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

006697

APR 29 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

SUBJECT: Bifenthrin Metabolism Studies

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767C)

FROM: Byron T. Backus, Toxicologist
Toxicology Branch (TS-769C)

THROUGH: Marcia van Gemert, Ph.D.
Section Head, Review Section III
Toxicology Branch (TS-769C)

and

Theodore M. Farber, Ph.D., D.A.B.T.
Branch Chief
Toxicology Branch (TS-769C)

EPA Record No. 209518/209905

Project No. 8-0498

Tox. Chem. 463F

Action Requested:

Review two metabolism studies on FMC 54800.

Comments and Recommendations:

1. The study titled "Absorption, Distribution and Excretion Studies of FMC 54800 in the Rat," previously classified as supplementary, has, in its resubmitted form, been reclassified (upgraded) to core minimum data.

2. The study titled "Preliminary Metabolism Study of Alcohol- and Acid-^{14}C FMC 54800 in the Rat. Excretion and Tissue Distribution" has been classified as core supplementary data.

3. Copies of the attached DER's should be provided to the registrant.

Reviewed by: Byron T. Backus B.T. Backus 04/20/88
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert
Section 3, Tox. Branch (TS-769C) Marcia van Gemert 4/22/88

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DATA EVALUATION REPORT I

STUDY TYPE: Metabolism - rat

TOX. CHEM. NO: 463F

ACCESSION NUMBER: 404151

MRID NO:

TEST MATERIAL: FMC 54800

SYNONYMS: [2-methyl-1,1'biphenyl)-3-yl]'methyl-cis, trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane carboxylate

STUDY NUMBER(S): BTC Study No. P00924
FMC Report No. PC-0047

SPONSOR: FMC Corporation

TESTING FACILITY: Biological Test Center ~~Kendall McGaw Laboratories, Inc.~~ Irvine, CA

TITLE OF REPORT: Absorption, Distribution and Excretion Studies of FMC 54800 in the Rat

AUTHOR: Selim, S.

REPORT ISSUED: 02/14/86; re-issued 8/17/87

BACKGROUND:

This report issued 02/14/86 was reviewed by van Gemert (2/24/87) and classified as supplementary. Among the problems noted with with this study was that males were administered material with the radiolabel in the acid position and females were administered material radiolabeled in the alcohol (biphenyl) structure.

CONCLUSION:

1. Despite the difference in ^{14}C-labeling position in the FMC 54800 administered to males and that given to females, the study is acceptable. This conclusion is based on the fact that most (>90%) of the radioactivity was eliminated via the urine and feces, with no significant differences between the sexes in this respect. Further, there were no significant differences between dosage groups in percentages excreted despite variations in amount of material administered or dosage schedule. This suggests that most of the material is excreted with little or no change, or in a form incorporating both of the labeled sites.

2. Females did retain slightly more radioactivity in their bodies (particularly in adipose tissue) than did males, particularly at the high-dose (adipose tissue in females: 23.895 ppm; males: 4.38 ppm). Labeling of the material given to the females was in the biphenyl group, and, given a splitting of the molecule between the two labeling sites, this would have tended to give a more lipophilic radiolabeled residue.

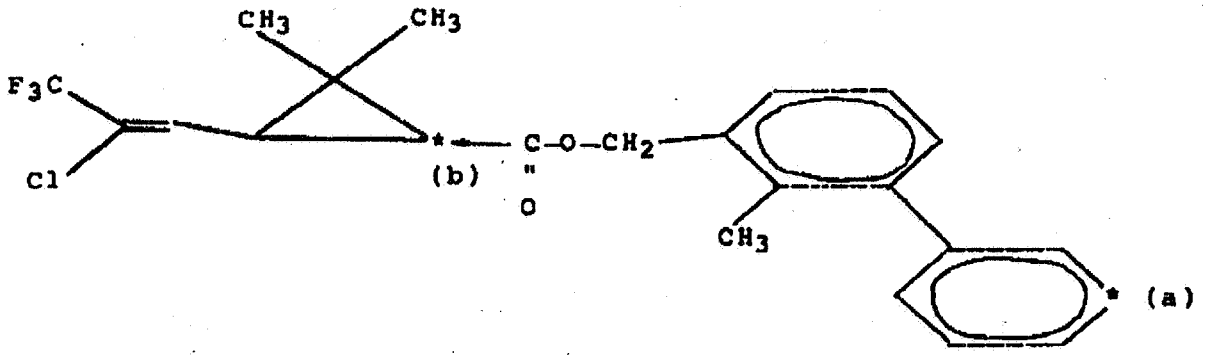
Classification: Core Minimum Data

A. MATERIALS:

1. Test Compound:

Unlabeled FMC 54800, reported as 96.2% active. No further information is given as to what impurities might have been present.

Labeled FMC 54800:



Two ^{14}C-labeled forms of FMC 54800 were separately prepared: a (the alcohol form, labeled in the phenyl ring) and b (the acid label, with ^{14}C in the cyclopropoxyl ring). The alcohol-labeled compound had a specific activity of 33.52 mCi/mmol; the acid-labeled form had 11.93 mCi/mmol. Purities are reported as 98% for the alcohol-labeled FMC 54800 and 97.3% for the acid-labeled material. In the studies males received only the material labeled in the cyclopropoxyl ring and females received only the material labeled in the phenyl ring. The test material was administered with Mazola corn oil as carrier.

2. Test Animals: adult male and female Sprague-Dawley rats (Charles River CD. Crl CD(SD)Br).

B. STUDY DESIGN:

All studies utilized rats which had been fasted for 18 hours before the test material was orally administered.

1. CO_2 study:

Two males and 2 females received by oral intubation 4 mg/kg of radiolabeled compound. Immediately after test material administration the rats were transferred to glass cages designed for separate collection of urine, feces and CO_2. Expired CO_2 was collected in 2:1 ethanolamine/cellusolve at intervals of 4, 8, 12, 24 and 48 hours.

2. Single Oral Low Dose:

Five males and 5 females received by oral intubation a single oral dose of 4 mg/kg of radiolabeled test material. Immediately after dosage the rats were transferred to individual cages "equipped with a urine/feces separator."

3. Single High Dose:

Five males and 5 females received by oral intubation a single oral dose of 35 mg/kg of radiolabeled test material. Immediately after being dosed the rats were transferred to individual metabolism cages.

4. Multiple Oral Dose:

Five males and 5 females were orally administered 4 mg/kg of unlabeled FMC 54800 in corn oil on a daily basis for 14 days. They were then fasted for 18 hours before administration of about 4 mg/kg of radiolabeled material.

5. Collecting and Sampling Procedure:

For the single oral low-dose, high-dose and multiple dose groups, urine, feces and urine/feces separator washing samples were collected for the following time intervals: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours. Weights of the urine and fecal samples were determined at the time of collection; the samples were then frozen and stored at -20° C until analysis. At the end of the study cages were washed and a sample of the wash was assayed assayed for radiolabel.

Seven days after dosing, the animals were exsanguinated. "The rats were dissected and the following tissues and organs removed: brain, heart, pancreas, leg muscles, lungs, adipose, spleen, bone, skin, hair, kidney, liver and gonads (uterus and ovaries for females, testes, seminal vesicle and prostate for males), and carcass. Each tissue was individually weighed and stored at -20° C until subjected to radioassay..."

6. There is a signed quality assurance statement on p. 4 of the report, and a signed "Compliance statement" (indicating adherence to GLP standards) on p. 3.

C. RESULTS:

1. CO_2 study:

Total administered radioactivity in collected CO_2 (from table 3, p. 25):

Time Interval (hrs)	Animal Number (and Sex) 2521(F)	2523(F)	2491(M)	2492(M)
0-4	0.001	0.001	0.005	0.003
4-8	0.005	0.005	0.010	0.008
8-12	0.006	0.008	0.008	0.010
12-24	0.008	0.011	0.007	0.011
24-48	0.004	0.007	0.030	0.013
Cumulative	0.024	0.032	0.060	0.045

Only the radioactivity from the collected CO_2 (not the urine and/or feces) was measured in this part of the study

2. Single Oral Low (4 mg/kg) Dose - Excreted Radioactivity:

From tables 5, 6, 8 and 9:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. in urine: Females	Males	in feces: Females	Males
0-8	1.19 ± 0.68	0.94 ± 0.62	<0.00 ± 0.00	0.00 ± 0.00
8-12	2.46 ± 1.12	2.15 ± 0.91	<0.00 ± 0.00	0.00 ± 0.00
12-24	8.03 ± 4.24	3.66 ± 1.57	40.23 ± 23.68	57.65 ± 13.81
24-36	4.10 ± 1.96	2.81 ± 1.64	5.20 ± 6.63	13.34 ± 3.92
36-48	1.71 ± 1.28	1.48 ± 0.67	*19.04 ± 17.76	7.39 ± 2.90
48-72	1.13 ± 0.63	1.50 ± 1.27	5.67 ± 6.62	2.64 ± 2.66
72-96	0.47 ± 0.24	0.37 ± 0.12	1.97 ± 1.25	0.71 ± 0.60
96-120	0.17 ± 0.05	0.18 ± 0.05	0.58 ± 0.18	0.45 ± 0.15
120-144	0.22 ± 0.07	0.17 ± 0.05	0.44 ± 0.07	0.27 ± 0.06
144-168	0.17 ± 0.07	0.16 ± 0.08	0.35 ± 0.16	0.37 ± 0.37
Cumulative	19.65 ± 4.93	13.39 ± 5.77	72.87 ± 4.98	82.80 ± 8.85

Cumulative radioactivity recovery in feces + urine: Males: 96.21 ± 3.8
Females: 92.53 ± 1.2

*Assumed that the value for animal #2535 was 13.22% (which would fit in with the reported cumulative for this animal as well as the reported average for this period) rather than 12.22% (p. 28).

3. Single Oral High (35 mg/kg) Dose - Excreted Radioactivity:

From tables 11, 12, 14 and 15:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. in urine: Females	Males	in feces: Females	Males
0-8	2.33 ± 2.70	2.51 ± 1.37	1.86 ± 3.08	3.39 ± 3.37
8-12	1.18 ± 0.46	2.49 ± 1.00	4.83 ± 4.61	12.78 ± 10.89
12-24	3.42 ± 1.20	4.77 ± 2.15	6.81 ± 10.70	11.39 ± 14.42
24-36	4.07 ± 1.19	6.22 ± 5.05	7.98 ± 9.72	14.25 ± 15.56
36-48	4.29 ± 0.85	2.32 ± 1.47	21.99 ± 5.37	¶14.64 ± 22.55
48-72	3.82 ± 1.54	1.55 ± 1.10	*20.97 ± 5.83	9.39 ± 11.70
72-96	1.51 ± 0.64	0.61 ± 0.38	4.27 ± 2.26	1.59 ± 1.67
96-120	0.55 ± 0.22	0.44 ± 0.20	1.24 ± 0.45	0.71 ± 0.72
120-144	0.34 ± 0.13	0.34 ± 0.23	0.55 ± 0.29	0.42 ± 0.32
144-168	0.25 ± 0.14	†0.32 ± 0.28	0.43 ± 0.09	0.35 ± 0.30
Cumulative	21.76 ± 1.85	21.60 ± 7.93	70.93 ± 5.69	68.89 ± 6.64

*Reported as 20.85 (p. 34); 20.97 is calculated from individual data.
†Reported as 0.19 (p. 36); 0.32 is calculated from individual data.
¶Reported as 13.61 (p. 37); 14.64 is calculated from individual data.

Cumulative radioactivity recovery in feces + urine: Males: 90.50 ± 4.31
Females: 92.70 ± 4.37

5. Single Labeled Dose after Multiple (14-Day) Non-labeled Dosage:

From tables 17, 18, 20 and 21:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. in urine: Females	Males	in feces: Females	Males
0-8	*1.31 ± 0.90	1.73 ± 1.04	0.00 ± 0.00	0.00 ± 0.00
8-12	3.70 ± 1.86	3.78 ± 1.59	0.17 ± 0.37	1.81 ± 4.05
12-24	6.39 ± 1.03	5.69 ± 2.34	18.51 ± 12.70	35.09 ± 14.54
24-36	5.55 ± 2.51	3.49 ± 0.80	17.31 ± 14.17	21.34 ± 14.16
36-48	4.10 ± 3.34	1.49 ± 0.42	13.60 ± 8.64	10.66 ± 5.12
48-72	2.03 ± 2.28	0.96 ± 0.31	5.13 ± 1.31	2.49 ± 0.91
72-96	1.10 ± 1.18	0.51 ± 0.30	9.10 ± 16.94	0.84 ± 0.31
96-120	†0.41 ± 0.25	0.34 ± 0.26	1.06 ± 0.72	0.34 ± 0.14
120-144	0.25 ± 0.11	0.19 ± 0.05	0.51 ± 0.16	0.38 ± 0.20
144-168	0.19 ± 0.06	0.19 ± 0.17	0.42 ± 0.04	0.28 ± 0.07
Cumulative	25.01 ± 7.26	18.36 ± 3.58	65.80 ± 9.60	73.22 ± 4.82

*Reported as 1.28 (p. 39); 1.31 is calculated from individual data.
†Reported as 6.55 (p. 39); 0.41 is calculated from individual data.

Cumulative radioactivity recovery in feces + urine: Males: 91.58 ± 4.56
Females: 90.81 ± 4.63

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6. Radioactivity in tissues:

The following is the mean "ppm radioactivity" in tissues at sacrifice; from tables 22A, 23A, 24A, 25A, 26A, 27A (p. 44, 46, 48, 50, 52, and 54):

	Single low-dose 4 mg/kg		Single high-dose 35 mg/kg		Multiple (14-day) Dosage + one labeled dose	
Tissue	Females	Males	Females	Males	Females	Males
Brain	0.008	0.006	0.087	0.036	0.013	0.009
Heart	0.036	0.028	0.260	0.108	0.042	0.024
Lungs	0.088	0.190	0.615	0.385	0.063	0.104
Liver	0.116	0.138	0.857	0.830	0.140	0.152
Kidney	0.047	0.045	0.315	0.225	0.077	0.047
Spleen	0.032	0.021	0.230	0.162	0.051	0.021
Adipose	1.502	1.087	23.895	4.380	2.532	1.087
Skel. mus.	0.043	0.044	0.719	0.102	0.040	0.021
Bone	0.101	0.041	0.396	0.153	0.056	0.041
Whole blood	0.017	0.010	0.130	0.052	0.025	0.012
Pancreas	0.341	0.272	3.055	0.436	0.345	0.344
Hair	0.155	0.075	0.303	0.649	0.055	0.069
Ovaries	0.357	-	3.366	-	0.340	-
Uterus	0.106	-	2.069	-	0.048	-
Seminal vesicle	-	0.011	-	0.238	-	0.054
Prostate	-	0.138	-	0.669	-	0.187
Testes	-	0.022	-	0.112	-	0.018
Skin	0.758	0.253	3.918	1.749	0.264	0.150
Final Carcass	0.120	0.200	1.060	0.199	0.134	0.104

"Percent of dose for bone, fat, hair, muscle and skin pertains to sample taken at necropsy. Remaining portion of each is in the carcass."

7. Total recoveries:

Total recoveries (in terms of % of administered dose) are given below (from tables 28, 29, 30, 31, 32 and 33; pages 56-61):

	Single low-dose 4 mg/kg		Single high-dose 35 mg/kg		Multiple (14-day) Dosage + one labeled dose	
	Females	Males	Females	Males	Females	Males
Body	3.94±0.95	3.76±2.65	4.22±1.93	3.40±1.83	4.05±1.27	3.13±1.09
Urine	19.65±4.93	13.39±5.77	21.76±1.85	21.60±7.93	25.01±7.26	18.36±3.58
Feces	72.87±4.98	82.80±8.85	70.93±5.69	68.89±6.64	65.80±9.60	73.22±4.82
Total	96.46±1.43	100.95±6.86	96.92±5.64	93.90±5.19	94.85±4.69	94.71±3.98

D. DISCUSSION:

Despite the differences in ^{14}C-labeling position in the FMC 54800 administered to males and that given to females, the study is acceptable. This conclusion is based on the fact that most of the radioactivity was eliminated via the urine

and feces in both sexes, and, despite the difference in labeling position, the relative percentages via each of these routes were remarkably constant for both sexes.

Further, there were no significant differences between groups despite differences in amount of material administered or dosage schedule. This also suggests that most of the material is excreted either unmodified, with relatively little change, or in a form incorporating both of the labeled sites.

It is noteworthy that females did retain slightly more radioactivity in their bodies (particularly the adipose tissue) than did males. This was particularly noticeable for the high-dose group (adipose tissue in females: 23.895 ppm; in males: 4.38 ppm). Labeling of the material given to the females was in the biphenyl group, and, given a splitting of the molecule between the two labeling sites, this would have tended to give a more lipophilic radio-labeled residue.

The CO_2 study demonstrates that very little of the administered radioactivity (a mean of 0.028% in females, 0.053% in males) is given off as $^{14}CO_2$. Even here, however, the slight difference between sexes may have been primarily due to difference in ^{14}C-labeling position.

Reviewed by: Byron T. Backus Byron T. Backus 07/24/88
Section 3, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert Marcia van Gemert 7/22/88
Section 3, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT II

STUDY TYPE: Metabolism - rat

TOX. CHEM. NO: 463F

ACCESSION NUMBER: 404151

MRID NO:

TEST MATERIAL: FMC 54800

SYNONYMS: [2-methyl-1,1'biphenyl)-3-yl]'methyl-cis, trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane carboxylate

STUDY NUMBER(S): 182RATM01

SPONSOR: FMC Corporation

TESTING FACILITY: FMC Corporation

TITLE OF REPORT: Preliminary Metabolism Study of Alcohol-nd Acid-^{14}C FMC 54800 in the Rat. Excretion and Tissue Distribution.

AUTHOR: ElNaggar, S.F.

REPORT ISSUED: 09/25/87

CORE CLASSIFICATION: Supplementary

CONCLUSIONS:

1. There is very little breakage of the ester linkage of the parent compound (FMC 54800) in the material eliminated via the feces in the period of 0-48 hours after dosage, when most of the administered radioactivity is identifiable as coming from unmodified parent compound. However, the material subsequently eliminated, although a relatively small proportion of the administered dose, appears to have undergone more modification. Since a greater proportion of the radioactivity eliminated via the feces in the period of 48-168 hours is in the form of 2-Methyl-3-phenylbenzyl alcohol and 2-Methyl-3-phenylbenzoic acid than the parent compound, this is evidence that extensive breakage of the ester linkage does occur, either in the material retained in the intestines for more than 48 hours, or in the material absorbed and subsequently eliminated via the feces.

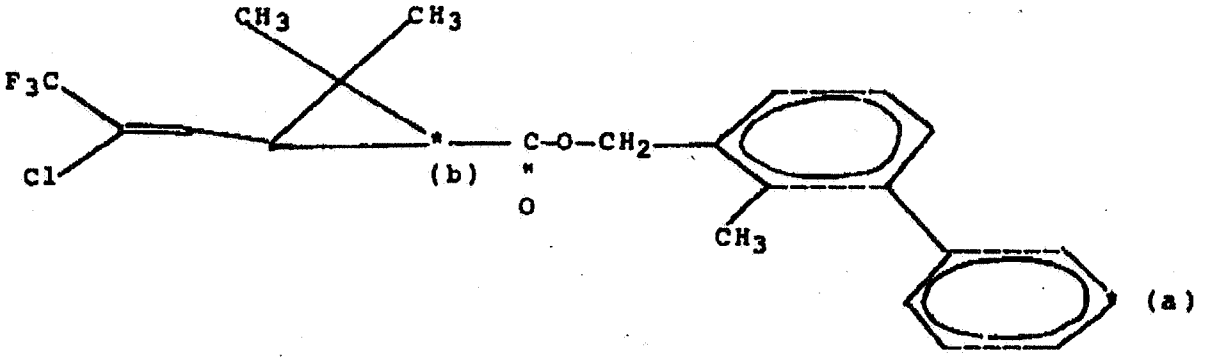
2. The study is classified as supplementary. While it does provide some insight into the incomplete absorption of FMC 54800 from the intestine, and the lack of modification of most of this unabsorbed material, particularly that eliminated via the feces during the period of 0-48 hours, the metabolism of the absorbed FMC 54800 (radioactivity primarily excreted via the urine, despite differences in labeling) is less clear.

A. MATERIALS:

1. Test Compound:

Unlabeled FMC 54800. No further information is given as to purity.

Labeled FMC 54800 (>90% cis product):



Two ^{14}C-labeled forms of FMC 54800 were separately prepared: a (the alcohol form, labeled in the phenyl ring) and b (the acid label, with ^{14}C in the cyclopropoxyl ring). The alcohol-labeled compound had a specific activity of 33.52 mCi/mmol; the acid-labeled form had 11.93 mCi/mmol. After dilution with non-labeled FMC 54800 activities were 7.31 and 9.06 mCi/mM respectively.

2. Test Animals: Male and female Sprague-Dawley rats, 6-7 weeks old, 150-256 grams, from Taconic Farms.

B. STUDY DESIGN:

1. Procedure

Rats were fasted for 18 hours before the test material was orally administered (with corn oil as the carrier).

Groups of 3 females received 5.15-5.79 mg/kg of alcohol-labeled FMC 54800 or 4.28-5.14 mg/kg acid-labeled FMC 54800. Groups of 3 males received either 4.83-5.66 mg/kg of the alcohol-labeled FMC 54800 or 4.90-5.33 mg/kg of the acid-labeled material. Animals were fed starting 6 hrs after dosage.

Urine and feces were collected for the following time intervals: 0-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours. Samples were frozen and stored at -20° C until analysis. At the end of the study cages were washed and a sample of the wash was assayed assayed for radiolabel.

Seven days after dosing, the animals were sacrificed by cervical dislocation. "The rats were then dissected, blood was collected, and the following tissues and organs obtained: Liver, brain, heart, kidney, spleen, skin, bone, muscle, lung, adipose tissue and gonads (uterus and ovaries for females; testes, prostate and seminal vesicles for males). Each tissue was individually weighed and stored at -20°C until analysis."

2. Analysis and TLC Comparison of Pooled Feces:

"The homogenized feces from the first 0-48 hours and 48-168 hour composite were separately pooled for male and female rats."

There was fractionation analysis of ^{14}C-residues. However, the only compounds analyzed for were the parent FMC 54800, FMC 56789 (2-Methyl-3-phenylbenzyl alcohol) and FMC 65328 (2-Methyl-3-phenylbenzoic acid). The remaining products were lumped together as "other metabolites."

From Figure 2 (p. 36) pooled (4 groups: males which had received ^{14}C-acid labeled FMC 54800; males which had received ^{14}C-alcohol labeled FMC 54800; and the two corresponding female counterpart groups) 0-48 hr feces extracts were run on thin layer chromatography and the results were compared by an autoradiogram.

3. There is a signed Good Laboratory Practices Statement on p. 3 of the report, and a signed "QA Statement" on p. 4.

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C. RESULTS:

1. Dose - Excreted Radioactivity:

From table 6 (p. 24):

Label excreted in urine:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. Alcohol-labeled Females	Alcohol-labeled Males	Acid-labeled Females	Acid-labeled Males
0-8	0.65 ± 0.36	1.08 ± 0.22	1.77 ± 0.57	1.05 ± 0.22
8-12	1.09 ± 0.57	0.72 ± 0.39	3.42 ± 2.29	2.67 ± 0.85
12-24	2.69 ± 1.02	1.82 ± 0.51	2.66 ± 0.65	2.93 ± 0.59
24-48	2.45 ± 0.71	1.98 ± 0.95	1.30 ± 1.15	1.68 ± 0.72
48-72	0.57 ± 0.17	0.56 ± 0.27	0.40 ± 0.29	0.71 ± 0.30
72-96	0.31 ± 0.18	0.24 ± 0.09	0.14 ± 0.08	0.26 ± 0.06
96-120	0.21 ± 0.16	0.15 ± 0.08	0.08 ± 0.03	0.15 ± 0.05
120-144	0.07 ± 0.02	0.10 ± 0.05	0.07 ± 0.03	0.35 ± 0.42
144-168*	0.29 ± 0.12	0.84 ± 1.01	0.13 ± 0.11	0.20 ± 0.12
Cumulative	8.31 ± 2.19	7.47 ± 1.21	9.98 ± 2.79	10.00 ± 2.86

*Includes final cage rinse

Label excreted in feces:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. Alcohol-labeled Females	Alcohol-labeled Males	Acid-labeled Females	Acid-labeled Males
0-8	<0.01 ± 0.01	0.37 ± 0.64	0.01 ± 0.01	0.00 ± 0.00
8-12	9.42 ± 2.69	36.30 ± 15.02	37.29 ± 24.16	38.85 ± 4.91
12-24	42.75 ± 8.54	29.41 ± 7.55	¶29.07 ± 17.83	29.54 ± 4.11
24-48	24.01 ± 8.06	13.37 ± 8.99	6.54 ± 7.27	5.53 ± 2.36
48-72	3.33 ± 0.70	1.91 ± 1.02	0.75 ± 0.67	0.78 ± 0.48
72-96	1.62 ± 1.35	0.81 ± 0.31	0.37 ± 0.31	0.70 ± 0.15
96-120	1.06 ± 0.93	0.46 ± 0.16	0.19 ± 0.10	0.22 ± 0.07
120-144	0.77 ± 0.80	0.31 ± 0.09	0.14 ± 0.06	0.18 ± 0.03
144-168	0.58 ± 0.6	0.24 ± 0.06	2.15 ± 3.51	0.19 ± 0.03
Cumulative	83.56 ± 8.23	83.17 ± 2.66	76.49 ± 3.15	76.01 ± 3.56

¶calculated assuming value for female 5 is 29.54, instead of reported 3.21.

Cumulative label excreted in combined urine + feces:

Time Interval (hrs)	Average radioactivity (as a % of the total dose) ± S.D. Alcohol-labeled Females	Alcohol-labeled Males	Acid-labeled Females	Acid-labeled Males
0-168	91.87 ± 6.13	90.65 ± 1.46	86.47 ± 1.71	86.01 ± 1.50

2. Tissue Residues:

Mean residues (ppm) in tissues at sacrifice:

From tables 9, 10, 11 and 12 (p. 27-30):

	Alcohol-labeled		Acid-labeled	
Tissue	Females	Males	Females	Males
Brain	0.011	0.013	0.008	0.007
Bone	0.098	0.033	0.041	0.012
Fat	1.650	0.776	0.607	0.780
Gonads	0.499	0.008	0.077	0.007
Heart	0.027	0.025	0.016	0.011
Kidney	0.051	0.027	0.020	0.019
Liver	0.117	0.066	0.049	0.085
Lung	0.019*	0.051*	0.029	0.026
Muscle	0.041	0.021	0.011	0.008
Skin	0.398	0.173	0.110	0.085
Spleen	0.039	0.019	0.015	0.016
Blood	0.036	0.030	0.012	0.010

*Calculations based on data from only 2 rats at this dose level; values obtained from the 3rd rat were aberrant (extremely high); thus, not used.

3. Metabolites Extracted from Feces:

Most (about 65-70% of the original administered dose) of the radioactivity in the feces was in the fractions eliminated in the period from 0-48 hours after dosage, with a considerably smaller quantity (2-6%) present in the 48-168 hour fraction. In males receiving both labels, as well as the females dosed with the acid-^{14}C labeled FMC 54800, most of the material eliminated in the 0-48 hour fraction was unmodified FMC 54800 54800; most of the material in the 48-168 hour fraction was "other metabolites," with the unmodified FMC 54800 representing only a small fraction. In the females receiving alcohol-^{14}C labeled FMC 54800, most of the material was excreted was "other metabolites." From table 16, p. 34:

Feces extracts (0-168 hrs after dosage):

	% of initial dose	
Alcohol Labeled	Females	Males
FMC 54800	27.5	46.2
Biphenyl alcohol	1.6	1.4
Biphenyl acid	1.3	1.5
Other Metabolites	40.3	23.7
Acid Label		
FMC 54800	46.7	37.3
Other Metabolites	21.6	26.9

4. TLC Autoradiography:

Both the acid-^{14}C and alcohol-^{14}C labeled materials yielded (in addition to FMC 54800) autoradiographs showing at least 4 metabolites or breakdown products. Refer to the appended copy of Figure 2.

D. DISCUSSION

The registrant's primary argument is that there is very little breakage of the ester linkage in the parent compound, and that most of the metabolites retain this ester linkage.

This appears to be true for the material eliminated via the feces, particularly that from the period of 0-48 hours after dosage, when most of the administered radioactivity is identifiable as coming from parent compound. However, the material subsequently eliminated, although a relatively small proportion of the administered dose, appears to have undergone considerably more modification. Since a greater proportion of the radioactivity eliminated via the feces in the period of 48-168 hours is in the form of 2-Methyl-3-phenylbenzyl alcohol and 2-Methyl-3-phenylbenzoic acid than the parent compound, this is evidence that extensive breakage of the ester linkage does occur, either in the material retained within the intestines for more than 48 hours, or in the material absorbed and subsequently eliminated via the feces.

The study is classified as supplementary. While it does provide some insight into the incomplete absorption of FMC 54800 from the intestine, and the lack of modification of most of this unabsorbed material, particularly that eliminated via the feces during the period of 0-48 hours, the metabolism of the absorbed FMC 54800 (radioactivity primarily excreted via the urine, despite differences in labeling) is less clear. It is noted that most of the metabolites of FMC 54800 are not identified in this study.

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