	0.3430	0.5966	37.3030	54.2117
Liver	0.0027	0.0028	0.1230	0.1381	13.1973	22.9536
Kidney	0.0090	0.0097	0.1793	0.3071	20.1589	42.4713
Spleen	0.0025	0.0024	0.1013	0.1740	11.1196	18.4062
Heart	0.0017	0.0016	0.0949	0.1533	10.2431	14.6184
Lung	0.0038	0.0033	0.1821	0.2902	19.6442	30.8677
Brain	0.0003	0.0003	0.0150	0.0188	2.0063	2.4224
Muscle	0.0012	0.0018	0.0323	0.0395	2.8618	3.5300
Gonad	0.0008	0.0042	0.0383	0.1766	3.9899	14.0838
Fat	0.0018	0.0030	0.0889	0.0679	7.6100	8.8003
Bone	0.0022	0.0026	0.0438	0.0430	5.7204	6.5507

a Data are from rats in Subgroup 3 and are the mean of five animals/group; data were obtained from Table 17, page 52 of the study report.

b Data are average of four animals.

Table 12. Radioactivity in blood, tissues, and organs of rats 72 hours after dosing with [phenyl-U-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents							
	Group A Single i.v. dose (1 mg/kg)		Group B Single low dose (10 mg/kg)		Group C Single high dose (1000 mg/kg)		Group D Repeated low dose (10 mg/kg)	
	Male	Female	Male	Female	Male	Female	Male	Female
Blood	0.0064	0.0057	0.1134	0.1953	26.0488	34.2718	0.2821	0.3943
Blood Cell	0.0077	0.0068	0.2233	0.3650	29.7760	39.8122	0.3245	0.4354
Serum	0.0049	0.0046	0.1085	0.2434	12.7851	19.4923	0.1932	0.2574
Liver	0.0029	0.0024	0.0396	0.0640	2.3553	5.0860	0.0625	0.0716
Kidney	0.0059	0.0062	0.0525	0.1032	5.5599	9.2648	0.0783	0.1095
Spleen	0.0016	0.0016	0.0365	0.0871	4.4939	9.0476	0.0542	0.0835
Heart	0.0014	0.0013	0.0339	0.0625	4.9570	6.5120	0.0502	0.0718
Lung	0.0032	0.0031	0.0644	0.1373	7.7081	13.3563	0.1124	0.1549
Brain	0.0002	0.0002	0.0042	0.0061	0.6610	0.9371	0.0046	0.0068
Muscle	0.0007	0.0013	0.0124	0.0159	1.5319	1.6492	0.0158	0.0194
Gonad	0.0006	0.0022	0.0112	0.0771	1.5810	7.5432	0.0186	0.0794
Fat	0.0010	0.0011	0.0197	0.0254	1.4101	2.1225	0.0312	0.0447
Bone	0.0013	0.0010	0.0168	0.0207	1.6980	2.3968	0.0339	0.0419

a Data are from rats in Subgroup 1 and are the mean of five animals/group; data were obtained from Table 18, page 53 of the study report.

e) Single intravenous dose with [pyridinyl-4,6-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in kidney (males, 0.0070 mg/kg; females, 0.0095 mg/kg) and liver (males, 0.0036 mg/kg; females, 0.0044 mg/kg). For both sexes, residue concentrations were intermediate to low in blood, blood cell, serum, and all other examined tissues and organs (0.0009-0.0040 mg/kg).

f) Single low oral dose with [pyridinyl-4,6-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in kidney (males, 0.2271 mg/kg; females, 0.2886 mg/kg) and liver (males, 0.1153 mg/kg; females, 0.2074 mg/kg). For both sexes, residue concentrations were generally intermediate to low in blood, blood cell, serum, and all other examined tissues and organs (0.0292-0.1581 mg/kg).

g) Single high oral dose with [pyridinyl-4,6-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in kidney (males, 105.4420 mg/kg; females, 90.5860 mg/kg) and liver (males, 53.0760 mg/kg; females, 54.6494 mg/kg). For both sexes, residue concentrations were intermediate in blood, blood cell, serum, spleen, heart, lung, brain, muscle, and gonad (22.8790-44.0770 mg/kg), and low in fat and bone (12.2865-17.7540 mg/kg).

h) Repeated low dose with [pyridinyl-4,6-^{14}C] label: At 24 hours post-dose, radioactivity in tissues from both sexes was highest in kidney (males, 0.5186 mg/kg; females, 0.2806 mg/kg) and liver (males, 0.3018 mg/kg; females, 0.2167 mg/kg), and in females only, muscle (0.3107 mg/kg). For both sexes, residue concentrations were intermediate to low in blood, blood cell, serum, and all other examined tissues and organs (0.0595-0.2447 mg/kg).

Table 13. Radioactivity in blood, tissues, and organs of rats **24 hours** after dosing with [pyridinyl-4,6-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents							
	Group E Single i.v. dose (1 mg/kg)		Group F Single low dose (10 mg/kg)		Group G Single high dose (1000 mg/kg)		Group H Repeated low dose (10 mg/kg)	
	Male	Female	Male	Female	Male	Female	Male	Female
Blood	0.0017[b]	0.0027	0.0586	0.1418	34.3345	43.1011	0.1636	0.2288
Blood Cell	0.0012	0.0024	0.0598	0.1396	32.3897	28.3202[b]	0.1669	0.2292
Serum	0.0019	0.0030	0.0684	0.1581	39.4658	35.4827	0.1908	0.2447
Liver	0.0036	0.0044	0.1153	0.2074	53.0760	54.6494	0.3018	0.2167
Kidney	0.0070	0.0095	0.2271	0.2886	105.4420	90.5860	0.5186	0.2806
Spleen	0.0017	0.0030	0.0520	0.0678	27.8172	38.1280	0.1877	0.2282
Heart	0.0014	0.0027	0.0472	0.1031	28.9724	39.1164	0.1608	0.2321
Lung	0.0032	0.0031	0.0435	0.1403	28.9764	38.2337	0.1629	0.1757
Brain	0.0009	0.0020	0.0359	0.0755	22.8790	31.3431	0.1114	0.1717
Muscle	0.0014	0.0040	0.0471	0.0987	26.7004	37.8453	0.1553	0.3107
Gonad	0.0013	0.0035	0.0534	0.0159	27.3592	44.0770	0.1869	0.2170
Fat	0.0011	0.0019	0.0313	0.0378	13.0498	12.2865	0.1126	0.0595
Bone	0.0014	0.0018	0.0292	0.0633	12.7919	17.7540	0.0947	0.0990

a Data are from rats in Subgroup 2 and are the mean of five animals/group; data were obtained from Table 19, page 54 of the study report.

b Data are average of four animals.

Table 14. Radioactivity in blood, tissues, and organs of rats **48 hours** after dosing with [pyridinyl-4,6-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents					
	Group E Single i.v. dose (1 mg/kg)		Group F Single low dose (10 mg/kg)		Group G Single high dose (1000 mg/kg)	
	Male	Female	Male	Female	Male	Female
Blood	0.0006	0.0006	0.0104	0.0074	27.7766	21.1533
Blood Cell	0.0006	0.0005	0.0057	0.0064	25.4473	20.9875
Serum	0.0007	0.0006	0.0062	0.0074	33.8646	23.9361
Liver	0.0013	0.0012	0.0314	0.0259	52.1893	27.0150
Kidney	0.0045	0.0036	0.0236	0.0282	61.0900	47.2000
Spleen	0.0008	0.0006	0.0053	0.0062	36.7255	20.3199
Heart	0.0006	0.0005	0.0050	0.0069	23.3966	20.5203
Lung	0.0007	0.0005	0.0060	0.0080	25.4609	19.8945
Brain	0.0003	0.0003	0.0059	0.0041	17.5214	16.4437
Muscle	0.0008	0.0007	0.0052	0.0057	20.2630	17.7590
Gonad	0.0005	0.0008	0.0040	0.0063	23.0455	18.3982
Fat	0.0016	0.0013	0.0037	0.0027	12.7494	9.6073
Bone	0.0006	0.0005	0.0041	0.0039	11.9954	7.7996

a. Data are from rats in Subgroup 3 and are the mean of five animals/group; data were obtained from Table 20, page 55 of the study report.

Table 15. Radioactivity in blood, tissues, and organs of rats 72 hours after dosing with [pyridinyl-4,6-^{14}C]diflufenzopyr.[a]

Tissue/ Organ	PPM in [^{14}C]Diflufenzopyr Equivalents							
	Group E Single i.v. dose (1 mg/kg)		Group F Single low dose (10 mg/kg)		Group G Single high dose (1000 mg/kg)		Group H Repeated low dose (10 mg/kg)	
	Male	Female	Male	Female	Male	Female	Male	Female
Blood	0.0004[b]	0.0003	0.0034	0.0045	0.3923	0.4165	0.0060	0.0053
Blood Cell	0.0003	0.0003	0.0025	0.0035	0.4675	0.5370	0.0143	0.0203
Serum	0.0003	0.0003	0.0021	0.0036	0.5086	0.4529	0.0082	0.0102
Liver	0.0008	0.0011	0.0123	0.0083	1.5043	2.2265	0.0149	0.0280
Kidney	0.0012	0.0016	0.0026	0.0027	0.5466	0.8395	0.0049	0.0101
Spleen	0.0003	0.0002	0.0020	0.0024	0.1823	0.3404	0.0022	0.0026
Heart	0.0003	0.0002	0.0011	0.0012	0.1827	0.3229	0.0014	0.0017
Lung	0.0005	0.0005	0.0020	0.0016	0.2158	0.3607	0.0024	0.0079
Brain	0.0001	0.0001	0.0007	0.0012	0.1015	0.5363	0.0007	0.0013
Muscle	0.0002	0.0001	0.0004	0.0021	0.1480	0.2471	0.0008	0.0020
Gonad	0.0002	0.0003	0.0006	0.0053	0.1247	1.1494	0.0013	0.0023
Fat	0.0003	0.0002	0.0046	0.0052	0.1309	1.2600	0.0034	0.0029
Bone	0.0004	0.0002	0.0006	0.0014	0.4114	0.1759	0.0014	0.0011

a Data are from rats in Subgroup 1 and are the mean of five animals/group; data were obtained from Table 21, page 56 of the study report.
b Data are average of four animals.

4. Excretion

The recovery of radioactivity in tissues and excreta of rats in the phenyl and pyridinyl label groups is summarized in Tables 16 and 17, respectively. Within 72 hours of dosing, intravenously-dosed rats dosed excreted the majority of radioactivity in urine (73-89%), whereas orally-dosed rats excreted most of the radioactivity in feces (49-79%), regardless of radiolabel or sex. Pretreatment did not appear to affect the pattern of excretion. Bile-duct cannulated rats dosed intravenously or orally with either radiolabel and sacrificed at 48 hours post-dose excreted 3-19% of the dose in bile. The estimated half-lives of radiocarbon elimination in urine and feces half-life of elimination was 5.3-6.9 hours for all single intravenous and

oral dose groups, and 7.7-10.8 hours for all repeat oral dose groups.

a) Intravenous dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing at 1 mg/kg, 89.99-93.09% of the administered dose was recovered in excreta from both sexes. For males and females, radioactivity in urine was 73.22-76.54% of the administered dose, and in feces was 19.86 and 13.44%, respectively. In bile-cannulated rats, radioactivity excreted in bile comprised 18.58% of the dose in males and 11.02% in females at 48 hours post-dose.

b) Single low oral dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing at 10 mg/kg, 92.62-102.25% of the administered dose was recovered in excreta from both sexes. For males and females, the majority of radioactivity was eliminated in feces, accounting for 79.05 and 67.45% of the administered dose, respectively, whereas 23.20-25.17% of the dose was excreted in urine. In bile-cannulated rats, radioactivity excreted in bile comprised 10.54% of the dose in males and 7.59% in females at 48 hours post-dose.

c) Single high oral dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing at 1000 mg/kg, 96.38-98.16% of the administered dose was recovered in excreta both sexes. For males and females, the majority of radioactivity was eliminated in feces, accounting for 71.84-71.99% of the administered dose. Urinary excretion for both sexes comprised 24.55-26.17% of the administered dose. In bile-cannulated rats, radioactivity excreted in bile comprised 6.36 and 7.48% of the dose in males and females, respectively at 48 hours post-dose.

d) Repeated low oral dose with [phenyl-U-^{14}C] label: Within 72 hours of repeated dosing at 10 mg/kg, 95.82-96.09% of the administered dose was recovered in excreta from both sexes. For males and females, the majority of radioactivity was eliminated in feces, accounting for 76.29 and 69.64% of the administered dose in males and females, respectively. Urinary excretion totaled 19.53% of the dose in males and 26.46% in females.

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Table 16. Recovery of radioactivity in tissues and excreta of rats dosed with [phenyl-U-^{14}C]diflufenzopyr at 1, 10 or 1000 mg/kg.[a]

	Percent of Administered Dose					
	Males			Females		
Intravenous Dose (1 mg/kg)						
SAMPLE	Subgroup 1 72 hrs[b]	Subgroup 2 24 hrs	Subgroup 3 48 hrs	Subgroup 1 72 hrs	Subgroup 2 24 hrs	Subgroup 3 48 hrs
Urine[c]	73.22	61.01	70.58	76.54	72.55[d]	68.01
Feces	19.86	21.75	1.57	13.46	13.05	1.49
Bile	--[e]	--	18.58	--	--	11.02[d]
Tissues	0.1230	0.2109	0.1433	0.1268	0.1929	0.1845
Total	93.21	82.97	90.87	90.12	85.79	81.88
Single low dose (10 mg/kg)						
Urine[c]	23.20	19.63	19.60	25.17	25.31	35.49
Feces	79.05	65.67	54.74	67.45	64.27	53.24[d]
Bile	--	--	10.54[d]	--	--	7.59[d]
Tissues	0.2187	0.7903	0.8056	0.2783	0.8666	0.9192
Total	102.47	86.09	85.68	92.90	90.45	97.24
Single high dose (1000 mg/kg)						
Urine[c]	24.55	24.17	26.39	26.17	26.68	33.58
Feces	71.84	52.23	57.56	71.99	49.23	46.44[f]
Bile	--	--	6.36	--	--	7.48
Tissues	0.3547	0.7913	0.6934	0.3710	0.9332	0.9193
Total	96.73	77.20	91.00	98.53	76.84	88.42
Repeated low dose (10 mg/kg)						
Urine[c]	19.53	19.79	--[g]	26.46	21.65	--
Feces	76.29	56.31	--	69.64	68.88[d]	--
Bile	NS	--	--	--	--	--
Tissues	0.4033	1.0268	--	0.4952	0.9089	
Total	96.22	77.13	--	96.59	91.44	--

a Data are the mean of five animals/group except when noted otherwise, and were obtained from Tables 4-7, pages 39-42 of the study report.
b Animals in Subgroups 1, 2, and 3 were sacrificed at 72, 24, and 48 hrs. post-dose, respectively.
c Includes cage washes.
d Data are the average of four animals.
e Not sampled.
f Data are the average of three animals.
g No Subgroup 3.

e) Intravenous dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing at 1 mg/kg, 88.39-96.47% of the administered dose was recovered in excreta of both sexes. For males and females, radioactivity in urine was 75.62 and 89.38% of the administered dose, respectively, and in feces was 12.77 and 7.09%, respectively. In bile-cannulated rats, radioactivity excreted in bile comprised 16.37% of the dose in males and 4.05% in females at 48 hours post-dose.

f) Single low oral dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing at 10 mg/kg, 92.88-99.89% of the administered dose was recovered in excreta of both sexes. For males and females, the majority of radioactivity was eliminated in feces, accounting for 65.95-70.19% of the administered dose, whereas 26.93-29.70% of the dose was excreted in urine. In bile-cannulated male and female rats, radioactivity excreted in bile comprised 10.09% of the dose in males and 3.08% in females at 48 hours post-dose.

g) Single high dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing at 1000 mg/kg, 84.02-100.98% of the administered dose was recovered in excreta of both sexes. For males and females, the majority of radioactivity was eliminated in feces, accounting for 68.94 and 49.21% of the administered dose, respectively. Urinary excretion for both sexes comprised 32.04-34.82% of the administered dose. In bile-cannulated rats, radioactivity in bile comprised 8.11% of the dose in males and 4.58% in females at 48 hours post-dose.

h) Repeat oral dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of repeated dosing at 10 mg/kg, 101.15-101.87% of the administered dose was recovered in excreta from both sexes. For males and females, the majority of radioactivity was excreted in feces, accounting for 64.21-64.26% of the dose. Urinary excretion totaled 36.94-37.61% of the administered dose in both sexes.

Table 17. Recovery of radioactivity in tissues and excreta of rats dosed with [pyridinyl-4,6-^{14}C]diflufenzopyr at 1, 10 or 1000 mg/kg.[a]

	Percent of Administered Dose					
	Males			Females		
Intravenous Dose (1 mg/kg)						
SAMPLE	**Subgroup 1 72 hrs[b]**	**Subgroup 2 24 hrs**	**Subgroup 3 48 hrs**	**Subgroup 1 72 hrs**	**Subgroup 2 24 hrs**	**Subgroup 3 48 hrs**
Urine[c]	75.62	66.24	63.71	89.38	86.02	70.21
Feces	12.77	21.32	1.63	7.09	8.40	1.28
Bile	--[d]	--	16.37	--	--	4.05
Tissues	0.0306	0.1202	0.0633	0.0199	0.2617	0.0647
Total	88.42	87.68	81.77	96.49	94.68	75.60
Single low dose (10 mg/kg)						
Urine[c]	29.70	32.38	38.19	26.93	34.27	43.57
Feces	70.19	50.96	50.13	65.95	56.07	43.98
Bile	--	-	10.09	--	--	3.08
Tissues	0.0170	0.3915	0.0522	0.0233	0.6415	0.0490
Total	99.91	83.73	98.46	92.90	90.98	90.68
Single high dose (1000 mg/kg)						
Urine[c]	32.04	23.48	38.14	34.82	21.09	35.80
Feces	68.94	26.12	19.97	49.21	17.16	36.04
Bile	--	--	8.11	--	--	4.58
Tissues	0.0246	2.0718	1.6190	0.0351	2.6673	1.2895
Total	101.00	51.67	67.84	84.06	40.92	77.71
Repeated low dose (10 mg/kg)						
Urine[c]	36.94	28.49	--[e]	37.61	29.32	--
Feces	64.21	50.45	--	64.26	50.91	--
Bile	--	--	--	NS	NS	--
Tissues	0.0217	1.0672	--	0.0258	1.7091	--
Total	101.17	80.01	--	101.90	81.94	--

a Data are the mean of five animals/group and were obtained from Tables 8-11, pages 43-46 of the study report.
b Animals in Subgroups 1, 2, and 3 were sacrificed at 72, 24, and 48 hrs. post-dose, respectively.
c Includes cage washes.
d Not sampled.
e No Subgroup 3.

5. Blood Kinetics

For all dose groups, blood residue levels accounted for <1% of the administered dose at all sampling intervals through 72 hours post-dose. Residue levels were higher in the phenyl label group rats than in the pyridinyl label group rats; the differences were more pronounced during the latter sampling intervals. In general, blood residue levels were proportional to the dose for the corresponding radiolabel. In intravenously-dosed rats treated with either label, blood residue levels declined steadily over time. In orally-dosed rats treated with label, blood residue levels generally increased up to 7 hours post-dose, then declined steadily through 72 hours post-dose.

B. Metabolite characterization studies:

TLC and HPLC analyses were conducted on 0-72 hour urine and feces samples from all dose groups (Subgroup 1), and on 0-48 hour urine, feces, and bile samples from all intravenous and single oral dose groups (Subgroup 2). The structures of the metabolites were confirmed using 2-D TLC, HPLC, LC/MS, DIP/MS, FAB/MS, and proton NMR. The results of metabolite analyses of urine and feces from Subgroup 1 animals (0-72 hr samples) dosed with [phenyl-U-^{14}C] label or [pyridinyl-4,6,-^{14}C] label are summarized in Tables 18 and 19, respectively. For each dose group, the metabolic profile was similar between sexes, except for differences in metabolite levels.

a) Intravenous dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 73.22-76.54% of the dose from male and female rats, respectively. Unchanged diflufenzopyr accounted for 51.9 and 62.1% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in urine fractions from both sexes included carbamoyl-phthalazinone (M5; males, 6.7%; females, 3.5%) and 3,5-difluoroaniline (M2; each at ≤0.3%). Within 72 hours of dosing, radioactivity in feces accounted for 19.86 and 13.45% of the dose from male and female rats, respectively. Compounds identified in the fecal fractions from both sexes included diflufenzopyr (males, 14.7%; females, 9.9%), M5 (0.9-1.3%), and carbamate (M8; each at 0.5%).

b) Single low dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 23.20-25.17% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 10.6 and 13.8% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in urine fractions from both sexes included M5 (males, 1.3%; females, 3.0%) and M2 (males only,

0.3%). Within 72 hours of dosing, radioactivity in feces accounted for 79.05 and 67.45% of the dose from male and female rats, respectively. Compounds identified in the fecal fractions from both sexes included diflufenzopyr (males, 62.5%; females, 49.6%), M5 (males, 7.0%; females, 3.2%), and M8 (2.3-2.6%).

c) Single high dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 24.55-26.17% of the dose in urine fractions from male and female rats. Unchanged diflufenzopyr accounted for 15.1-15.8% of the administered dose in both sexes. Metabolites identified in urine fractions from both sexes included M5 (1.3-1.5%) and M2 (each at 0.4%). Within 72 hours of dosing, radioactivity in feces accounted for 71.85-71.99% of the dose from both sexes. Compounds identified in the fecal fractions from both sexes included diflufenzopyr (57.5-57.7%), M5 (4.8-5.1%), and M8 (2.3-2.4%).

d) Repeated low dose with [phenyl-U-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 19.53-26.48% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 8.3 and 15.3% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in urine fractions from both sexes included M5 (0.9-1.3%) and M2 (each at ≤0.2%). Within 72 hours of dosing, radioactivity in feces accounted for 76.29 and 69.64% of the dose from male and female rats, respectively. Compounds identified in fecal fractions from both sexes included diflufenzopyr (each at 57.0%), M5 (males, 2.9%; females, 3.8%), and M8 (3.0-3.1%).

Table 18. Metabolite profile in urine and feces from rats dosed with [phenyl-U-^{14}C]diflufenzopyr.[a]

Dose Group	Percent of administered dose							
	Group A Intravenous dose 1 mg/kg		Group B Single low dose 10 mg/kg		Group C Single high dose 1000 mg/kg		Group D Repeated dose 10 mg/kg	
Compound/fraction	Male	Female	Male	Female	Male	Female	Male	Female
Diflufenzopyr	66.6	72.0	73.1	63.4	73.3	72.8	65.3	72.3
3,5-Difluoroaniline (M2)	0.3	0.2	0.3	0.0	0.4	0.4	0.2	0.1
Carbamoyl-phthalazinone (M5)	8.0	4.4	8.3	6.2	6.3	6.4	3.8	5.1
Carbamate (M8)	0.5	0.5	2.6	2.3	2.4	2.3	3.1	3.0
Total identified	**75.4**	**77.1**	**84.3**	**71.9**	**82.4**	**81.9**	**72.4**	**80.5**
Unidentified Fractions Urine[b]	9.7	6.2	9.7	7.6	5.1	7.8	9.1	8.4
Feces[c]	2.3	1.7	6.9	8.3	6.7	7.7	9.7	8.6
Total Unidentified	**12.0**	**7.9**	**16.6**	**15.9**	**11.8**	**15.5**	**18.8**	**17.0**
Unanalyzed fractions[d]	**3.0**	**2.6**	**3.3**	**3.8**	**3.5**	**2.8**	**3.5**	**4.1**
Unextracted fecal residues[e]	**0.9**	**0.6**	**2.1**	**2.0**	**1.5**	**1.7**	**2.2**	**1.7**
Total accounted for[f]	91.3	88.2	106.3	93.6	99.2	101.9	96.9	103.3

a Data are from TLC and HPLC analyses of pooled urine (0-72 hour) and fecal (0-72 hour) samples from rats in Subgroup 1 (5 rats/sex/group) and were obtained from Table 22, page 57 of the study report.
b Urine samples include cage washes; In each urine sample, 10-11 unknown bands of radioactivity were detected, with each band accounting for 0.1-2.5% of the administered dose.
c Fecal unknowns were comprised of 4 to 10 unknown bands of radioactivity each accounting for 0.1-2.7% of the administered dose.
d Unanalyzed aqueous fractions from urine and feces.
e Radioactivity in residual fecal solids following extraction.
f Total accounted for = (Total identified) + (Total unidentified) + (Total Unanalyzed).

e) Intravenous dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 75.62-86.02% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 58.4-60.4% of the administered dose in urine fractions from both sexes. Metabolites identified i urine fractions from both sexes included M5 (males, 7.6%; females, 0.1%); M1 (4.3-4.6%); 2-acetyl nicotinic acid (M6; males, 3.4%; females, 5.1%); and, 2-keto-8-hydroxymethyl-M1 (M19); 2-keto-M1 (M9); and 8-hydroxymethyl-M1 (M10), each at ≤0.6% of the dose. Within 72 hours of dosing, radioactivity in feces accounted for 12.77 and 7.09% of the dose from male and female rats, respectively. Compounds identified in the fecal fractions from both sexes included diflufenzopyr (males, 8.3%; females, 4.9%), and M1, M5, M6, M9, and M10, each at ≤1.2% of the dose.

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f) Single low dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 26.93-29.70% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 11.7 and 15.2% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in the urine fractions from both sexes included M10 (males, 4.8%; females, 3.1%) and M5, M1, M9, M6, and M19, each at ≤2% of the dose. Within 72 hours of dosing, radioactivity in feces accounted for 65.95-70.19% of the dose from both sexes. Compounds identified in the fecal fractions from both sexes included diflufenzopyr (49.0-52.7%), and M1 (11.0-11.9%), M5 (2.1-3.6%), and M6, M9, and M10, each at ≤2.0% of the dose.

g) Single high dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 32.04-34.82% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 13.9 and 19.1% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in urine fractions from both sexes included M5 (1.1-1.8%), M10 (4.3-4.9%), M1, M9, M6, and M19, each at ≤1.0% of the dose. Within 72 hours of dosing, radioactivity in feces accounted for 68.94 and 49.21% of the dose from male and female rats, respectively. Compounds identified in fecal fractions from both sexes included diflufenzopyr (males, 59.9%; females, 42.3%), M1 (both sexes, 5.9-6.1%), and M5, M6, and M10, each at ≤2.1% of the dose.

h) Repeated low dose with [pyridinyl-4,6-^{14}C] label: Within 72 hours of dosing, radioactivity in urine accounted for 36.94-37.61% of the dose from male and female rats. Unchanged diflufenzopyr accounted for 13.7 and 16.6% of the administered dose in urine fractions from males and females, respectively. Metabolites identified in urine fractions from both sexes included M10 (6.4-6.9%), and M1, M5, M6, M9, and M19, each at ≤2.0% of the dose. Within 72 hours of dosing, radioactivity in feces accounted for 64.21-64.26% of the dose from both sexes. Compounds identified in fecal fractions from both sexes included diflufenzopyr (males, 42.4%; females, 50.8%), and M1 (males, 10.0%; females, 7.6%), M5 (each at 2.4%), M6 (males, 4.8%; females, 1.3%), and M9 and M10, each at ≤2.1% of the dose.

Table 19. Metabolite profile in urine and feces from rats dosed with [pyridinyl-4,6-^{14}C]diflufenzopyr.[a]

Dose Group	Percent of administered dose							
	Group E Intravenous dose 1 mg/kg		Group F Single low dose 10 mg/kg		Group G Single high dose 1000 mg/kg		Group H. Repeated dose 10 mg/kg	
Compound/fraction	Male	Female	Male	Female	Male	Female	Male	Female
Diflufenzopyr	66.7	65.3	64.4	64.2	73.8	61.4	56.1	67.4
Phthalazinone (M1)	5.8	4.9	11.6	12.1	7.4	7.1	10.6	9.6
Carbamoyl-phthalazinone (M5)	7.9	1.3	5.6	3.2	3.9	2.4	4.4	2.9
2-acetyl nicotinic acid (M6)	4.1	5.3	2.0	3.6	2.0	0.3	5.8	1.8
2-keto-M1 (M9)	0.4	0.1	0.0	1.0	0.1	0.4	0.6	0.3
8-Hydroxymethyl-M1 (M10)	0.5	0.6	4.8	3.5	5.5	4.9	8.1	9.0
2-keto-8-hydroxymethyl-M1 (M19)	0.3	0.4	1.1	0.1	1.0	0.7	0.5	1.1
Total identified	**85.7**	**77.9**	**89.5**	**87.7**	**93.7**	**77.2**	**86.1**	**92.1**
Unidentified Fractions Urine[b]	1.8	2.0	9.1	5.4	10.9	6.5	11.8	9.6
Feces[c]	0.3	0.0	0.1	0.6	0.8	0.8	2.0	0.4
Total Unidentified	**2.1**	**2.0**	**9.2**	**6.0**	**11.7**	**7.3**	**13.8**	**10.0**
Total Unanalyzed[d]	**0.2**	**0.2**	**1.4**	**1.2**	**0.5**	**0.3**	**3.1**	**1.2**
Unextracted residues[e]	**1.0**	**0.7**	**5.3**	**2.1**	**3.8**	**1.4**	**4.2**	**4.0**
Total accounted for[f]	89.0	80.8	105.4	97.0	109.7	86.2	107.2	107.3

a Data are from TLC and HPLC analyses of pooled urine (0-72 hour) and fecal (0-72 hour) samples from rats in Subgroup 1 (5 rats/sex/group) and were obtained from Table 24, page 60 of the study report.
b Urine samples include cage washes; In each urine sample, 4 or 5 unknown bands of radioactivity were detected, with each band accounting for 0.1-6.5% of the administered dose.
c Fecal unknowns were comprised of up to 5 bands of radioactivity each accounting for ≤0.4% of the administered dose.
d Unanalyzed aqueous fraction from urine.
e Radioactivity in residual fecal solids following extraction.
f Total accounted for = (Total identified) + (Total unidentified) + (Total Unanalyzed).

HPLC and TLC analyses were also conducted on 0-48 hour samples of urine, feces, and bile from Subgroup 3 rats (bile-duct cannulated) treated with either radiolabel. Metabolite profiles for the 0-48 hour bile samples were similar to those obtained for the 0-72 hour urine and fecal samples from the corresponding label group. The 0-48 hour bile samples from rats treated with either radiolabel contained unchanged diflufenzopyr (≤14.9% of the dose). Two minor metabolites also identified in the bile were M5 (≤0.8%) and M1 (pyridinyl label only, ≤0.2% of the dose).

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The registrant's proposed metabolic pathways for diflufenzopyr in the rat are presented as Attachment 2. Diflufenzopyr was excreted primarily as unchanged parent in urine, feces, and bile. Diflufenzopyr also directly hydrolyzed to M5 and M6, and M5 can be further hydrolyzed to M1 and M2. M1 is then hydroxylated to M9 and M10, which undergo further hydroxylation to form the urinary metabolite, M19.

III. DISCUSSION

A. Investigator's Conclusions

Diflufenzopyr is partially absorbed, partially metabolized, and rapidly eliminated from rats dosed via oral administration. Radioactive residues in intravenously-dosed rats were primarily excreted in urine (73-89%), whereas orally-dosed rats excreted the majority of radioactivity in feces (57-79%). In bile-cannulated rats dosed by intravenous or oral administration, 3-19% of the dose was excreted in bile. Unchanged diflufenzopyr comprised the majority of radioactivity excreted in urine, feces, and bile from all dose groups. Absorption, distribution, metabolism, and elimination did not appear to differ significantly between sexes in each dose group. The half-life for elimination of [^{14}C]residues in urine and feces from all dose groups was approximately 6 hours. For all dose groups, the metabolic profiles in urine, feces, and bile were similar between sexes. Diflufenzopyr did not appear to bioaccumulate in rats; residue levels for the repeated dose groups were only slightly higher than levels for the single dose groups. [^{14}C]Residues in tissues and organs were low for all dose groups; the highest levels of radioactivity were associated with kidney, liver, spleen, and lung. Blood residue concentrations (<1% of dose/sampling interval) were higher and decreased more slowly in the phenyl label groups compared to the pyridinyl label groups. The presence of hydroxylated metabolites, M9, M10, and M19 in rats in the present study, and in goat and hen excreta and corn silage from previous metabolism studies, suggest that the metabolic profiles for these species have similarities.

B. Reviewer's Discussion

[^{14}C]Diflufenzopyr was partially absorbed from the GI tract of male and female rats dosed orally with diflufenzopyr radiolabeled in either the phenyl or pyridinyl rings. For all orally dosed rats, 20-44% of the administered dose was excreted in urine. The level of absorption for rats in each dose group was similar between sexes. Dose level and pretreatment had little effect on the proportion of the dose

excreted in urine following oral administration. Enterohepatic circulation plays a role in the elimination of [^{14}C]diflufenzopyr in rats dosed with either radiolabel. Bile-duct cannulated rats dosed intravenously or orally with either radiolabel excreted 3-19% of the dose in bile.

Within 72 hours of dosing, intravenously-dosed rats dosed excreted the majority of radioactivity in urine (73-89%), whereas orally-dosed rats excreted most of the radioactivity in feces (49-79%), regardless of radiolabel or sex. Pretreatment did not appear to affect the pattern of excretion. Bile-cannulated rats excreted lesser amounts in the feces compared to non-cannulated rats; 3-19% of the dose was excreted in bile. The estimated half-lives of radiocarbon elimination in urine and feces was 5.3-6.9 hours for all single intravenous and oral dose groups, and 7.7-10.8 hours for all repeated oral dose.

Total tissue residue levels for all dose groups were <3% of the administered dose in rats sacrificed at 24, 48 or 72 hours post-dose, and were highest in rats sacrificed at 24 hours post-dose. For each dose group, tissue residue concentrations were higher in females than males. In rats sacrificed at 24 hours post-dose, residue concentrations for the phenyl label groups were highest in blood, blood cell, and serum; and for the pyridinyl label groups, residue concentrations were highest in liver and kidney.

Blood residue levels for all dose groups (<1% of dose/sampling interval) were higher in the phenyl label groups than the pyridinyl label groups. In general, blood levels were proportional to dose level. For both labels, the decline in blood residue levels was steady for intravenously-dosed rats, whereas, blood residue levels generally increased up to 7 hours post-dose, then declined in orally-dosed rats.

The metabolic profile for urine and feces samples (0-48 and 0-72 hour) from each treatment regimen was similar between sexes, except for differences in metabolite levels. Unchanged diflufenzopyr was identified in urine, feces, and bile samples from both label groups. For the ^{14}C-phenyl label groups, M2 and M5 were identified in urine, and M5 and M8 were identified in feces. For the ^{14}C-pyridinyl label groups, M1, M5, M6, M9, M10 and M19 were identified in urine and feces; M19 was also identified in the urine. In addition to parent, bile samples from both label groups contained minor amounts of M5 (both labels) and M1 (pyridinyl label groups only).

The data indicate that diflufenzopyr is excreted primarily as unchanged parent in urine, feces, and bile. Minor amounts of

hydrolysis products (M1, M5, and M6) and hydroxylation products (M9, M10, and M19) were identified in excreta.

IV. STUDY DEFICIENCIES

No scientific deficiencies were noted in the study

ATTACHMENTS

THE FOLLOWING ATTACHMENTS ARE NOT AVAILABLE ELECTRONICALLY.
SEE FILE COPY.

Attachment 1

Table I. TLC and HPLC Characteristics of SAN 835 H and its Model Metabolites.

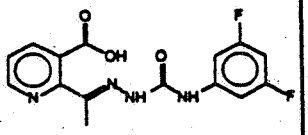
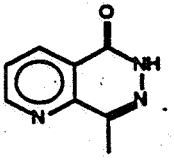
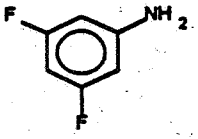
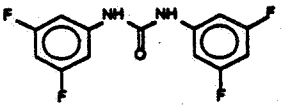
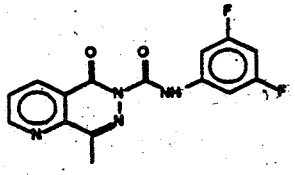
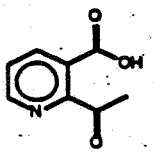
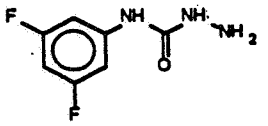
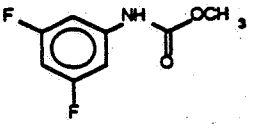
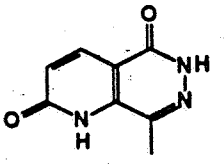
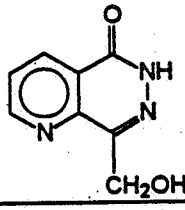
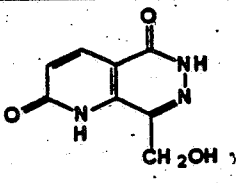
Compound designation	Structure	TLC R_f in Solvent Systems [1] B	L	A	I	T	N	R_t (min.) HPLC [2]
SAN 835 H		0.45	0.43	0.31	0.55	0.57		5.2
M1 Phthalazinone		0.54	0.72	0.43	0.50	0.91		3.5
M2 3,5-difluoro-aniline		0.86	0.84	0.75				6.3
M3 Symmetric-urea		0.89	0.85	0.79				19.7
M5 Carbamoyl-Phthalazinone		0.66	0.64	0.55	0.74	0.95		8.6
M6 2-Acetyl nicotinic acid		0.37	0.16		0.42	0.54		3.5

Table 1 (Cont'd)

Compound designation	Structure	TLC R_f in Solvent Systems [1] B	L	A	I	T	N	R_t (min.) HPLC [2]
M7 Semicarbazide		0.76	0.77	0.25				4.2
M8 Carbamate		0.87	0.84	0.78				7.4
M9 2-keto-M1		0.38	0.21		0.47	0.79	0.42	3.5
M10 8-hydroxymethyl-M1		0.35	0.57	0.25		0.71		3.2
M19 2-keto-8-hydroxymethyl-M1		0.23					0.24	

[1] TLC solvent systems:
A = ethyl acetate/toluene/acetic acid/water 90:6:2:2;
B = ethyl acetate/acetic acid/water 92:4:4;
L = ethyl acetate/methanol/ammonium hydroxide 70:25:5;
I = acetonitrile/acetic acid/water 95:2.5:2.5;
T = chloroform/methanol/acetic acid/water 68:25:5:2;
N = ethyl acetate/toluene/formic acid/water 87:3:5:5.

[2] HPLC conditions:
Phenomenex Bondclone 10 C_{18} column; mobile phase isocretic acetonitrile:water (1% acetic acid) 50:50. Flow rate; 1 ml/min.

Attachment 2

Figure 178. *Proposed Metabolic Pathways for SAN 835 H in the Rat.*