DATA EVALUATION RECORD

ESFENVALERATE AND FENVALERATE

STUDY TYPE: METABOLISM AND PHARMACOKINETICS - MOUSE, RAT
[OPPTS: 870.7485 (§85-1)]
MRID 45351601

Prepared for

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

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism (Comparative) - Rat and Mouse [OPPTS 870.7485 (§85-1)]

DP BARCODE:D273580 SUBMISSION CODE: S594051
P.C. CODE: 109303

TEST MATERIAL (PURITY): Esfenvalerate (>99%); Fenvalerate (>99%)

SYNONYMS: Fenvalerate - Sumicidin®, (RS)-α-cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)isovalerate; S-5602.
Esfenvalerate (containing three chiral isomers of fenvalerate) - [2S, αR](esfenvalerate), [2R, αS](esfenvalerate), and [2R, αR](esfenvalerate)

CITATION: Kaneko, H., Isobe, N., Shiba, K., Saito, K., Yanagita, S., Kitamura, N., Ohe, A., Yoshitake, A., Miyamoto, J. 1985. Comparative metabolism of esfenvalerate and fenvalerate in rats and mice. I. Single or 10 consecutive oral administration. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Hyogo 665, Japan. LLM-50-0007. MRID 45351601. December, 1985. Unpublished.

SPONSOR: E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.

EXECUTIVE SUMMARY: In a non-guideline metabolism and disposition study (1985, MRID 45351601), groups of five male and five female rats (Sprague-Dawley strain) and mice (ddY strain) were given single or 10-day repeated oral doses of ^{14}C-esfenvalerate (sp. act. 33.5-35.5 mCi/mmol, >99% purity, no lot number, phenoxy phenyl or chlorophenyl ring label position), ^{14}C-fenvalerate (sp. act. 34.0-35.5 mCi/mmol, >99% purity, no lot number, phenoxy phenyl or chlorophenyl ring label position), or ^{14}C-esfenvalerate containing three isomers at doses of 2.5 or 10 mg/kg in corn oil by gavage. Nonlabeled fenvalerate (Lot no. LUG-50205) or esfenvalerate (Lot no. KS-5210) were given concurrent with the radiolabeled test article. Absorption, excretion, distribution, and metabolite characterization were performed.

Overall recovery of administered radioactivity was an acceptable 94.2-102.7% among the experimental groups and was independent of label position.

Absorption of the test material indicated that systemic absorption over the time periods and doses tested ranged from approximately 20-60%. For both label positions, absorption was greater for mice than for rats (49-53% vs 24-35% for the alcohol label and 38-51% vs 20-39% for the acid label position).

Fecal elimination was more prominent than urinary excretion. Since biliary elimination was not assessed, what proportion, if any, of the fecal radioactivity represented absorbed dose. Over

a 7-day post-dose period, urinary excretion was greater in mice (~35-60% of the dose) than in rats (~20-39%) when considering all dose and label positions. Urinary excretion was essentially complete 24-48 hours after dosing. Fecal excretion was also essentially complete 48 hours after dosing. There were no significant gender- or dose-related differences in excretion patterns.

The time-course data based upon 24 to 48 hour sampling intervals was insufficient for estimating elimination half-times and no plasma time-course data were available to determine C_{max}, t_{cmax}, and AUC values.

Although the test article and/or its metabolites were distributed to most of the examined tissues and organs, concentrations were minimal and generally accounted for <50 ng eq/g tissue in the 2.5 mg/kg dose groups and <100-200 ng eq/g tissue for the 10 mg/kg fenvalerate group. There did not appear to be gender-related differences and individual variability did not seem out of the ordinary for this type of study.

For rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate, six biotransformation products were characterized from the feces. Four fecal biotransformation products were characterized. Substantial amounts of parent compound (44.5-59.9% of the administered dose) were detected in the fecal samples at 0-2 days following a single dose. The major fecal metabolite was a 4'- hydroxylation product (2 to 5.5%). There were no significant differences in metabolism processes relative to the acid or alcohol moieties. Unchanged parent compound was also detected in the feces of mice (25.6 to 48.1% of the dose for both label positions). Four biotransformation products were detected but only the 4'-hydroxylation product consistently represented >2% of the administered radioactivity. There did not appear to be biologically relevant gender-related differences in the fecal metabolite profiles of mice.

Five biotransformation products were characterized in the urine of rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate. CPIA-glucuronide was the most prevalent metabolite. For rats given ^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, three biotransformation products were characterized. A sulfate conjugate of OH-PB acid was the primary urinary metabolite (16.4-23.9% of the dose). For mice, three urinary metabolites were characterized. Little parent compound was detected in the urine and most radioactivity (7.9-17.3% of the administered dose) was associated with a taurine conjugate of PB acid.

This metabolism study is **Acceptable/Non-Guideline** and does not satisfy the requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in rats and mice. This study provides useful data that described the absorption, excretion, tissue distribution, and metabolite characterization of esfenvalerate and fenvalerate in male and female mice and rats following single and repeated oral dosing. There were, however, key deficiencies (no data on dose confirmation, stability or homogeneity, no Quality Assurance statement, no confirmation of GLP compliance) that precluded its acceptance as an 85-1 Guideline study.

COMPLIANCE: A signed and dated Data Confidentiality Claim statement was included with the study. No Quality Assurance statement was available and the GLP Compliance statement disavowed ability to confirm GLP compliance.

I. MATERIALS AND METHODS

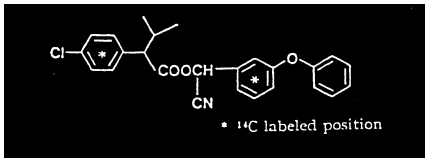
A. MATERIALS

1. Test compound

Radiolabeled

Test article: ^{14}C-Esfenvalerate (contained three isomers), sp. act. 33.5-35.5 mCi/mol
^{14}C-Fenvalerate, sp. act. 34.0-35.5 mCi/mol
Test articles were labeled at the phenoxy phenyl ring (^{14}C-alcohol) or the chlorophenyl ring (^{14}C-acid)

Lot No.: not provided; synthesized by performing laboratory
Radiochemical purity: >99% for both compounds
Description: not provided
Contaminants: none noted
Structure:



Non-radiolabeled

Test article: fenvalerate, esfenvalerate
Lot No.: LUG-50205 (fenvalerate); KS-5210 (esfenvalerate)
Chemical purity: "analytical grade" for both compounds
Description: not provided
Contaminants: none noted

2. Vehicle

The test articles were dissolved in corn oil.

3. Test animals

Species: mice, rats
Strains: ddY mice (Shizouka Agricultural Cooperative Association for Laboratory Animals, Shizouka, Japan);
CD-derived Sprague-Dawley rats (Charles River, Shizuoka, Japan)
Age and weight at study initiation:
mice: 6 weeks; 28-30 g (males); 24-26 g (females)
rats: 6 weeks; 155-185 g (males); 130-160 g (females)
Housing: all-glass metabolism cages (Metabolica CO-2®, Sugiyamagen Iriki Co., Ltd., Tokyo, Japan)
Diet: CE-2 (Clea Japan, Inc., Japan) *ad libitum*
Water: tap water *ad libitum*
Environmental conditions:
Temperature: 25±2°C
Humidity: 55±15%
Air changes: not specified
Photoperiod: 12 hrs light/dark
Acclimation period: 7 days

4. Preparation of dosing solution

The dosing solutions were prepared by diluting the radiolabeled materials with analytical grade unlabeled test compound and dissolving them in corn oil. The dosing solutions were stored at -20°C prior to use.

Results –
Homogeneity: No information provided
Stability: No information provided.
Dose confirmation: No information provided.

Note: Although homogeneity, stability and dose confirmation data are desirable, they are not critical to the acceptance of this type of study. Stability data are available from other studies.

B. STUDY DESIGN AND METHODS

1. Group arrangements

The experimental groups were established as shown in Table 1. Control groups received vehicle only.

TABLE 1. Study design for

Experimental group (species)	Dose (mg/kg)	Number/sex	Remarks[a]
A (rat)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-esfenvalerate
B (rat)	2.5	5_, 5_	Single oral dose of ^{14}c-alcohol-esfenvalerate
C (mouse)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-esfenvalerate
D (mouse)	2.5	5_, 5_	Single oral dose of ^{14}c-alcohol-esfenvalerate
E (rat)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-esfenvalerate containing three isomers (aβ, bα, and bβ)
F (rat)	2.5	5_, 5_	Single oral dose of ^{14}c-alcohol-esfenvalerate containing three isomers (aβ, bα, and bβ)
G (mouse)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-esfenvalerate containing three isomers (aβ, bα, and bβ)
H (mouse)	2.5	5_, 5_	Single oral dose of ^{14}c-alcohol-esfenvalerate containing three isomers (aβ, bα, and bβ)
I (rat)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-fenvalerate
J (mouse)	2.5	5_, 5_	Single oral dose of ^{14}c-acid-fenvalerate
K (rat)	10	5_, 5_	Single oral dose of ^{14}c-acid-fenvalerate
L (mouse)	10	5_, 5_	Single oral dose of ^{14}c-acid-fenvalerate
M (rat)	10	5_, 5_	Single oral dose of ^{14}c-alcohol-fenvalerate
N (mouse)	10	5_, 5_	Single oral dose of ^{14}c-alcohol-fenvalerate
O (rat)	10	5_, 5_	10-Day repeated oral dosing with ^{14}c-fenvalerate
P (mouse)	10	5_, 5_	10-Day repeated oral dosing with ^{14}c-fenvalerate
Q (rat)	2.5	5_, 5_	10-Day repeated oral dosing with ^{14}c-esfenvalerate
R (mouse)	2.5	5_, 5_	10-Day repeated oral dosing with ^{14}c-esfenvalerate
S (rat)	2.5	5_, 5_	10-Day repeated oral dosing with ^{14}c-esfenvalerate containing three isomers (aβ, bα, and bβ)
T (mouse)	2.5	5_, 5_	10-Day repeated oral dosing with ^{14}c-esfenvalerate containing three isomers (aβ, bα, and bβ)

[a] Animals in all groups were terminated for tissue collection 7 days after dosing.
Data taken from pp. 13-15, MRID 45351601.

2. Dosing and sample collection

Doses were given as described in Table 1. Each oral dose volume was 5 mL/kg. Specific activities were approximately 32-36 mCi/mmol for single low-dose ^{14}C-esfenvalerate, ^{14}C-fenvalerate, and the ^{14}C-esfenvalerate isomeric mixture, and 8-9 mCi/mmol for the single high-dose ^{14}C-fenvalerate. For the repeat-dose groups, low-dose ^{14}C-esfenvalerate specific activity was approximately16-17 mCi/mmol (isomer mixture) and high-dose ^{14}C-fenvalerate specific activity was approximately 4 mCi/mmol. Expired air was not analyzed because previous experiments indicated that

no measurable $^{14}CO_2$ was generated. The following were collected for various analyses:

Blood - Blood samples were collected at terminal sacrifice. There was no indication that hourly or daily samples were taken.

Urine - Urine was collected daily for 7 days after a single dose or for 16 days after the 10 consecutive doses. Although collection intervals were not specified in the Materials/Methods section of the study report, data tables indicated that urine was collected daily and days 3-4 and 5-7 pooled for the single dose groups. For the 10-day repeated dose groups, urine sample analysis was provided for days 2, 4, 6, 8, 10, 13, and 16.

Feces - Collection of feces paralleled that for urine.

Tissues - Tissues were collected at terminal sacrifice (7 days following the single dose or the last dose of the 10-day repeat dose regimen). The following tissues (in addition to blood) were collected: adrenal glands, bone (location not specified), brain, fat (type/location not specified), heart, lungs, kidneys, liver, mesenteric lymph node, muscle (type/location not specified), skin, spleen, testis, ovaries, and uterus. No further details were provided.

3. Sample preparation/analysis

Study report (MRID 45351601) descriptions of the methods/procedures for preparation and analyses of collected samples were cursory.

Blood - Blood samples were collected but apparently only at terminal sacrifice. There were no data indicative of time-course analysis of blood radioactivity.

Urine - Radioactivity in urine samples was determined directly by LSC. The 0-4, 5-8, and 9-11 urine samples were analyzed by thin-layer chromatography (TLC). The 0-2 day samples from the single-dose groups and the 0-4, 5-8, and 9-11 day samples from the repeat-dose groups were analyzed for metabolites by preparative/analytical TLC. There was indication that autoradiographic analysis was also performed on urine samples and the resulting metabolite components analyzed by TLC following the methanol extraction of the appropriate gel region; details were not provided in the study report.

Feces - Fecal samples (0-4, 5-8, and 9-11 day) were homogenized in acetone-water and the homogenates filtered. Samples of unextractable residues and acetone-water homogenates were combusted and analyzed by LSC. Acetone extracts were also concentrated and analyzed by TLC. The 11-16 day fecal samples were homogenized in water and aliquots combusted prior to LSC analysis. There was indication that autoradiographic analysis was also performed on fecal samples and the resulting metabolite components analyzed by TLC following the methanol extraction of the appropriate gel region; details were not provided in the study report.

Tissues - Description of methods for tissue preparation were limited to statements alluding to homogenized/combusted samples. No details were provided.

4. Analytical techniques

Thin-Layer Chromatography (TLC) - TLC, using silica gel 60 F_{254} plates and various solvent systems was used for both the separation and analysis of metabolites. The following solvent systems were used:

n-hexane-toluene-acetic acid (3:15:2)
benzene saturated with formic acid-diethyl ether (10:3)
toluene-ethyl formate-formic acid (5:7:1)
n-butanol-acetic acid-water (6:1:1)
petroleum ether-diethyl ether-acetic acid (90:10:1)

Rf values for metabolites were compared to those of known standards (previously developed and reported in earlier references). Detection was by UV light and by autoradiography.

Liquid Scintillation Counting (LSC) - LSC was conducted using a Packard Model 460CD liquid scintillation spectrophotometer with external standards and toluene scintillation fluid. Counting was for 5 minutes, 30-50 dpm background (80 dpm for tissue samples), and 70% counting efficiency.

5. Calculations and statistics

Means and standard deviations were provide for some of the data.

II. **RESULTS**

A. DISTRIBUTION/EXCRETION STUDIES

1. Mass balance

Overall recovery of administered radioactivity was an acceptable 94.2-102.7% among the various experimental groups (Tables 2 and 3). Label position (acid or alcohol) did not affect the overall recovery of administered radioactivity nor did it significantly affect excretion pattens.

TABLE 2. Overall recovery of administered radioactivity (% of dose) at 7 days post-dosing in rats and mice given ^{14}C-acid esfenvalerate or fenvalerate

Matrix	^{14}C-acid esfenvalerate 2.5 mg/kg	^{14}C-acid esfenvalerate (isomeric mix) 2.5 mg/kg	^{14}C-acid fenvalerate 2.5 mg/kg	^{14}C-acid fenvalerate 10 mg/kg
Rats				
Urine				
–	27.3±9.5	20.0±3.4	27.9±7.8	29.0±8.2
–	31.5±9.6	36.1±11.2	33.1±7.1	39.0±10.8
Feces				
–	71.2±8.9	79.4±4.0	69.0±7.0	72.3±10.0
–	67.1±9.1	63.9±10.4	63.4±9.7	58.5±11.8
Total				
–	98.5±3.1	99.4±1.5	96.8±0.9	101.3±2.4
–	98.6±0.8	100.0±0.8	96.5±3.1	97.7±1.2
Mice*				
Urine				
–	37.9	41.4	44.6	51.2
–	48.9	35.4	56.8	50.8
Feces				
–	63.5	56.6	55.1	51.5
–	49.9	61.3	37.4	46.3
Total				
–	101.4	98.0	99.7	102.7
–	98.8	96.7	94.2	97.1

*S.D. for mouse data not provided in study report; individual animal data unavailable for calculation.
Data taken from Tables 3-1 to 3-4, pp. 26-29, MRID 45351601.

TABLE 3. Overall recovery of administered radioactivity (% of dose) at 7 days post-dosing in rats and mice given ^{14}C-alcohol esfenvalerate or fenvalerate

Matrix	^{14}C-alcohol esfenvalerate 2.5 mg/kg	^{14}C-alcohol esfenvalerate (isomeric mix) 2.5 mg/kg	^{14}C-alcohol fenvalerate 2.5 mg/kg	^{14}C-alcohol fenvalerate 10 mg/kg
Rats				
Urine	24.1±5.5	29.4±2.6	– [a]	34.9±18.9
–	33.0±13.6	34.8±7.4	–	32.5±9.1
Feces	70.9±7.1	65.4±2.1	–	60.9±17.8
–	65.7±15.0	65.8±6.7	–	67.4±11.7
Total	95.0±3.0	94.8±0.8	–	95.8±1.5
–	98.7±1.9	100.6±1.0	–	99.9±3.2
Mice*				
Urine	52.4	52.8	–	49.2
–	51.0	49.7	–	59.6
Feces	45.1	43.5	–	48.3
–	48.6	45.6	–	42.1
Total	97.5	96.3	–	97.5
–	99.6	95.3	–	101.7

[a] No low-dose group for ^{14}C- alcohol-fenvalerate.
*S.D. for mouse data not provided in study report; individual animal data unavailable for calculation.
Data taken from Tables 3-5 to 3-8, pp. 30 -33, MRID 45351601.

2. Absorption

Absorption of the test material, implied from the urinary excretion data (no cage wash data were provided), indicated that absorption over the time periods and doses tested ranged from approximately 20-60% of the administered dose. For both label positions, absorption was greater for mice than for rats (49-53% vs 24-35% for the alcohol label and 38-51% vs 20-39% for the acid label position) based upon urinary excretion. Because biliary excretion was not assessed, it is uncertain what proportion, if any, of the fecal radioactivity represented absorbed dose. Most of the urinary excretion (~75-95%) occurred within 24 hours of dosing (data not shown in this Data Evaluation Record) suggesting that absorption was moderately rapid.

3. Excretion

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Administered radioactivity was eliminated via both the urine and feces. As previously noted in Section II.A.2, urinary excretion was greater for mice than for rats. For all experimental groups, urinary excretion was rapid and essentially complete 24-48 hours after dosing. Fecal excretion accounted for the balance of the administered radioactivity. Excretion via this route was also essentially complete 48 hours after dosing for all experimental groups. There were no significant gender-related difference in excretion patterns. The absence of biliary excretion data did not allow for determining if any of the radioactivity recovered in the feces represented absorbed material.

4. Tissue distribution

Analysis of tissue residue data showed that, although the test article and/or its metabolites were distributed to most of the examined tissues and organs, these levels were minimal and generally accounted for <50 ng eq/g tissue in the 2.5 mg/kg dose groups and <100-200 ng eq/g tissue for the 10 mg/kg fenvalerate group (Tables 4 and 5). Fat tissue consistently showed the greatest residue levels for both labels and for esfenvalerate, the esfenvalerate isomer mixture, and fenvalerate. Mesenteric lymph nodes, adrenal glands, and skin also had higher residue levels than other tissues. Generally, the tissue residues for the high-dose fenvalerate (10 mg/kg) group were correspondingly higher than those for the low-dose (2.5 mg/kg) group. Based on the tissue residue data from groups of five animals (four in some groups), there did not appear to be gender-related differences and individual variability did not seem out of the ordinary for this type of study.

TABLE 4. ^{14}C tissue residues (ng eq./g) in mice and rats following a single oral dose of ^{14}C-acid esfenvalerate or fenvalerate[a]

Tissue	^{14}C-acid esfenvalerate 2.5 mg/kg	^{14}C-acid esfenvalerate (isomeric mix) 2.5 mg/kg	^{14}C-acid fenvalerate 2.5 mg/kg	^{14}C-acid fenvalerate 10 mg/kg
Rats				
Adrenal gland	<11 <9	<13 15±5	45±16 36±12	188±104 198±71
Fat	178±45 201±102	185±33 311±112	182±41 301±85	1318±657 1323±511
Mesenteric lymph nodes	27±1 31±3	10±7 10±3	14±8 23±9	122±60 199±122
Skin	17±19 12±3	11±7 24±16	14±5 32±27	34±20 80±16
Testes Ovaries	<2 11±10	<2 <10	<2 64±24	8±5 273±24
Mice				
Adrenal gland	<130 <72	<80 80±54	119±50 200±39	938±371 946±112
Fat	301±61 389±55	329±52 484±92	118±26 235±68	1340±297 1570±1161
Mesenteric lymph nodes	28±18 30±25	39±21 34±17	40±32 84±80	509±315 384±244
Skin	38±15 151±41	64±33 106±33	44±14 96±25	175±84 313±58
Testes Ovaries	<3 5±6	<2 24±11	5±1 62±18	44±7 395±106

[a] n=4 or 5 animals.

Data taken from Tables 4-1 through 4-4, pp. 38-41, MRID 45351601.

TABLE 5. ^{14}C tissue residues (ng eq./g) in mice and rats following a single oral dose of ^{14}C-alcohol esfenvalerate or fenvalerate[a]

Tissue	^{14}C-alcohol esfenvalerate 2.5 mg/kg	^{14}C-alcohol esfenvalerate (isomeric mix) 2.5 mg/kg	^{14}C-alcohol fenvalerate 2.5 mg/kg	^{14}C-alcohol fenvalerate 10 mg/kg
Rats				
Adrenal gland – –	<16 <10	<20 <9	–[b]	<72 <34
Fat – –	294±98 294±264	295±80 350±164	–[b]	1289±898 819±178
Mesenteric lymph nodes – –	30±16 20±11	31±12 35±18	–[b]	103±59 73±40
Skin – –	10±6 28±24	7±5 26±18	–[b]	42±26 64±40
Testes Ovaries	<2 17±14	<3 35±18	–[b]	<9 73±40
Mice				
Adrenal gland – –	<80 <80	<100 <100	–[b]	<360 <360
Fat – –	384±108 362±78	266±85 260±61	–[b]	1160±804 1579±367
Mesenteric lymph nodes – –	40±42 35±21	32±21 <20	–[b]	129±58 155±93
Skin – –	57±45 78±29	55±22 98±49	–[b]	108±73 320±60
Testes Ovaries	7±3 <40	9±4 <50	–[b]	16±9 <180

[a] n=4 or 5 animals.
[b] No low-dose group for ^{14}C- alcohol-fenvalerate.
Data taken from Tables 4-5 through 4-8, pp. 42-45, MRID 45351601.

B. PHARMACOKINETIC STUDIES

Pharmacokinetic investigations were not conducted. No blood time-course data or typical kinetic parameters (e.g., C_{max}, tC_{max}, elimination half-time, area-under-the-curve, etc.) were provided nor were data available to estimate these parameters. The only time-course analyses was 24–hour interval data for urinary and fecal excretion.

C. METABOLITE CHARACTERIZATION STUDIES

Both quantitative and qualitative data were provided regarding metabolite characterization. These evaluations were conducted for both rats and mice and for all test article forms and dose groups. Data for major metabolites in rats are summarized in Tables 6 and 7 and for mice in Table 8.

1. Feces

For rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate, six biotransformation products were characterized from the feces. Substantial amounts of parent compound (44.5-58.2% of the administered dose) were detected in the fecal samples at 0-2 days following a single dose of the test articles. Parent compound excepted, the major component in the feces of rats in all test groups was a 4'- hydroxylation metabolite. Non-characterized components were minimal (<5% of the dose) and unextractable ^{14}C in the feces represented <3.4% of the administered dose. The metabolite profiles of males and females given ^{14}C-acid test labeled test article were not significantly different quantitatively or qualitatively. For rats given ^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, four fecal biotransformation products were characterized. Unchanged parent compound in the 0-2 day fecal samples represented 50.2- 59.9% of the administered dose. Similar to the rats given the ^{14}C-acid label test article, the 4'-hydroxylation product was the most prominent metabolite in the feces (up to 5% of the administered dose) of both male and female rats. Non-characterized components (<5% of the dose) and unextractable ^{14}C (1-2% of the dose) were inconsequential.

Unchanged parent compound was also detected in the feces of mice (7.5-39.3% of the dose when considering both label positions) but to a lesser extent than for rats (Table 8). Four biotransformation products were detected in the feces of mice but only the 4'-hydroxylation product consistently and individually represented >2% of the administered radioactivity. Non-characterized components accounted for 1.9-5.3% of the total dose and 1.6-2.8% of the radioactivity was reported as unextractable. There did not appear to be biologically relevant gender-related differences in the fecal metabolite profiles.

2. Urine

For rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate, five biotransformation products were characterized from the urine. In the urine, a CPIA-glucuronide was the most prevalent metabolite. For rats given

^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, three biotransformation products were characterized from the urine. A sulfate conjugate of OH-PB acid was quantitatively the most important urinary metabolite (16.4-23.9% of the dose).

For mice, three urinary metabolites were characterized (Table 8). Parent compound was not detected in the urine and most radioactivity (11.2-17.3% of the administered dose) was associated with a taurine conjugate of PB acid.

TABLE 6. Metabolite profiles (% of dose) for rats following a single oral dose of ^{14}C-acid esfenvalerate or Fenvalerate[a]

Metabolite	^{14}C-acid esfenvalerate 2.5 mg/kg		^{14}C-acid esfenvalerate (isomeric mix) 2.5 mg/kg		^{14}C-acid fenvalerate 2.5 mg/kg		^{14}C-acid fenvalerate 10 mg/kg	
	Feces	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**
Parent compound – –	48±7.7 55.2±10.7	ND ND	58.2±3.6 52.0±12.3	ND ND	54.7±9.1 51.0±13.3	ND ND	54.1±12.8 44.5±13.4	ND ND
4'-OH-parent compound – –	5.5±1.4 4.0±0.9	ND ND	4.4±0.6 4.3±1.3	ND ND	2.0±0.6 2.5±1.0	ND ND	3.3±0.7 2.7±0.4	ND ND
CPIA-free – –	2.8±1.3 0.9±0.4	2.8±1.9 3.4±2.7	1.9±0.8 0.5±0.2	2.4±1.3 4.8±2.4	1.5±0.6 0.7±0.7	4.3±3.1 5.3±7.7	3.1±0.7 0.8±0.2	7.9±5.2 11.0±6.6
CPIA- glucuronide – –	ND ND	4.0±1.2 9.9±5.0	ND ND	2.1±0.4 5.7±2.8	ND ND	8.2±3.8 10.6±4.8	ND ND	7.3±3.3 12.3±10.3
2,3-OH-CPIA-glucuronide – –	ND ND	5.0±2.3 3.9±1.6	ND ND	3.5±0.5 6.0±2.5	ND ND	1.9±0.5 3.3±0.6	ND ND	2.5±0.8 2.6±0.7
Others – –	6.8±4.2 2.2±0.6	4.5±1.6 0.64.8±1.6	6.3±2.0 1.8±0.4	3.9±0.1 6.6±1.5	2.1±0.3 1.7±0.4	3.7±1.1 4.5±1.0	3.1±0.7 2.3±0.7	2.5±0.6 4.2±0.8
Unextractable ^{14}C – –	1.6±1.2 1.8±0.3	ND ND	1.9±0.4 1.9±0.5	ND ND	3.4±0.6 2.8±0.9	ND ND	2.7±0.6 2.5±0.3	ND ND

[a] Only major metabolites (those components that for one group or another accounted for ≥5% of the dose), unextractable, and unidentified components are tabled; 0-2 day samples.
ND: not detected.
Data taken from Tables 5-1 and 5-2 , pp. 46-47, MRID 45351601.

TABLE 7. Metabolite profiles (% of dose) for rats following a single oral dose of ^{14}C-alcohol esfenvalerate or fenvalerate[a]

Metabolite	^{14}C-alcohol esfenvalerate 2.5 mg/kg		^{14}C-alcohol esfenvalerate (isomeric mix) 2.5 mg/kg		^{14}C-alcohol fenvalerate 10 mg/kg	
	Feces	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**
Parent compound						
–	59.8±7.9	<0.1	53.6±4.2	<0.1	50.2±14.3	<0.1
–	55.2±17.1	<0.1	56.4±8.1	<0.1	59.9±13.4	<0.1
4'-OH-parent compound						
–	5.3±1.4	ND	4.6±0.9	ND	3.9±3.8	ND
–	5.0±1.6	ND	3.5±1.8	ND	2.5±0.6	ND
4'-OH-PB acid sulfate conjugate						
–	ND	16.4±3.7	ND	20.2±2.1	ND	23.9±13.2
–	ND	18.8±7.6	ND	21.8±5.1	ND	19.0±4.3
Others						
–	2.9±0.7	1.6±0.5	4.2±1.8	1.8±0.4	3.8±3.5	2.8±1.8
–	3.6±2.3	2.2±1.3	2.9±2.0	2.0±1.2	1.7±0.8	2.2±1.0
Unextractable ^{14}C						
–	1.3±0.2	ND	1.3±0.5	ND	1.5±1.4	ND
–	1.5±0.5	ND	1.3±0.3	ND	1.0±0.4	ND

[a] Only major metabolites (those components that for one group or another accounted for ≥5% of the dose), unextractable, and unidentified components are tabled; 0-2 day samples; no low-dose ^{14}C-alcohol fenvalerate group.
Data taken from Tables 5-5 and 5-6, pp. 50-51, MRID 45351601.

TABLE 8. Metabolite profiles (% of dose) in mice* following a single oral dose of ^{14}C-alcohol esfenvalerate or fenvalerate[a]

Metabolite	^{14}C-alcohol esfenvalerate 2.5 mg/kg		^{14}C-alcohol esfenvalerate (isomeric mix) 2.5 mg/kg		^{14}C-alcohol fenvalerate 10 mg/kg	
	Feces	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**
Parent compound						
–	30.2	0.2	31.9	0.7	35.8	0.4
–	39.3	<0.1	35.1	1.1	33.6	<0.1
4'-OH-parent compound						
–	4.4	ND	3.8	ND	2.4	ND
–	3.5	ND	3.5	ND	2.2	ND
PB acid taurine conjugate						
–	ND	11.2	ND	17.3	ND	11.7
–	ND	10.2	ND	7.9	ND	12.8
4'-OH-PB acid (free)						
–	0.8	6.1	0.6	3.3	1.1	3.7
–	0.4	0.9	0.6	2.8	0.7	1.8
Others						
–	5.3	23.8	3.3	16.3	5.3	20.3
–	2.6	11.9	3.4	18.6	1.9	14.7
Unextractable ^{14}C						
–	2.8	ND	2.2	ND	2.3	ND
–	1.8	ND	1.6	ND	1.9	ND

* S.D. for mouse data not provided in study report; individual animal data unavailable for calculation.

[a] Only major metabolites (those components that for one group or another accounted for ≥5% of the dose), unextractable, and unidentified components are tabled; 0-2 day samples; no low-dose ^{14}C-alcohol fenvalerate group.

Data taken from Tables 5-7 and 5-8, pp. 52-53, MRID 45351601.

III. DISCUSSION

A. DISCUSSION

In a metabolism and disposition study (1985, MRID 45351601), groups of five male and five female rats and mice were given single or 10-day repeated oral doses of ^{14}C-esfenvalerate (sp. act. 33.5-35.5 mCi/mmol, >99% purity, no lot no., phenoxy phenyl or chlorophenyl ring label position), ^{14}C-fenvalerate (sp. act. 34.0-35.5 mCi/mmol, >99% purity, no lot no., phenoxy phenyl or chlorophenyl ring label position), or ^{14}C-esfenvalerate containing three isomers at doses of 2.5 or 10 mg/kg. Nonlabeled fenvalerate (Lot no. LUG-50205) or esfenvalerate (Lot no. KS-5210) were given concurrent with the radiolabeled test article. Absorption, excretion, distribution, and metabolite characterization were preformed.

Overall recovery of administered radioactivity was an acceptable 94.2-102.7% among the various experimental groups and was not affected by label position.

Absorption of the test material, implied from the urinary excretion data (no cage wash data were provided), indicated that absorption over the time periods and doses tested ranged from approximately 20-60% of the administered dose. For both label positions, absorption was somewhat greater for mice than for rats (49-53% vs 24-35% for the alcohol label and 38-51% vs 20-39% for the acid label position) based upon urinary excretion. Because individual animal data were not provided in the study report, the role of individual variability in the ranges of absorption could not be assessed. Additionally, biliary elimination was not an experimental protocol element and, therefore, it is uncertain what proportion, if any, of the fecal radioactivity represented absorbed dose. Most of the urinary excretion (~75-95%) occurred within 24 hours of dosing implying that absorption was moderately rapid.

The various test materials were eliminated via both the urine and feces with fecal elimination being somewhat more prominent. Over a 7-day post-dose period, urinary excretion was greater in mice (~35-60% of the dose) than in rats (~20-39%) when considering all dose and label positions. For all experimental groups, urinary excretion was rapid and essentially complete at 24-48 hours after dosing. Fecal excretion accounted for the balance of the administered radioactivity. Excretion via this route was also essentially complete at 48 hours after dosing for all experimental groups. There were no significant gender-related difference in excretion patterns and excretion profiles were not affected by dose. Biliary excretion was not assessed and, therefore, it was not possible to determine if the radioactivity recovered in the feces represented absorbed material subsequently excreted via the biliary.

Analysis of tissue residue data showed that, although the test article and/or its metabolites were distributed to most of the examined tissues and organs, concentrations were minimal and generally accounted for <50 ng eq/g tissue in the 2.5 mg/kg dose groups and <100-200 ng eq/g tissue for the 10 mg/kg fenvalerate group. The tissue burdens were consistent with the dose differential and not indicative of bioaccumulation. Fat tissue consistently showed the greatest residue levels regardless of label position, and for esfenvalerate, the esfenvalerate isomer mixture, and fenvalerate. Mesenteric lymph nodes, adrenal glands, and skin also had higher residue levels than other tissues. Based upon the tissue residue data from groups of five animals

(four in some groups), there did not appear to be gender-related differences and individual variability did not seem out of the ordinary for this type of experimental data.

Beyond the daily time-course data for urinary and fecal excretion, no pharmacokinetic parameters were estimated. The time-course data based upon 24 to 48 hour sampling intervals was insufficient for estimating elimination half-times and no plasma time-course data were available with which to determine C_{max}, t_{cmax}, and AUC values.

Metabolic characterizations were performed for both rats and mice, and for all test article forms and dose groups. For rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate, six biotransformation products were characterized from the feces. Substantial amounts of parent compound (44.5-58.2% of the administered dose) were detected in the fecal samples at 0-2 days following a single dose of the test articles. The major metabolite in the feces of rats in all test groups was a 4'- hydroxylation product. Non-characterized components were minimal (<7% of the dose) and unextractable ^{14}C in the feces represented <3.4% of the administered dose. The metabolite profiles of males and females given ^{14}C-acid test labeled test article were not significantly different quantitatively or qualitatively. For rats given ^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, four fecal biotransformation products were characterized. Similar to the rats given the ^{14}C-acid label test article, the 4'-hydroxylation product was the most prominent metabolite in the feces (up to 5% of the administered dose) of both male and female rats. Unchanged parent compound in the 0-2 day fecal samples represented 50.2- 59.9% of the administered dose; similar to the acid-labeled compounds. These findings indicate that there were no significant differences in metabolism processes relative to the acid or alcohol moieties of the test material. Non-characterized components (<5% of the dose) and unextractable ^{14}C (1-2% of the dose) were inconsequential. Unchanged parent compound was also detected in the feces of mice (25.6-48.1% of the dose for both label positions) but to a lesser extent than for rats. Four biotransformation products were detected in the feces of mice but only the 4'-hydroxylation product consistently and individually represented >2% of the administered radioactivity. Non-characterized components accounted for 1.9-5.3% of the total dose and 1.6-2.8% of the radioactivity was reported as unextractable. There did not appear to be biologically relevant gender-related differences in the fecal metabolite profiles of mice.

Five biotransformation products were characterized in the urine of rats given ^{14}C-acid esfenvalerate, ^{14}C-acid esfenvalerate isomer mix, or fenvalerate. CPIA-glucuronide was the most prevalent metabolite. For rats given ^{14}C-alcohol esfenvalerate, ^{14}C-alcohol esfenvalerate isomer mix, or fenvalerate, three biotransformation products were characterized from the urine. A sulfate conjugate of OH-PB acid was quantitatively the most important urinary metabolite (16.4-23.9% of the dose) in rats. For mice, three urinary metabolites were characterized. Parent compound was not detected in the urine of mice and most radioactivity (7.9-17.3% of the administered dose) was associated with a taurine conjugate of PB acid. The free PB-acid and hydroxylated fenvalerate and esfenvalerate were quantitatively insignificant metabolites.

This metabolism study is **Acceptable/Non-Guideline** and does not satisfy the requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in mice or rats. Although the study adequately described the absorption, excretion, tissue distribution, and metabolite characterization of esfenvalerate and fenvalerate in male and female mice and rats

following single and repeated oral dosing, there were key deficiencies (no data on dose confirmation, stability or homogeneity, and no Quality Assurance statement) that prevented its acceptance as an 85-1 Guideline study in metabolism and pharmacokinetics.

B. STUDY DEFICIENCIES

The study report (MRID 45351601) was deficient in that several items and data elements normally provided were unavailable. These included absence of a Quality Assurance statement, no lot/batch nos. for the radiolabeled test material, and no data regarding homogeneity, stability, or dose confirmation.

Additionally, there were no variability estimates (e.g., standard deviations, standard error) for mouse excretion data and no individual animal data were provided to make such an assessment. The nomenclature for isomers was not consistent (two different formats were used; *R,S* and α, β). CPIA and PB-acid were not defined.