DATA EVALUATION RECORD

ESFENVALERATE AND FENVALERATE

STUDY TYPE: METABOLISM AND PHARMACOKINETICS - MOUSE
[OPPTS: 870.7485 (§85-1)]
MRID 45351602

Prepared for

Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - 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: Isobe, N, Kaneko, H., Yanagita, S., Saito, K., Ohe, A., Yoshitake, A., Miyamoto, J. 1985. Comparative metabolism of esfenvalerate and fenvalerate in rats and mice. II. 28-Days dietary administration in mice. Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Hyogo 665, Japan. LLM-5-0008. MRID 45351602. December, 1985. Unpublished.

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

EXECUTIVE SUMMARY: In a metabolism study (1985, MRID 45351602) groups of 54 male and 54 female ddY mice were given ^{14}C-esfenvalerate (Lot number not provided; radiochemical purity >98%) or ^{14}C-fenvalerate (Lot number not provided; radiochemical purity >98%) in the diet for 28 days. Nonlabeled esfenvalerate (Lot No. LUG-50205, analytical grade, no purity stated) and fenvalerate (Lot. No. KS-5210, analytical grade, no purity stated) were incorporated into the respective diets to achieve concentrations of 25 ppm and 100 ppm (fenvalerate only). Groups of six mice were sacrificed at various time points during the 28-day treatment period.

Based upon body weight data and feed consumption, the study reported doses of 115-119 µg esfenvalerate/mouse/day (25-ppm dose group), and 112-118 and 424-477 µg/mouse/day, respectively, for the 25-ppm and 100-ppm fenvalerate groups.

Tissue analysis indicated that the test articles and/or biotransformation products were widely distributed in mice. Radioactivity in individual tissues, however, were quiet low. During the treatment period, radioactivity in tissues tended to increase up to Day 10, after which the concentrations fluctuated slightly or tended to decrease. Absorption, excretion, and overall mass balance data were *not* reported.

Parent compound and two metabolites, 2-chlorophenyl-isovaleric acid (CPIA) and hydroxylated CPIA, were characterized from the liver and kidneys of mice treated with esfenvalerate. For mice fed fenvalerate, these metabolites and an additional metabolite,

CPIA-cholesterol ester were detected. Although CPIA and hydroxyl CPIA levels decreased to below detection limits rapidly after cessation of treatment with fenvalerate or esfenvalerate, the CPIA-cholesterol ester formed from fenvalerate was more persistent and was still detectable in the liver and kidney four days after cessation of treatment. The levels of metabolites in the liver and kidney of fenvalerate-treated mice reflected the 4-fold dose difference for this test compound, suggesting that absorption of parent compound and metabolism were not saturated at the 100 ppm dietary exposure.

This metabolism study (MRID 45351602) is **Acceptable/Non-Guideline** and does not satisfy the complete requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in mice. Although the study adequately described the metabolite burdens in tissues of mice following 28-day dietary exposure to esfenvalerate (25 ppm) and fenvalerate (25 ppm and 100 ppm), the study protocol was not consistent with 85-1 requirements. This study is an appropriate and important ancillary study to an 85-1 Guideline report (MRID 45351601) in rats and mice that addressed absorption and excretion of the test articles.

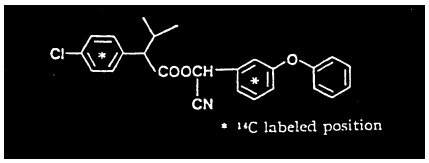
COMPLIANCE: A signed and dated Data Confidentiality Claim statement was included with the study. No Quality Assurance statement was available and the GLP Compliance statement disavowed ability to confirm GLP compliance.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test compound

Radiolabeled
Test article: ^{14}C-Esfenvalerate, sp. act. 34.9 mCi/mol
^{14}C-Fenvalerate, sp. act. 34.5 mCi/mol
Test articles were labeled on the chlorophenyl ring of the acid moiety
Lot No.: not provided; synthesized by performing laboratory
Radiochemical purity: >98% 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 prior to mixing with diet.

3. Test animals

Species: mice
Strain: ddY mice (Shizouka Agricultural Cooperative Association for Laboratory Animals, Shizouka, Japan).
Age and weight at study initiation:
mice: 6 weeks; 31.9-32.6 g (males); 25.9-26.2 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 doses

The dosing solutions were prepared by diluting the radiolabeled materials with analytical grade unlabeled compound to obtain specific activities of 12 and 3 mCi/mmol for esfenvalerate and fenvalerate, respectively. These preparations were then suspended in corn oil (to provide 2% v/w in the diet) and the suspension mixed with pulverized CE-2 rat chow to provide test article concentrations of 25 ppm (esfenvalerate) or 25 and 100 ppm fenvalerate.

Results –
Homogeneity: Homogeneity was determined by combustion analysis and liquid scintillation counting of 3-5 samples.

Stability: No stability data were provided.

Dose confirmation: Concentrations of test article in the diets were found to be 23 ppm and 93 ppm, respectively, for the 25-ppm and 100-ppm diets. Daily feed consumption was monitored to calculate daily doses of 115-119 µg

esfenvalerate/mouse/day (25-ppm dose group), and 112-118 and 424-477 µg/mouse/day, respectively, for the 25-ppm and 100-ppm fenvalerate groups.

B. STUDY DESIGN AND METHODS

1. Group arrangements

The experimental groups were established as shown in Table 1. No control groups were described in the study report (MRID 45351602). Six mice of each sex were terminated at Day 0, 10, 19, 24, and 28 of treatment (treated diet), and on Day 4, 7, 21, and 28 following treatment (basal diet).

TABLE 1. Study design for metabolism and disposition studies (MRID 45351602) of dietary ^{14}C-fenvalerate and ^{14}C-esfenvalerate in mice

Experimental group	Conc. in feed (ppm)	Number/sex	Remarks
A	25	30/sex plus 24/sex on basal diet	28-Day dietary exposure to ^{14}C-esfenvalerate followed by basal diet for 28 days; tissue distribution, tissue metabolite levels; 6 mice of each sex sacrificed at various time points throughout the study period
B	25	30/sex plus 24/sex on basal diet	28-Day dietary exposure to ^{14}C-fenvalerate followed by basal diet for 28 days; tissue distribution, tissue metabolite levels
C	100	30/sex plus 24/sex on basal diet	28-Day dietary exposure to ^{14}C-fenvalerate followed by basal diet for 28 days; tissue distribution, tissue metabolite levels

Data taken from pp. 1-12 , MRID 45351602.

2. Dosing and sample collection

Doses were given as described in Table 1.

Blood - Blood samples were collected on Day 0, 10, 19, 24, and 28 of treatment, and on Day 4, 7, 21, and 28 following treatment (basal diet).

Tissues - Following termination by exsanguination, the following tissues were collected: adrenal glands, brain, fat, kidney, liver, mesenteric lymph nodes, ovaries, testes, skin and hair, and spleen. Tissues were collected from mice sacrificed on the same schedule as described for blood collection.

3. Sample preparation/analysis

Blood - Blood samples collected at terminal sacrifice were analyzed for radioactivity by liquid scintillation counting (LSC). No further details were provided regarding the treatment of blood samples.

Tissues - Tissues (except adrenal glands, lymph nodes, and ovaries) were homogenized with methanol in a Polytron and centrifuged at 1500 x g for 10 minutes. The precipitate was extracted twice in ethyl acetate and again centrifuged at 1500 x g for 10 minutes. Adrenal glands and lymph nodes were homogenized manually in ethyl acetate:methanol (2:1, v/v) and the homogenate filtered. The supernatants, precipitates, filtrates, and filters from these procedures were radioassayed and extracts subjected to thin-layer chromatography (TLC).

4. Analytical techniques

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

A: *n*-hexane-toluene-acetic acid (3:15:2)
B: 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 (Kodak SB-5 film, one week exposure time at 4-8°C).

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

Combustion/oxidation - Following extraction, air-dried tissue samples (200 mg) were combusted in a Packard Model 306 sample oxidizer prior to radioassay by LSC. Oxisorb-CO_2® and Oxiprep-2® (New England Nuclear) were used for carbon dioxide absorption and as scintillants, respectively. Combustion efficiency was reported as >95%.

5. Calculations and statistics

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

II. RESULTS

A. DISTRIBUTION/EXCRETION STUDIES

1. Mass balance

The primary objective of this study was to identify tissue metabolites following dietary exposure to the test articles. Therefore, overall recovery of administered radioactivity was not determined.

2. Absorption

Determination of absorption was not a component of the study protocol and, therefore, no data were generated allowing for such an assessment.

3. Excretion

Assessment of excretory patterns was not a protocol element.

4. Tissue distribution

The concentration of total radioactivity (expressed as µg eq. test article/g tissue) following 28 days of dietary exposure to the test articles are summarized in Table 2. Although values were available for blood, brain, spleen, and testes, these tissues showed relatively low levels of radioactivity (generally <1 µg eq./g for the 25-ppm groups and <2 µg eq./g for the 100-ppm groups. Brain levels were <0.1 and 0.2 µg eq./g for the 25- and 100-ppm groups, respectively. Blood levels also remained low (<1.0 and 0.5 µg eq./g for the 25- and 100-ppm groups, respectively) at all time points examined. During treatment, the highest radioactivity levels were detected in the adrenal glands and fat, both of which decreased notably following removal from treatment. At Day 28 of the post-treatment period (basal diet only), all tissues/organs exhibited burdens considerably less than that observed during treatment. At this time, fat and liver exhibited greater burdens than did other tissues. Based on the available data, there were no biologically significant gender-related differences in tissue burdens. The tissue burdens in the high-dose fenvalerate (100 ppm) group were correspondingly greater than the low-dose (25 ppm) group. For most tissues, the greatest tissue burdens were observed midway into the treatment period, although levels in the adrenal glands and fat tissue continued to increase for several days following cessation of treatment. Radioactivity in the tissues of esfenvalerate-treated mice decreased on subsequent days following removal from treatment. For fenvalerate-treated mice, however, levels in the adrenal glands tended to exhibit slight increases, and levels in fat and skin decreased slowly compared to the other tissues examined. Based upon analysis of data presented in the study report, most (~50 to >95%) of the radioactivity in the tissues of fenvalerate-treated mice was associated with the CIPA-cholesterol ester metabolite (Section IIC).

TABLE 2. ^{14}C tissue residues (µg eq./g) in tissues of mice following a 28-day dietary exposure to ^{14}C-Esfenvalerate or ^{14}C-Fenvalerate[a]

Tissue	25 ppm ^{14}C- Esfenvalerate Males	Females	25 ppm ^{14}C- Fenvalerate Males	Females	100 ppm ^{14}C-Fenvalerate Males	Females
During treatment						
Adrenal						
Day 10	0.5	0.4	2.3	2.4	7.6	9.1
Day 19	1.4	0.7	4.6	4.8	20.5	16.3
Day 24	1.1	1.2	4.3	5.0	18.3	16.7
Day 28	1.3	1.0	5.3	5.9	17.7	19.6
Fat						
Day 10	4.15	4.47	4.69	4.43	13.2	17.7
Day 19	5.56	6.27	5.66	5.36	24.3	23.2
Day 24	7.23	7.02	5.30	5.69	23.7	23.7
Day 28	6.56	6.50	5.41	6.69	17.1	23.9
Kidney						
Day 10	0.62	0.39	0.32	0.47	1.5	1.2
Day 19	1.00	0.22	0.52	0.47	1.7	1.5
Day 24	0.90	0.51	0.79	0.58	2.3	1.9
Day 28	0.63	0.32	0.59	0.55	1.8	1.9
Liver						
Day 10	0.62	0.53	1.32	1.79	5.81	5.85
Day 19	0.53	0.42	1.99	2.06	6.98	8.51
Day 24	0.69	0.69	2.43	2.50	8.44	8.98
Day 28	0.50	0.54	1.83	2.89	7.45	10.65
Lymph nodes						
Day 10	0.7	0.6	1.4	1.2	3.2	4.2
Day 19	1.1	1.0	2.0	2.8	7.2	7.0
Day 24	0.6	1.5	3.6	2.9	11.7	11.4
Day 28	1.1	1.7	3.3	3.5	9.6	11.7
Skin						
Day 10	1.07	1.96	0.94	1.46	3.46	5.33
Day 19	1.30	1.20	1.20	1.75	3.82	7.42
Day 24	1.23	1.79	1.12	1.73	5.56	5.79
Day 28	1.26	2.03	1.24	2.22	5.01	7.31
Post treatment						
Adrenal						
Day 4	0.7	1.1	7.8	4.3	28.7	18.0
Day 7	1.7	0.6	3.7	5.0	13.9	15.1
Day 21	0.1	0.1	1.9	2.5	7.3	6.8
Day 28	ND	ND	6.0	5.0	34.7*	16.8
Fat						
Day 4	6.38	8.03	6.63	6.68	28.6	25.6
Day 7	8.93	6.66	5.43	6.52	22.3	21.8
Day 21	3.31	3.05	3.34	1.81	11.4	6.9
Day 28	1.97	1.19	3.84	1.31	8.9	7.0
Kidney						
Day 4	0.07	0.09	0.35	0.35	1.0	1.5
Day 7	0.05	0.03	0.27	0.31	0.6	1.1
Day 21	0.01	0.01	0.11	0.14	0.7	1.6

TABLE 2. ^{14}C tissue residues (µg eq./g) in tissues of mice following a 28-day dietary exposure to ^{14}C-Esfenvalerate or ^{14}C-Fenvalerate[a]

Tissue	25 ppm ^{14}C- Esfenvalerate Males	25 ppm ^{14}C- Esfenvalerate Females	25 ppm ^{14}C- Fenvalerate Males	25 ppm ^{14}C- Fenvalerate Females	100 ppm ^{14}C-Fenvalerate Males	100 ppm ^{14}C-Fenvalerate Females
Day 28	0.01	0.00	0.09	0.17	0.3	0.4
Post-treatment (con't)						
Liver						
Day 4	0.12	0.18	1.60	2.52	7.64	10.77
Day 7	0.07	0.10	0.63	2.61	7.17	8.83
Day 21	0.01	0.03	0.55	0.57	1.83	2.28
Day 28	0.01	0.01	0.28	0.44	1.53	1.68
Lymph nodes						
Day 4	0.9	0.6	3.9	1.8	14.2	12.3
Day 7	1.3	0.5	2.1	2.5	10.0	10.2
Day 21	0.1	0.1	2.3	2.0	6.4	8.6
Day 28	0.1	0.1	1.4	2.4	7.9	6.8
Skin						
Day 4	0.69	1.25	0.86	1.07	3.03	4.26
Day 7	0.40	1.04	0.48	0.64	1.95	3.04
Day 21	0.07	0.24	0.35	0.38	1.22	1.77
Day 28	0.06	0.21	0.33	0.35	1.15	1.28

[a] n= 6 mice. Data taken from Tables 4 a-f, pp. 21-26, MRID 45351602.
ND: below detection limit
* Value is inordinately high because it is based upon dry weight rather than wet tissue weight.

B. PHARMACOKINETIC STUDIES

Pharmacokinetic investigations were not conducted.

C. METABOLITE CHARACTERIZATION STUDIES

Distribution of metabolites among tissues was a key objective of this study. Parent compound and two metabolites were characterized from the liver and kidneys of mice treated with esfenvalerate; 2-chlorophenyl-isovaleric acid (CPIA) and hydroxlated CPIA (Table 3). In mice fed fenvalerate, an additional metabolite, CPIA-cholesterol ester, was identified (Tables 4 and 5). Although CPIA and hydroxyl CPIA levels decreased to below detection limits rapidly after cessation of treatment, CPIA-cholesterol ester metabolite was more persistent and was still detectable 4 days after cessation of treatment. The levels of metabolites in the liver and kidney of fenvalerate-treated mice inconsistently reflected the 4-fold dose difference.

TABLE 3. Metabolites (µg eq. g tissue) in the liver and kidney of mice following dietary exposure to ^{14}C-Esfenvalerate (25 ppm)[a]

Metabolite	Liver			Kidney		
	Treatment		Post-treatment	Treatment		Post-treatment
	Day 24	Day 28	Day 4	Day 24	Day 28	Day 4
Esfenvalerate						
Male	0.04	0.03	–	0.03	0.03	–
Female	0.03	0.02	–	0.05	0.03	–
Cpia						
Male	0.08	0.04	–	0.43	0.22	–
Female	0.03	0.02	–	0.09	0.05	–
3-oh-cpia						
Free						
Male	0.04	0.03	–	0.02	0.02	–
Female	0.03	0.03	–	0.01	-	–
Lactone						
Male	0.05	0.02	–	0.02	0.02	–
Female	0.04	0.02	–	0.03	–	–
Others						
Male	0.10	0.13	0.04	0.25	0.21	0.04
Female	0.16	0.13	0.05	0.23	0.17	0.04
Unextractable ^{14}c						
Male	0.38	0.24	0.08	0.14	0.13	0.03
Female	0.39	0.32	0.13	0.09	0.07	0.05
Total						
Male	0.69	0.50	0.12	0.90	0.63	0.07
Female	0.69	0.54	0.18	0.51	0.32	0.09

[a] Repeat extraction resulted in recovery of additional but minor amounts of parent compounds but no characterized metabolites. Data taken from Tables 5a and 5b, pp. 27-28, MRID 45351602.

TABLE 4. Metabolites (µg eq. g tissue) in the liver and kidney of mice following dietary exposure to ^{14}C-Fenvalerate (25 ppm)[a]

Metabolite	Liver			Kidney		
	Treatment		Post-treatment	Treatment		Post-treatment
	Day 24	Day 28	Day 4	Day 24	Day 28	Day 4
Fenvalerate						
Male	0.02	–	–	–	–	–
Female	-	0.04	–	0.06	–	
Cpia-cholesterol Ester						
Male	0.60	1.12	0.84	0.07	0.25	0.21
Female	0.46	2.00	1.42	0.28	0.30	0.26
Cpia						
Male	0.10	0.05	–	0.15	0.07	–
Female	0.06	0.02	–	0.03	0.02	–
3-oh-cpia						
Free						
Male	0.03	0.03	–	–	–	–
Female	0.06	0.02	–	–	–	–
Lactone						
Male	0.04	0.02	–	0.02	0.01	–
Female	0.04	0.02	–	–	–	–
Others						
Male	0.19	0.13	0.05	0.42	0.15	0.08
Female	0.73	0.20	0.10	0.14	0.16	0.07
Unextractable ^{14}c						
Male	1.44	0.47	0.71	0.13	0.11	0.06
Female	1.15	0.59	1.00	0.07	0.07	0.02
Total						
Male	2.43	1.83	1.60	0.79	0.59	0.35
Female	2.50	2.89	2.52	0.58	0.55	0.35

[a] Repeat extraction resulted in recovery of additional amounts of CPIA-cholesterol ester and minor amounts of uncharacterized components but no parent compound.

Data taken from Tables 5c and 5d, pp. 29-30, MRID 45351602.

TABLE 5. Metabolites (µg eq. g tissue) in the liver and kidney of mice following dietary exposure to ^{14}C-fenvalerate (100 ppm)[a]

Metabolite	Liver			Kidney		
	On-treatment Day 24	On-treatment Day 28	Post-treatment Day 4	On-treatment Day 24	On-treatment Day 28	Post-treatment Day 4
Fenvalerate						
Male	0.1	–	–	0.1	–	–
Female	-	0.1	–	–	–	
Cpia-cholesterol Ester						
Male	3.4	4.5	3.6	1.1	0.7	0.7
Female	4.4	8.1	5.8	1.0	1.2	1.2
Cpia						
Male	0.3	0.3	–	0.3	0.2	–
Female	0.2	–	–	–	–	–
3-oh-cpia						
Free						
Male	0.2	0.2	–	–	–	–
Female	0.2	–	–	–	–	–
Lactone						
Male	0.1	0.2	–	–	–	–
Female	0.1	–	–	–	–	–
Others						
Male	0.4	0.5	0.2	0.4	0.5	0.2
Female	1.3	0.6	0.4	0.7	0.5	0.2
Unextractable ^{14}c						
Male	3.9	1.7	3.8	0.4	0.4	0.1
Female	2.8	1.9	4.6	0.2	0.2	0.1
Total						
Male	8.4	7.4	7.6	2.3	1.8	1.0
Female	9.0	10.7	10.8	1.9	1.9	1.5

[a] Repeat extraction resulted in recovery of additional amounts of CPIA-cholesterol ester and minor amounts of uncharacterized components, but no parent compound.

Data taken from Tables 5e and 5f, pp. 31-32, MRID 45351602.

III. **DISCUSSION**

A. DISCUSSION

In a metabolism study (MRID 45351602) groups of 54 male and 54 female ddY mice were given ^{14}C-esfenvalerate (Lot no. not provided; radiochemical purity >98%) or ^{14}C-fenvalerate (Lot no. not provided; radiochemical purity >98%) in the diet for 28 days. Nonlabeled esfenvalerate (Lot no. LUG-50205, analytical grade, no purity stated)

and fenvalerate (Lot. No. KS-5210, analytical grade, no purity stated) were incorporated into the respective diets to achieve concentrations of 25 ppm and 100 ppm (fenvalerate only).
Groups of six mice were sacrificed at various time points during the 28-day treatment period. The remaining mice were fed untreated diet up to an additional 28 days.

Because the primary objective of this study was to assess tissue burdens of various metabolites of ^{14}C-esfenvalerate and ^{14}C-fenvalerate in mice following 28-day dietary exposure, determination of absorption and excretion patterns were not study protocols. Therefore, data were unavailable for making such assessments. Feed consumption and body weights were monitored allowing estimation of test article intake by the investigators. Daily doses of 115-119 µg esfenvalerate/mouse/day (25-ppm dose group), and 112-118 and 424-477, respectively, for the 25-ppm and 100-ppm fenvalerate groups were reported.

Based upon tissue analysis data presented in the study report, the test articles and/or biotransformation products were widely distributed in mice following dietary exposure. Radioactivity levels in individual tissues, however, were quiet low. During the treatment period, radioactivity in tissues tended to increase up to Day 10, after which the concentrations fluctuated slightly or tended to decrease.

Parent compound and two metabolites, 2-chlorophenyl-isovaleric acid (CPIA) and hydroxylated CPIA, were characterized from the liver and kidneys of mice treated with esfenvalerate. For mice fed fenvalerate, these metabolites were present as well as an additional metabolite, CPIA-cholesterol ester. Although CPIA and hydroxyl CPIA levels decreased to below detection limits rapidly after cessation of treatment with esfenvalerate or fenvalerate, the CPIA-cholesterol ester resulting from the metabolism of fenvalerate was more persistent and was still detectable in the liver and kidney four days after cessation of treatment. The levels of metabolites in the liver and kidney of fenvalerate-treated mice reflected the 4-fold dose difference for this test compound, suggesting that absorption of parent compound and metabolism were not saturated at the 100 ppm dietary exposure.

This metabolism study (MRID 45351602) is **Acceptable/Non-Guideline** and does not satisfy the requirements for a Metabolism and Pharmacokinetics Study [OPPTS 870.7485 (§85-1)] in mice. Although the study adequately described the metabolite burdens in tissues of mice following 28-day dietary exposure to esfenvalerate (25 ppm) and fenvalerate (25 ppm and 100 ppm), the study protocol was not consistent with 85-1 requirements nor was it apparently designed to be consistent with the guidelines. This study is an appropriate and important ancillary study to an 85-1 Guideline report (MRID 45351601) in rats and mice that addressed absorption and excretion of the test articles.

B. STUDY DEFICIENCIES

Review of this study report (MRID 45351602) revealed no deficiencies that would compromise the study quality or the validity of the results. Based upon the available data, the study authors interpretations and conclusions appear valid.