2-20-87

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

005731

FEB 20 1987
FEB 20 [illegible]

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

Subject: F petition for bifenthrin on cottonseed, meat/milk.

To: Ms. Chris Dively, PM-15
Registration Division, TS-767C

From: Marcia van Gemert, Ph.D. [signature] 2/17/87
Head, Section III
Toxicology Branch, HED

Thru: Theodore M. Farber, Ph.D. Theodore M. Farber 2/19/87
Chief, Toxicology Branch, HED

Chemical FMC-54800, Bifenthrin, Talstar

Proj No 2350

EPA ID NO. 6F 3453

Caswell No: 463F

Action Requested:

Please review data for adequacy to fulfill data requirements.

Comments:

FMC has submitted an F petition to establish tolerances for cottonseed, milk and meat (fat and meat byproducts) of cattle, goats hogs, horses and sheep.

The submitted data indicate that FMC-54800 and/or metabolites have a significant potential for bioaccumulation in fat, skin and other fat-containing organs. The half-life of elimination from these organs is extremely slow (around 50 days) and establishing an acceptable tolerance would be difficult in view of the significant bioaccumulation problem. In addition, 6(a)(2) data have been submitted by FMC indicating that FMC-54800 has oncogenic potential. Until these issues can be presented before the Peer Review Committee, the Toxicology Branch cannot recommend approval of this petition.

The eight studies submitted along with this petition are briefly reviewed below.

PC 128825

005731

1. The kinetics of FMC 54800 in the blood of rats following a single oral dose. Study # p99025. Feb. 3 1986.

Plasma radioactivity in the low dose (4 mg/kg) animals after dosing slowly rises, indicating a slow rate of absorption from the GI tract. The half-life of absorption is calculated to be about 1 1/2 hours, with a lag-time of 1/2 hours following first order kinetics. Radioactivity peaks in plasma for low dose animals in 4 hours. The elimination of ^{14}C-FMC 54800 from the plasma is equally slow, with significant radioactivity still remaining in blood at 72 hours. High dose (35 mg/kg) plasma radioactivity appears to follow a similar course to the low dose. However, I did not calculate the half-life of absorption since the dose surpassed first order kinetics. The peak radioactivity for the high dose group appeared to be somewhat delayed, peaking at about 6 hours. Significant radioactivity still remained after 72 hours in high dose animals.

Core Classification: Minimum

2. Analysis of FMC 54800 residues in plasma from rats dosed orally with ^{14}C FMC 54800/ Study No. G-182, 7/22/86.

The major metabolic route in plasma of FMC 54800 appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Protein binding of radioactive components or metabolites appears to increase with time.

Core Classification: acceptable

3. Bioaccumulation of ^{14}C FMC 54800 in the rat. Study No: G-182 Feb. 21, 1986.

60 animals were orally dosed with 0.5 mg/kg/day for up to 70 days. 3 rats/time period were sacrificed at numerous days during dosing and kidney, liver, fat, ovaries, sciatic nerve, skin and blood were removed and analyzed for radioactive content. Half-lives of radioactive components for each tissue were determined. Fat and skin half lives were longest with half-lives of 51 and 50 days respectively. The half-lives of ovaries, liver, kidneys and sciatic nerve were 37.4, 19.0, 28.5, and 42 days respectively. Radioactive components in fat were measured at numerous time intervals before and after daily dosing. The major component in fat is parent compound FMC 54800 with a half-life of 47.5 days. Other unidentified components included a somewhat polar (R_f 0.65) compound and 2 other relatively minor components. From the data presented it is clear that bifenthrin significantly bioaccumulates.

Core Classification: acceptable

005731

4. A dermal absorption study in rats with ^{14}C-FMC 54800. . .dy # 182RATMO6 8/15/86.

^{14}C FMC 54800 appears to be rapidly absorbed through the skin during the first half hour after application, with the amounts of absorption remaining fairly constant with time. There was a direct correlation between the concentration applied and the amount absorbed. Approximately half the amount applied was absorbed. Overall recovery for the three dose groups was 109%, 105%, and 105% for groups 1, 2, and 3 respectively.

Core Classification: acceptable

5. Excretion/tissue distribution of alcohol-^{14}C FMC 54800 in rat. Study # 1828305. 12/6/83.

Within 7 days nearly all FMC 54800 and/or metabolites are excreted in either urine or feces. The majority of radioactivity is excreted in the feces within 48 hours. As seen in previous studies, the major tissues to retain FMC 54800 or metabolites beyond 7 days are fat, skin in both males and females and gonads in females.

Core Classification: Supplementary, the number of animals/group were 3, not 5/sex/group are recommended in the Section F guidelines and no quality assurance statement accompanied this report.

6. Absorption, distribution and excretion of FMC 54800 in the rat. Study No. 182RATMO2, Feb. 14, 1986.

Very little of the administered radioactivity is expired as $^{14}CO_2$ (0.028% for males and 0.053% for females). The majority of the administered radioactivity is found (about 70%) in feces with about 20% found in urine. Tissue accumulation data were of very little value since summary tables were not furnished to compare males with females and single doses with multiple dosing animals. Additionally, much of the data were not presented on the tissue residue tables calling these missing data "N/A" or not applicable, when in fact these data, if presented, would have added tremendously to the quality and usefulness of this study. A further complication in this study was that males were administered a radioactive dose with the label in the acid position, while females were administered a radioactive dose with the label in the alcohol position. This could make comparisons between males and females difficult. Finally, chemical purity specifications for the unlabeled compound were supposed to be presented in Appendix I according to the study text, but are missing.

Core classification: supplementary

7. Metabolism of FMC 54800 in rats- Identification of products in excreta. Study #, 182PATMO2, 7/9/86.

The problems inherent in the previous study (# 5 above) are also the same problems inherent in this study, since they employ the same

protocol and urine and fecal samples for analysis. One of the outstanding complications in this study as pointed out in the last study was that males were administered a radioactive dose with the label in the acid position, while the females were administered a radioactive dose with the label in the alcohol position. This could make comparisons between males and females difficult. The majority of radioactivity excreted in the feces was the parent compound and its intact hydroxylated metabolites. Much of the radioactivity excreted in urine was hydrolytic and hydrolytic oxidative degradation products of the parent compound.

Core Classification: supplementary

c. 52-week chronic oral toxicity study in dogs. Study #. A83-821, June 17, 1985.

Tremors were noted in groups 4 (3 mg/kg/day) and 5 (5 mg/kg/day). Sodium levels were increased in group 4 and 5 at 52 weeks and chloride levels were increased at 52 weeks in group 5 males. Creatinine phosphokinase levels appeared to drop in females in groups 3, 4, and 5 at 52 weeks. There was some indication that this was occurring at week 26, however one animal in the control group had a value that was extremely high. There was a significant increase in platelets at 52 weeks in group 5 males. No other treatment-related effects were noted.

NOEL = 0.75 mg/kg
LEL = 1.5 mg/kg based on the increased C.P. at 52 weeks.

Core classification = minimum

Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 2/5/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore H. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

005731

Study Type: Metabolism study in rats Tox. Chem No. 463F

Accession No.: 264659

Test Material: FMC 54800

Synonyms: Bifenthrin, Talstar

Study Number: p00925

Sponsor: FMC Corp.

Testing Facility: Biological Testing Center 2525 McGaw Av
Irvine Ca. 92710

Title of Report: The kinetics of FMC 54800 in the blo.. ..ts following a single oral dose

Author: S. Salim

Report Issued: Feb. 3, 1986

Conclusions: Plasma radioactivity in the low dose (4 mg/kg) animals after dosing slowly rises, indicating a slow rate of absorption from the GI tract. The half-life of absorption is calculated to be about 1 1/2 hours, with a lag-time of 1/2 hour following first order kinetics. Radioactivity peaks in plasma for low dose animals in 4 hours. The elimination of ^{14}C-FMC-54800 from the plasma is equally slow, with significant radioactivity still remaining in blood at 72 hours. High dose (35 mg/kg) plasma radioactivity appears to follow a similar course to the low dose. However, I did not calculate the half-life of absorption since the dose surpassed first order kinetics. The peak radioactivity for the high dose group appeared to be somewhat delayed, peaking at about 6 hours. Significant radioactivity still remains after 72 hours in high dose animals.

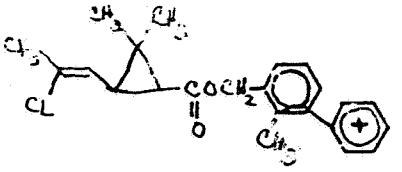
Core Classification: Minimum

Quality Assurance Statement accompanied the report and was signed.

005734

A. Materials:

1. Test Compound: Unlabeled FMC 54800, Purity 96.2%, C^{14} labelled FMC54800 was labelled in alcohol position.
Description: Label[illegible] FMC 54800. Structure below:



Batch: Radiolabeled compounds were synthesized by Pathfinder Labs Inc. Lot #830222 with specitic activity of 33.52mCi/mMole
Purity: 98% after repurification at the Biological Test Center

Dosing solution: Radiolabel vehicle was Mazola corn oil, doses were 4 mg/kg or 35 mg/kg

2. Test Animals:

Species: rats

Strain: Sprague Dawley

Age: adult male

Weight: Pilot study: low dose rat: 202.2 gm (given dose of (3.9 mg/kg and 18.3 uCi)
High dose rat: 202.0 gms (given dose of (33.5 mg/kg and 13.6 uCi)
Main study: single low dose rats: 143.2 ± 7.3 gms (given dose (of 5.4 mg/kg or 12.6 ± 0.6 uCi)
single high dose rats: 184.6 ± 14.6 gms (given dose (ot 7.0 ± 0.4 mg/kg and 17.2 ± 1.3 uCi
Serial sacrifice animal body weights are on tables I and II below.
Source: not reported.

Study Design:

Objectives: Objective was to determine the rate of absorption of ^{14}C-FMC 54800 from the GI tract and rate of elimination from blood of rats after an oral dose.

Animal assignments and study procedures:

For the pilot study 2 males were orally dosed by gavage with a single dose of 4 mg/kg or 35 mg/kg labeled FMC 54800 Animals were bled by tail vein at 1, 2, 3, 4, 8, 12, 16, 24, 48, and 72 hours for radioactivity. In the main study low dose animals, 2 test groups (A + B) were used for the low dose group. Group A contained 5 rats Group B contained 20 rats subdivided into 4 subs of 5 rats each. Rats were fasted 18 hours predosing. Dose was by gavage. Amount of compound delivered to each animal was determined

by weighing the syringe before and after dosing.

Group A post dosing were transferred to individual restrainers and blood samples were taken at 1, 2, 3, 4, 6, 8, 10, 12, 48 and 72 hours. After 4 hours the animals were returned to their cages and given food and water ad libitum. Group B animals were sacrificed 5/time period by heart puncture at 2, 4, 10 and 24 hours post dosing.

The high dose group: 2 test groups were employed similar to the procedure for the low dose. There are 5 animals in group C and group D has 20 animals. The only difference is that group B animals will be sacrificed at 3, 6, 10, and 24 hours.

Sample collection, preparation and calculations: are on appended page 1 from the study text.

Results:

Pilot study: peak blood levels of radioactivity for both animals were at 8 hours post dosing. These results can be seen on appended page 2. There was still significant amounts of radioactivity in the blood by 72 hours post dosing.

Main study: Single dose Groups A + C : Peak blood radioactivity occurred around 4 hours for the low dose and 6 hours for the high dose group with significant amounts of radioactivity remaining in the plasma of both groups after 72 hours. Data can be found on appended pages 3 and 4 for reference.

Serial Sacrifice (Groups B and D): Low dose animals: data for the 2, 4, 10 and 24 hour sacrifices are tabulated below in table I.

TABLE I

Low dose plasma levels of radioactivity at sacrifice

Time	Body wt.	Dose mg/kg	uCi	Plasma DPM	total DPM	uCi/ml of plasma
2 hr						
mean±	184.7 ±	4.2 ±	7.1 ±	5964 ±	15,761,439 ±	0.262 ±
S.D.	8.2	0.1	0.3	2080	692,595	0.092
4 hr						
mean±	191.3 ±	4.2 ±	7.3 ±	42861 ±	16,327,353 ±	1.885 ±
S.D.	9.5	0.1	0.4	24,746	737,957	1.089
10 hr						
mean±	188.0 ±	4.2 ±	7.2 ±	14,110 ±	15,948,659 ±	0.499 ±
S.D.	12.4	0.1	0.4	1,891	1,000,008	0.083
24 hr						
mean±	186.2 ±	4.1 ±	7.0 ±	3,630 ±	15,639,610 ±	0.163 ±
S.D.	7.3	0.1	0.2	361	483,141	0.016

Highest radioactive samples taken appear to be at 4 hours, with significant radioactivity still remaining after 24 hours.

High dose animals:
These data for 3, 6, 10 and 24 hour sacrifice are tabulated in

table II below.

TABLE II

005731

High Dose plasma levels of radioactivity at sacrifice

time	Body wt.	Dose mg/kg	uCi	Plasma DPM	Total DPM	ug/ml of plasma
3 hr						
mean ±	178.5 ±	36.5 ±	11.1 ±	14,046 ±	24,664,589 ±	3.709 ±
S.D. ±	10.1	0.9	0.5	6,856	1,114,329	1.810
6 hr						
mean ±	180.5 ±	36.5 ±	11.2 ±	33,260 ±	24,892,532 ±	8.783 ±
S.D. ±	10.0	0.6	0.5	10,953	1,191,980	2.892
10hr						
mean ±	180.0 ±	37.1 ±	11.4 ±	20,528 ±	25,260,748 ±	5.423 ±
S.D. ±	10.9	0.5	0.6	4,780	1,379,180	1.262
24hr						
mean ±	183.9 ±	36.3 ±	10.1 ±	6276 ±	22,496,504 ±	1.994 ±
S.D. ±	41.3	0.6	1.7	1,344	3,723,032	0.372

Highest radioactivity appeared in the 6 hour sacrifice blood samples. Again, there was significant radioactivity remaining after 24 hours.

Discussion:
Plasma radioactivity in the low dose animals after dosing slowly rises, indicating a slow rate of absorption from the GI tract and the radioactivity appears to peak at about 4 hours. The elimination from plasma is equally slow, with significant radioactivity still remaining in the blood at 72 hours.

High dose plasma radioactivity appears to follow a similar course to the low dose. However, the peak appears to be somewhat delayed to 6 hours.

Using the pharmacokinetic "method of residuals" and the low dose single dose data it is determined that absorption is a first order process. The lag time for absorption is approximately one/half hour, and the absorption half-life is approximately 1 1/2 hours. A semi-log graph of these data are on appended page 5. The data for calculating this are tabulated in table III.

005731

Table III

Low dose plasma concentration-time data following single oral administration of 4 mg/kg FMC 54800

Low dose: time	C mg/L	$\overleftarrow{C}$ extrapolated plasma ccns (mg/l)	Difference in $\overleftarrow{C}$ - C ccns (mg/L)
1	0.15	0.90	0.75
2	0.32	0.81	0.49
3	0.43	0.73	0.3
4	0.66	0.66	0.0
5	0.61	0.61	
8	0.45	0.45	
10	0.36	0.36	
12	0.30	0.30	
24	0.11	0.11	

The high dose data are plotted on appended page 6. It is clear from the plotted data that the high dose of 35 mg/kg has exceeded the first order kinetics for absorption. A further calculation of the kinetics of absorption would not be in order.

Bifenthrin

RIN 4688-96

Page_____ is not included in this copy.

Pages 10 through 15 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marcia van Gemert, Ph.D. *[signature]* 2/6/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

005731

DATA EVALUATION REPORT

Study Type: Plasma residue analysis in rats of ^{14}C-FMC-54800 — Tox. Chem No. 463F

Accession No.: 264639

Test Material: FMC-54800

Synonyms: Bifenthrin, Talstar

Study Number: G-182

Sponsor: FMC Corporatio

Testing Facility: Biological Test Center, Irvine Ca.

Title of Report: Analysis of FMC 54800 residues in plasma from rats dosed orally with ^{14}C- 54800

Author: R.H. Tullman

Report Issued: 7/22/86

Conclusions: The major metabolic route in plasma of FMC-54800 appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Protein binding of radioactive components or metabolites appears to increase with time.

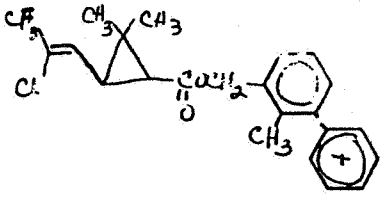
Core Classification: acceptable

Quality Assurance Statement accompanied the report and was signed.

005731

A. Materials:

1. Test Compound: Unlabeled FMC 54800, purity 96.2%. C^{14} labelled FMC 54800 was labeled in the alcohol position.
Description: Labeled FMC 54800 structure is given below.



Batch: Radiolabeled compounds were synthesized by Pathfinder Labs Inc. Lot # 830222 with specific activity of 33.52 mCi/mMole
Purity: 98% after repurification at the Biological Test Center

Dosing solution: Radiolabel vehicle was Mazola corn oil. doses were 4 mg/kg or 35 mg/kg and given by gavage

2. Test Animals:

Species: rats

Strain: Sprague Dawley

Age: not given, males

Weight: not given

Source: not given

Study Design:

Objectives: Determine the plasma metabolites of FMC 54800 at various time periods after dosing.
Animal assignments and study procedures:

40 rats were subdivided into 8 groups of 5 rats each. There were 4 groups/dose level. Low dose (4 mg/kg) group had animals (5/time period) sacrificed at the 2, 4, 10, and 24 hour time periods while the high dose (35 mg/kg) group had 5 animals/time period sacrificed at 3, 6, 10 and 24 hours post dosing.

Fortification extraction procedures, extraction of plasma procedures from the low and high dose groups, counting procedures and calculations are supplied on appended pages 1, 2, 3 and 4, from the study text for details. The plasma extraction scheme appears on appended page 5.

Results:

1. Fortified Plasma with ^{14}C-FMC 54800

As can be seen on appended page 6, plasma fortified with 23,730 DPM of ^{14}C-FMC 54800 contained 93.2% of the recovered radioactivity.

005731

71% of the added radioactivity) when deproteinized with aqueous acetone. Another 6% was recovered as protein bound and 0.8% was recovered in the culture tube rinses. The percent recovery from the fortified check was 76.1%.

2. Bifenthrin (BP) acid fortification:
The recovery from aqueous acetone of BP-acid was 90.7% of the recovered radioactivity (88.9% of the added radioactivity.) 8.6% was protein bound and tube rinsing yielded an additional 0.7%. Recovery from the fortified check was 98.0%

3. Plasma extraction- low dose
Data in tabular form from the study text are on appended page 7. Plasma aliquots taken at 2, 4, and 10 hours contained 12,480, 43,660, and 16,260 DPM respectively. The extraction counts are tabulated on appended page 7. The aqueous acetone extraction fraction contained 9.0, 88.3, and 64.6% of the total radioactivity for the 2, 4, and 10 hour samples respectively. The percent of total protein bound was 9.0, 8.5, and 34.2% respectively. Rinses of the glassware yielded 0.0, 2.82, and 1.2% respectively. Recoveries based on the direct counts of plasma before extraction were 88.1, 98.8, and 99.5% of the total radioactivity for 2, 4, and 10 hour samples respectively according to the study text.

4. Plasma extraction - high dose
Data in tabular form from the study text are on appended page 8. Plasma aliquots taken at 3, 6, 10 and 24 hours contained 18,280, 23,400, 31,920, and 16,980 DPM of radioactivity respectively. As can be seen on appended page 8, aqueous acetone extractions contained 89, 81.6, 60.3 and 53% respectively. Protein bound fractions contained 9.7, 15.0, 38.1 and 43.7% of the radioactivity in 3, 6, 10 and 24 hour samples respectively. Rinses only accounted for 1.3, 3.4, 1.6, and 3.3% of the total radioactivity respectively. Total overall percent recoveries were 89.8, 85.3, 110.2, and 89.7% for 3, 6, 11, and 24 hours respectively.

5. HPLC results- low dose
Data from the study text are tabulated on appended page 9. HPLC was performed on aqueous acetone extracts, except a sample was injected directly for the 4 hour low dose and the 6 and 10 hour high dose samples.
The major peaks on the HPLC profile correspond to the parent compound FMC 54800, the hydrolysis product, BP-alcohol and the further oxidized product, BP acid for both low dose and high dose HPLC results.

In the low dose group HPLC profile parent compound remained between 35-40% of the total metabolites for the three time periods. BP-alcohol was roughly similar to parent compound in amounts for the 2 and 4 hour time period, but dropped slightly to 27.9% by 10 hours. BP acid remained relatively the same over the three time periods, with 15.7%, 19% and 17.2% of the total metabolites for the 2, 4, and 10 hour time periods. There was a hydroxylated metabolite, 4'-hydroxy FMC 54800 which was not detected at 2 hours but was 0.5% at 4 hours and up to 5.1% by 10 hours. The study

text stated that there were several unidentified products with retention times between 1 and 3 minutes and 5-7 minutes which appeared in the aqueous acetone extracts. However, the amounts recovered were not large (1.7-6.7%), except for the direct whole plasma which had 8.3% polar unknowns.
Total DPMs recovered/DPM injected was 101.2%, 100.1% and 104.7% for the 2, 6, and 10 hour aqueous extract samples and 90.6% for the direct plasma injection sample.

b. HPLC results- high dose
Data from the study text are on appended page 10.
The distribution of high dose metabolites is somewhat different from the low dose distribution. For example, the parent compound in the aqueous extracts drops from 22.2% at 3 hours and 24.6% at 6 hours to 15.2% at 10 hours and 12.2% at 24 hours. Direct plasma injection samples showed similar results with 24.6% at 6 hours and 8.6% at 10 hours for the parent compound. BP acid, which remained a fairly constant percentage of the total throughout the low dose time periods, appears to rise in the high dose groups with time, from 29.4% at 3 hours, 8.9% at 6 hours, 39.7% at 10 hours to 47.6% at 24 hours for aqueous acetone extracts. Direct injection samples followed a similar course, with 34% at 6 hours and 45.4% at 10 hours. BP alcohol, on the other hand, appears to drop in a similar fashion to the low dose group over similar time periods measured. The aqueous acetone extracts at 3 hours are 42.9%, 6 hours are 40.0%, 10 hours is 25.1% and 24 hours is 14.7%. Direct injection samples follow a more precipitous course with 30.1% seen at 6 hours and 9.4% recovered by 10 hours. The hydroxylated metabolite 4'-hydroxy FMC 54800 was only a very minor component of the metabolic profile of the high dose group. Unidentified polar metabolites appeared to be more prominent with time than in the low dose group. Aqueous acetone extracts yielded 2.5% at 3 hours, 0.6% at 6 hours 12.7% at 10 hours, and 25.6% at 24 hours. Direct injection samples yielded 1.5% at 6 hours and 23.7% at 10 hours. Other unknown metabolites occurred between 3.1 and 7.2% of the total for aqueous acetone extracts and 7-11% for direct injection samples. Total DPMs recovered/DPMs injected for aqueous extracts were 101.2%, 99.9%, 99.9% and 102.0% for 3, 6, 10, and 24 hours respectively, and 93.9%, and 81.6% for the 6 and 10 hour direct injection samples.

Discussion:

The structures for the standards used and major metabolites found are on appended page 11. The major metabolic route of plasma of FMC 54800 appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Protein binding of the radioactive components or metabolites appears to increase with time.

Core classification = acceptable

B. fenthrin

RiN 4688-96

Page_____ is not included in this copy.

Pages 20 through 30 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__✓__ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marcia van Gemert, Ph.D. M. van Gemert 2/9/87
Head Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

095731

095731

DATA EVALUATION REPORT

Study Type: Bioaccumulation in rat Tox. Chem No. 463F

Accession No.: 264639

Test Material: FMC 54800

Synonyms: Bifenthrin, Talstar

Study Number: G-182

Sponsor: FMC Corp.

Testing Facility: Huntingdon Research Center Ltd. Huntingdon, Cambridgeshire, PE-18-6ES England

Title of Report: Bioaccumulation of ^{14}C FMC 54800 in the rat

Author: D.R. Hawkins, L.F. Elson, R. Jackson

Report Issued: Feb. 21, 1986

Conclusions:
60 animals were orally dosed with 0.5 mg/kg/day for up to 70 days. 3 rats/time period were sacrificed at numerous days during dosing and kidney, liver, fat, ovaries, sciatic nerve, skin and blood were removed and analyzed for radioactive content. Half-lives of radioactive components for each tissue were determined. Fat and skin half lives were the longest with half-lives of 51 and 50 days respectively. The half-lives for ovaries, liver, kidneys and sciatic nerve were 37.4, 19.0, 28.5, and 42 days respectively. Radioactive components were measured in fat at numerous time intervals before and after daily dosing. The major component in fat is parent compound FMC 54800 with a half-life of 47.5 days. Other unidentified components included a somewhat polar (R_f 0.65) compound and 2 other relatively minor components. From the data presented it is clear that bifenthrin significantly bioaccumulates.

Core Classification: Acceptable

Quality Assurance Statement accompanied the report and was signed.

31

005731

A. Materials:

1. Test Compound: Non-radioactive FMC 54800 (Batch E2823-2) chemical purity of 96.2%
Labeled ^{14}C FMC 54800 had a specific activity of 33.52mCi/mMole with 90% radiochemical purity. Repurified by Huntingdon in two batched to give > 99% purity.

2. Test Animals:

Species: rat, female

Strain: CD (Sprague Dawley)

Age: 7 weeks

Weight: 180 gms

Source: Charles River, Margate Kent

Study Design:

Animal assignments and study procedures:

60 animals were orally dosed for up to 70 days. Rats were weighed weekly and doses adjusted to body weight. Nominal doses were 0.5 mg/kg body weight of FMC 54800. 20 animals received no treatment and were used as control animals. Groups of 4 animals (3 test and 1 control) were sacrificed at 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 73, 78, 85, 92, 99, 113, 127, and 155 days after commencement of dosing. Kidneys, ovaries, fat, skin, and blood were removed from animals sacrificed at 56, 63, 70, 73, 99, 113, 127 and 155 days. Blood samples were both counted as whole blood for radioactivity and centrifuged for cell components. All blood samples were stored at 4°C and tissue and plasma samples were stored at -20°C until analysis. Measurement of radioactivity analysis of ^{14}C 54800 in fat, thin layer chromatography methods and calculations of half-lives are all on appended pages 1 and 2.

Results:

Tabulated results for all mean radioactive tissue levels at the various sacrifice times are on appended page 3.

Plasma and whole blood:
The mean plasma concentration of radioactivity rose slowly from 0.01 ug/ml after day 1 to 0.06 ug/ml after day 70. At withdrawal the concentration declined to 0.02 ug/ml at 73 days and 0.01 ug/ml at 78 days. thereafter the mean plasma concentrations were below the limit of detection. Whole blood concentrations were similar to plasma, with a peak radioactivity concentration emerging a little sooner than plasma at 49 days. After dosing whole blood levels of radioactivity became undetectable by 113 days.

Liver:
Concentrations of radioactivity in liver rose rapidly with 0.07 ug/g by day 1, rising to a peak of 0.4 ug/g by day 70. During the withdrawal phase radioactivity slowly dropped from 0.16 ug/g at day 73 to 0.01 ug/g by day 155 with a half-life of approximately 19 days. Half-life data are tabulated on appended page 4.

Kidneys:
Concentrations of radioactivity in the kidney were similar to those in the liver with 0.04 ug/g by day 1, rising to a peak of 0.32 ug/g by day 63. During the withdrawal phase mean radioactivity concentrations dropped slowly from 0.16 ug/g at day 73 to 0.03 ug/g at day 155, with a half-life of approximately 28 days. (see appended page 4)

Fat:
Concentrations of radioactivity in fat rose extremely rapidly with 0.33 ug/g recovered by day 1. The peak concentration was at day 70 with 9.62 ug/g tissue. During the withdrawal phase, mean concentrations declined very slowly with time from 6.47 ug/g at day 73 to 2.74 ug/g at day 155. The approximate half-life is 51 days. (see appended page 4)

Skin:
Skin showed a similar pattern to fat, perhaps because there is so much fat in association with skin. By day 1 skin concentrations were 0.08 ug/g tissue and rose to a peak of 2.06 ug/g by day 73 (4 days after the last dose). Half-life in skin was 50 days, similar to that in fat. Levels of radioactivity started declining in fat after withdrawal of compound by day 78 and 0.3 ug/g still remained in skin by day 155.

Ovaries:
Ovaries showed a similar pattern to skin. This can be graphically illustrated on appended page 5. Concentrations of radioactivity were 0.11 ug/g by day 1 and peaked by day 70 with 1.69 ug/g after treatment. The levels of radioactivity slowly declined to 0.30 ug/g by day 155. The half life was calculated to be approximately 40 days.

Sciatic nerve:
Concentrations of radioactivity in sciatic nerve were measured at a few of the time intervals. During days 56-70 the mean concentrations were 1.91-3.25 ug/g. These levels were higher than in corresponding fat. After treatment withdrawal, levels dropped to 0.14 ug/g by day 155 with a half-life of 42 days.

Radioactive Components in fat:
Representative autoradiographs and thin layer radiochromatograms are illustrated on appended pages 6 and 7.
Appended page 8 details the radioactive components by their R_f values and expressed as a percent of the total radioactivity. The major component in fat at all sacrifice times according to the study text was unmetabolized FMC 54800 (R_f 0.71) with a mean proportion of between 72% and 85% of the total radioactivity between days 57 and 155.

Another component, somewhat polar (R_f 0.65), accounted for 9.3-11.6% of the radioactivity between days 1-78. After dosing this component increased to 13.3-13.8% radioactivity at 92-127 days and was 19.5% at 155 days.
Except for days 1-3 the mean proportions of the two other components accounted for a relatively small percentage of total radioactivity up to day 70, and decreased thereafter. The calculated half-life for the parent compound FMC 54800 in fat was approximately 47.5 days.

Discussion:

From the data presented concerning the tissue half-lives it is clear that FMC 54800 bioaccumulates. Of the half-lives determined for the selected tissues, fat and skin half-lives were the longest with half-lives of 51 and 50 days respectively. The half-lives for ovaries, liver, kidneys and sciatic nerve were 37.4, 19.0, 28.5, and 42 days respectively.

Radioactive components were measured in fat at numerous time intervals before and after daily dosing. The major component in fat is parent compound FMC 54800 with a half-life of 47.5 days. Three other unidentified components comprised the balance of the radioactivity and were relatively minor in comparison to the parent compound.

Bifenthrin

Rin 4688-96

Page_____ is not included in this copy.

Pages 35 through 42 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marsha van Gemert, Ph.D. 2/11/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

095731

Study Type: Dermal Absorption in Rats Tox. Chem No. 463F

Accession No.: 264639

Test Material: ^{14}C-FMC 54800

Synonyms: Bifenthrin, Talstar

Study Number: 182RATM06

Sponsor: FMC Corp.

Testing Facility: WIL Laboratories Inc., Ashland, Ohio

Title of Report: A dermal absorption study in rats with ^{14}C-FMC 54800

Author: E.M. Craine

Report Issued: 8/15/86

Conclusions: ^{14}C-FMC 54800 appears to be rapidly absorbed through the skin during the first half hour after application, with the amounts of absorption remaining fairly constant with time. There was a direct correlation between the concentration applied and the amount absorbed. Approximately half the amount applied was absorbed. Overall recovery for the three dose groups was 109% (group 1), 105% (group 2) and 105% (group 3).

Core Classification: Acceptable

Quality Assurance Statement accompanied the report and was signed and dated 2/18/86.

A. Materials:

1. Test Compound: Labeled FMC 54800 was uniformly labeled in the B ring of the alcohol moiety. Specific activity was 4.23 mCi/mMole or 10 uCi/mg dissolved in 3.0 ml of acetone.

Dosing solution was an aqueous suspension of ^{14}C-labeled FMC 54800 each group received 49.2 ug, 514 ug, or 5253 ug/rat

2. Test Animals:

Species: rats, male

Strain: Crl:CD (SD) BR

Age: 51-57 days at study initiation

Weight: 240-303 gms

Source: Charles River Breeding Labs, Portage Mich.

Study Design:

Animal assignments and study procedures:
Three groups of rats (24/group) received single doses of either 49.2 ug, 514 ug, or 5253 ug/rat ^{14}C-FMC 54800. Four rats were sacrificed for each dose at either 0.5, 1, 2, 4, 10 or 24 hours after compound administraton.
Each dose was applied with a rubber ring cemented to a shaved area of skin. Following application of the dose a circle of filter paper was cemented in place on the rubber ring to cover the application zone and the rat was placed in a metabolism cage.

Disposition and analysis of ^{14}C-FMC 54800 and irritation score ranking are on appended pages 1, 2, and 3.

Results:

Elimination of ^{14}C-FMC 54800 equivalents in excreta
After dermal application of the three doses and sacrifice at various time periods, measurable amounts of test material were not found in excreta in group 1 during the first 10 hours after exposure. At 24 hours there was 0.5% of the dose administered in urine and feces. Groups 2 and 3 were similar to group 1 in that detectable amounts of ^{14}C-FMC 54800 were not detected before the 4 hour sample time, at which time 0.5% of the administered dose was present in excreta of group 2 and 0.2% in group 3.

^{14}CFMC 54800 equivalents in blood:
Tabulated data on levels of ^{14}C-FMC 54800 expressed in ug/ml are on appended page 5. Groups 1 and 2 did not have measurable amounts of ^{14}C-FMC 54800 at any time period. Group 3 however after 4 hours had 0.01 ug/ml which rose to 0.02 ug/ml after 24 hours.

^{14}C-FMC 54800 equivalents in carcass:
Carcass after skin was removed was extracted with acetone to give two fractions: and extract and a dried carcass which was processed to a homogeneous meal. Measureable amounts of ^{14}C-FMC54800 were not present in group 1 rats before 10 hours. Group 2 animals had ^{14}C-FMC-54800 present after 4 hours of exposure. Group 3 animals had test material present as early as 0.5 hours after dosing.

Absorption of ^{14}C-FMC 54800:

The study text defined the amount absorbed through the skin as the sum of ^{14}C present in excreta, the ^{14}C in the carcass and the ^{14}C which penetrated the skin and was not washed away with water. The latter value calculated to include the skin of the application site and skin adjacent to the application site. A tabular summary of the amounts absorbed into the through the skin are on appended page 6. There appears to be a fairly rapid absorption through the skin during the first half hour after dosing, and the amount did not appear to increase with time. There was also a direct correlation between the concentration applied and the amount absorbed. Approximately half the concentration applied was absorbed. These percentage data are tabulated on appended page 7.
Overall disposition of the radioactivity is on appended page 8.
Overall recovery for the three dose groups was 109% for group 1, 105% for group 2 and 105% for group 3.

Dermal Irritation:
No erythema, edema or other findings of irritation were evident at the site of application.

Discussion:
^{14}C-FMC 54800 appears to be rapidly absorbed through the skin during the first half hour after application, with the amounts of absorption remaining fairly constant with time. There was a direct correlation between the concentration applied and amount absorbed. Approximately half the amount applied was absorbed. Overall recovery for the three dose groups was 109% (group 1) 105% (group 2), and 105% (group 3).

Bifenthrin

RiN 4688-96

Page_____ is not included in this copy.

Pages 46 through 54 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__✓__ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marci[redacted]an Gemert, Ph.D. 12-6-83
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

005731

DATA EVALUATION REPORT

Study Type: Distribution and Excretion in Rat Tox. Chem No. 463F

Accession No.: 264638

Test Material: FMC 54800 A synthetic pyrethroid

Synonyms: Bifenthrin, Talstar

Study Number: 1828305

Sponsor: FMC Corp.

Testing Facility: FMC Corp.

Title of Report: Excretion/tissue distribution of alcohol-^{14}C FMC 54800 in rat

Author: S.G. El-Naggar

Report Issued: 12/6/83

Conclusions: Within 7 days nearly all FMC 54800 and/or metabolites are excreted in either urine or feces. The majority of radioactivity is excreted in the feces within 48 hours. As seen in previous studies, the major tissues to retain FMC 54800 or metabolites beyond 7 days are fat, skin in both males and females and gonads in females.

Core Classification: Supplementary, the number of animals/group were 3, not 5/sex/group as recommended in Section F guidelines and no quality Assurance Statement accompanied the report.

55

A. Materials:

1. Test Compound: ^{14}C FMC 54800, predominantly [redacted] product (98.4% labelled in alcohol [redacted]) Specific Activity = 33.52 mCi/mMole or 7.31 mCi/mMole after isotopic dilution. Source was Pathfinders Laboratory >99% radioactive purity

Description: Unlabeled FMC 54800 used for isotopic dilution

Batch: E2129:25B

Purity: 96.5% , Cis >99%

2. Test Animals:

Species: Rat

Strain: Sprague Dawley

Age: Not given

Weight: 188-252 gms

Source: Taconic Farms

Study Design:

Animal assignments and study procedures:

Three/sex were dosed with a single oral gavage dose of 7.31 mCi/mMole (5 mg/kg) FMC 54800 after an 18 hour fast. Section F guidelines recommend 5/sex/group for a study of this type. Appended page 2 tabulates actual amounts of both FMC 54800 in mg/kg and total radioactive dose in uCi per group.

Urine and Fecal Sampling:

Urine samples were collected at 0-8 hours, 8-12 hours, 12-24 hours, 24-48 hours, 48-72 hours, 72-96 hours, 96-120 hours, 120-144 hours, 144-168 hours. Fecal samples were collected for the same time periods.
Urine was freeze-trapped and fecal samples were frozen upon collection. All urine and fecal samples were stored at -20°C. Cage urine/fecal separators were rinsed daily with methanol and distilled water and the whole cage was rinsed at sacrifice with methanol and distilled water. Rinse samples were stored frozen at -20°C until analysis.

Tissues and Organs:

Seven days post dosing all rats were sacrificed. Blood was collected and liver, brain, heart, kidneys, spleen, skin, bone,

muscle, fat and gonads (uterus and ovaries for females: testes, prostate and seminal vesicles for males). Tissues and carcass were weighed and stored at -20°C until analysis.

005731

Sample preparations for radioassay extraction of ^{14}C residues from feces, fecal extraction scheme, HPLC methods, residue analysis, LSC and calculations are on appended pages 3-7.

Results:

Urine and Fecal excretion of ^{14}C:

Females excreted 83.54% ± 5.23 (mean ± S.D.) of total ^{14}C-dose in feces, (appended page 8) and 8.31% ± 2.19% in urine for a total of 91.87 ± 6.13% within seven days after dosing. These data are illustrated on appended page 9.
Males excreted 83.18 ± 2.66% of the total ^{14}C-dose in feces (appended page 8) and 7.49 ± 1.21% in urine for a total of 90.65 ± 1.46% cumulative average within 7 days. These data for males are illustrated on appended page 10.

Tissue Residues of ^{14}C

Females: Total residues for tissues are on appended page 11. Average total residues ranged from 0.011 to 0.117 ppm for tissues and blood except for fat, gonads and skin which were 1.650, 0.449 and 0.398 ppm respectively.
Males: Total residues varied from 0.08 to 0.066 ppm except for fat and skin which were 0.776 and 0.173 ppm respectively.
These data are in agreement with the previous metabolism study which showed high residues in fat and skin remaining 7 days after treatment.

Analysis of ^{14}C-residues in Feces

According to the study text, fractionation of the collective fecal samples from 0-48 and 48-168 hours showed 56.3% and 39.4% of excreted radioactively respectively for females were in the acetonitrile-A fraction, which contained the parent compound. Males showed 53.3% and 30.5% of excreted activity in the acetonitrile-A fraction. These data are on appended page 13.

HPLC analysis

The HPLC data are in tabular form on appended page 14, and showed that most of the fecal ^{14}C excreted was parent compound. Negligable amounts of excreted radioactivity, 1.4-1.6% and 1.3-1.5% was biphenyl alcohol and biphenyl ether respectively. The remainder of the radioactivity was other metabolites.

Analysis of ^{14}C residues in urine.

Male and female urine at 8-12 hours showed that 99-100% of the radioactivity was conjugated polar produces. Less than 1% total radioactivity was parent FMC 54800.

Discussion:

Within 7 days nearly all FMC 54800 and its metabolites are excreted in either the urine or feces. The majority is excreted in the feces within 48 hours. As seen in previous studies, the major tissues to retain FMC 54800 or its metabolites after 7 days are fat, skin in both males and females, and gonads in females.

Bifenthrin

RIN 4688-96

Page_____ is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

__✓__ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marcia van Gemert, Ph.D.
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

005731

Study Type: Metabolism study in rats Tox. Chem No. 463F

Accession No.: 264638

Test Material: FMC 54800

Synonyms: Bifenthrin, Talstar

Study Number: 182RATM02

Sponsor: FMC Corp

Testing Facility: Biological Test Center, Irvine Ca.

Title of Report: Absorption, Distribution and excretion of FMC 54800 in the rat.

Author: S. Selim

Report Issued: Feb. 14, 1986

Conclusions: Very little of the administered radioactive is expired as ^{14}C-CO_2 (0.028% for males and 0.053% for females). The majority of the administered radioactivity is found (about 70%) in feces with about 20% found in urine. Tissue accumulation data were of very little value since summary tables were not furnished to compare males with females and single doses with multiple dosing animals. Additionally, much of the data were not presented on the tissue residue tables, calling these missing data "N/A" or not applicable, when in fact these data, if presented, would have added tremendously to the quality and usefulness of this study. A further complication in this study was that males were administered a radioactive dose with the label in the acid position, while females were administered a radioactive dose with the label in the alcohol position. This could make comparisons between males and females difficult. Finally, chemical purity specifications for the unlabeled compound were supposed to be presented in appendix I according to the study text but are missing.

Core Classification: supplementary

Quality Assurance Statement accompanied the report and was signed.

A. Materials:

1. Test Compound: Unlabeled FMC 54800- purity 96.2%, specifications were supposed to be in appendix 1 but are not there.
Radiolabeled FMC 54800
Alcohol labeled: synthesized by Pathfinders Labs Inc. (lot #830222) Specific Activity of 33.52 mCi/mMole
Acid labeled: synthesized by New England Nuclear (lot #1001-078) with specific activity of 11.93 mCi/mMole
Both of these labeled compounds were repurified at Biological Testing Center prior to initiation of the studies. Purity was then 98% for alcohol label and 97.3% for the acid label.

Dosing solution- vehicle was Mazola corn oil. Specific activity for dosing solutions are on appended page 1.

2. Test Animals:

Species: rats, male and female

Strain: Sprague Dawley CD Crl(SD) Br)

Age: adult

Weight: not given

Source: not given

Study Design:

Animal assignments and study procedures.

The procedures used in this study are not clearly written out in the study text. The summary of the study states that 5 females were given a single oral dose of 4 mg/kg or 35 mg/kg alcohol-^{14}C-FMC 54800 and 5 males were given a single oral dose of 4 mg/kg or 35 mg/kg acid ^{14}C-FMC 54800. In addition 5/sex were given daily doses for 14 days of 4 mg/kg unlabeled FMC 54800 and of the 15th day were given 4 mg/kg radiolabeled FMC 54800. All animals were placed in metabolism cages and urine and feces were collected for 7 days post dosing. After 7 days the animals were sacrificed and tissues were analyzed for radioactivity.
However, in the main study text, the author states:

Single oral low dose (4 mg/kg)
5/sex were given 4 mg/kg by gavage after 18 hours fast. Animals were given food ad libitum 6 hours after dosing. However, it isn't stated whether this solution given by gavage is the labeled alcohol or acid compound.

Single oral high dose (35 mg/kg)

5/sex were given 35 mg/kg by oral gavage after 18 hours fast and 7 d

treated in a manner similar to low dose group. However, again, the radiolabeled compound given was not defined.

Multiple oral dose

005731

5/sex were given unlabeled FMC 54800 at a dose of 4 mg/kg for 14 days. After 14 days animals were fasted for 18 hours and administered a labeled dose of FMC 54800 and transferred to metabolism cages. Animals were given food and water ad libitum 6 hours post dosing. Again, the labeled compound given was not defined.

CO_2 study (4 mg/kg)

2 rats/sex were given an oral gavage dose of 4 mg/kg after an 18 hour fast and transferred to Roth glass metabolism cages. Expired CO_2 was collected in 2:1 ethanolamine/cellusolve at intervals of 4, 8, 12, 24 and 48 hours. 6 hours post dosing, animals were given food ad libitum.

Sample collection

Urine, feces and cage rinse samples were collected at 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours post dosing. Urine was freeze trapped and feces were frozen upon collection. Cages were rinsed with water at the end of the study.

Tissues and organs

7 days post dosing, single low and high dose animals were exsanguinated. Blood was taken and plasma separated. Tissues and organs were removed and included. Tissues taker were brain, heart, pancreas leg muscles, lungs, adipose, spleen, bone, skin, hair, kidney, liver and gonads (uterus and ovaries for females and testes seminal vesicles and prostate for males) and carcass. Tissues and organs were weighed and stored frozen at -20°C until analysis.

Sample preparation for radioassay and calculations are on appended page 2.

Results:

Rats CO_2-C^{14} study

Body weights, sex and dose and expired C^{14}-CO_2 are on appended page 3. Females expired 0.028% of the dosed radioactivity as volatiles and males expired an average of 0.053% radioactivity. These data are on appended page 4.

Single low dose- 4 mg/kg

Females: animal body weights and doses given are on appended page 5. Excretion in the urine was 19.65 ± 4.93% as an average of the dose administered. Appended page 6 gives individual urine values and cumulative percent of dose administered for each treated animal. Total fecal excretion was 72.87 ± 4.98% (data are on

appended page 7. Total average excretion in both urine and feces was 92.3± 1.26%.

Males: Animal body weights and individual doses for males are on appended page 8. Average total excretion in urine after 7 days was 13.39 ± 5.77% of administered dose. Data and cumulative percent data are on appended page 9. Average total fecal excretion for 7 days was 82.80 ± 9.85%. An average total of 96.21 ± 3.85% was excreted in both urine and feces. Data are on appended page 10.

Single oral high dose (35 mg/kg)

6 females and 5 males were dosed with 35 mg/kg-C^{14} FMC 54800 in corn oil. All rats showed signs of toxicity 6 hours after dosing. These signs included salivation, diarrhea, spasma, tremor, convulsions, bleeding noses, erratic behavior. The study text claims one male died leaving 5/sex left. (??) I assume this is a mis-statement and the death actually occurred to one female, since the tabular data indicate that there were 5 males and 5 females for the study.

females: Animal body weights and individual doses of radioactivity for females are on appended page 11. Appended page 12 summarizes urinary excretion of radioactivity. The total excreted percent of radioactivity was 21.76± 1.85% of the total dose administered. Appended page 13 details the percent of the dose excreted in feces along with the total radioactivity found in feces which was 70.93 ± 5.19% when expressed as percent of total dose administered. Total urine and fecal excretion after 7 days was 92.70 ± 4.37%.

males: Animal body weights and individual doses of radioactivity are on appended page 14. Page 15 summarizes urinary excretion of radioactivity. The total excretion in urine was 21.60± 7.93%, and total fecal excretion was 68.89 ± 6.64% giving a total of 90.50 ± 4.31% for combined urine and fecal excretion. (appended page 16)

Multiple dose

females: body weights and doses are on appended page 17. Appended page 18 details the excretion of radioactivity in urine for 7 days after the radioactive bolus was given. The total percent excreted in the urine after 7 days was 25.01 ± 7.26%. The total fecal excretion was 65.80 ± 9.60%. Total combined urine and fecal excretion was 90.81 ± 4.63%. (appended page 19)

males: Animal body weights and doses are on appended page 20. They excreted 18.36 ± 3.58% of the radioactivity in urine and 73.22 ± 4.82% in feces for a total of 91.59 ± 4.56% excreted in both urine and feces over 7 days. (appended pages 21 and 22)

Tissue residues:

Fat appeared to be the major depot for ^{14}C-FMC 54800 or metabolites with greater than 100 times the level seen in blood.
Male and female residue data are tabulated on appended pages 23-25

Unfortunately, none of these data have been summarized, so the tissue residue data from single and multiple dose groups could have been compared.
It is also unclear why so many tissues and percent of doses were categorized as "N/A" or not applicable, when clearly both residue data and percent of dose administered would have been important information, if provided. For example adipose tissue was missing. There is little value in analyzing these data until explanations by the firm are given to the above questions.

Discussion:

Very little of the ^{14}C-dose administered either with the label in the acid or alcohol position is excreted in the expired air. Females expired 0.028% and males expired 0.053% of administered dose.

Excretion of radioactivity:
The majority of radioactivity was recovered in feces by 7 days post dosing. Actual numbers are in table I below. Tissue residue data are not included since so much of the tissue data was unusable, and it is not clear where the tabulated numbers for tissue residues in the final summary tables came from.

TABLE I

Percent of the dose administered

Group	Urine	Feces	Total
Single low dose			
males	13.39 ± 5.77	82.80 ± 8.85	96.21 ± 3.85
females	19.65 ± 4.93	72.87 ± 4.98	92.53 ± 1.26
Single high dose			
males	21.60 ± 7.93	68.89 ± 6.64	90.50 ± 4.31
females	21.76 ± 1.85	70.93 ± 5.69	92.70 ± 4.37
Multiple dose			
males	18.36 ± 4.58	73.22 ± 4.82	91.58 ± 4.56
females	25.01 ± 7.26	65.80 ± 9.60	90.81 ± 4.63

Bifenthrin

RN 4688-96

Page_____ is not included in this copy.

Pages 78 through 105 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marcia van Gemert, Ph.D. 2/17/87
Head, Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: Metabolite identification study. Tox. Chem No. 460735731

Accession No.: 264638

Test Material: FMC 54800

Synonyms: Bifenthrin, Talstar

Study Number: 182RATMO2

Sponsor: FMC Corp.

Testing Facility: Biological Test Center, Irvine, Ca.

Title of Report: Metabolism of FMC 54800 in rats- Identification of products in excreta

Author: S.F. ElNaggar, I. Wu

Report Issued: 7/9/86

Conclusions: The problems inherent in the previous study titled Absorption, Distribution and excretion of FMC 54800 in the rat Feb. 14, 1986 (182RATMO2) are also the same problems inherent in this study, since they employ the same protocol and urine and fecal samples for analysis. One of the outstanding complications in this study as pointed out in the last study, was that males were administered a radioactive dose with the label in the acid position, while females were administered a radioactive dose with the label in the alcohol position. This could make comparisons between males and females difficult. Additionally, it could complicate the metabolite picture somewhat between males and females.
The majority of radioactivity excreted in the feces was the parent compound and its intact hydroxylated metabolites. Much of the radioactivity excreted in urine was hydrolytic and hydrolytic/oxidative degradation products of the parent compound.

Core Classification: supplementary

Quality Assurance Statement accompanied the report and was signed.

005731

A. Materials:

1. Test Compound: Unlabeled FMC 54800- purity 96.2%, specifications were supposed to be in appendix 1 but are not there.
Radiolabeled FMC 54800
Alcohol labeled: synthesized by Pathfinders Labs Inc. (lot #830222) Specific Activity of 33.52 mCi/mMole
Acid labeled: synthesized by New England Nuclear (lot #1001-078) with specific activity of 11.93 mCi/mMole
Both of these labeled compounds were repurified at Biological Testing Center prior to initiation of the studies. Purity was then 98% for alcohol label and 97.3% for the acid label.

Dosing solution- vehicle was Mazola corn oil. Specific activity for dosing solutions are on appended page 1.

2. Test Animals:

Species: rats, male and female

Strain: Sprague Dawley CD Crl(SD) Br)

Age: adult

Weight: not given

Source: not given

Study Design:

Animal assignments and study procedures:

The procedures used in this study are not clearly written out in the study text. The summary of the study states that 5 females were given a single oral dose of 4 mg/kg or 35 mg/kg alcohol-^{14}C-FMC 54800 and 5 males were given a single oral dose of 4 mg/kg or 35 mg/kg acid ^{14}C-FMC 54800. In addition 5/sex were given daily doses for 14 days of 4 mg/kg unlabeled FMC 54800 and of the 15th day were given 4 mg/kg radiolabeled FMC 54800. All animals were placed in metabolism cages and urine and feces were collected for 7 days post dosing. After 7 days the animals were sacrificed and tissues were analyzed for radioactivity. However, in the main study text, the author states:

Single oral low dose (4 mg/kg)
5/sex were given 4 mg/kg by gavage after 18 hours fast. Animals were given food ad libitum 6 hours after dosing. However, it isn't stated whether this solution given by gavage is the labeled alcohol or acid compound.

Single oral high dose (35 mg/kg)

5/sex were given 35 mg/kg by oral gavage after 18 hours fast and

treated in a manner similar to low dose group. However, again, the radiolabeled compound given was not defined

Multiple oral dose

005731

5/sex were given unlabeled FMC 54800 at a dose of 4 mg/kg for 14 days. After 14 days animals were fasted for 18 hours and administered a labeled dose of FMC 54800 and transferred to metabolism cages. Animals were given food and water ad libitum 6 hours post dosing. Again, the labeled compound given was not defined.

Sample collection

Urine, feces and cage rinse samples were collected at 0-4, 4-8, 8-12, 12-24, 24-36, 36 48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours post dosing. Urine was freeze trapped and feces were frozen upon collection. Cages were rinsed with water at the end of the study.

Tissues and organs

7 days post dosing, single low and high dose animals were exanguinated. Blood was taken and plasma separated. Tissues and organs were removed and included. Tissues taken were brain, heart, pancreas leg muscles, lungs, adipose, spleen, bone, skin, hair, kidney, liver and gonads (uterus and ovaries for females and testes, seminal vesicles and prostate for males) and carcass. Tissues and organs were weighed and stored frozen at -20°C until analysis.

Preparation of fecal sample samples for radioassay is on appended page 1. Extraction and fortification recovery from feces are on appended page 2. Extraction from urine and TLC are on appended page 3. HPLC procedures are on appended page 4 and 5. Preparation of metabolites for structure elucidation is on page 5. Isolation and purification of urinary metabolites are on page 6. Gas chromatography and ether derivative preparation are on appended page 7. GC mass spectrometer preparation is on page 8. NMR total residues LSC and calculations are on appended pages 9 and 10.

Results:

Total material balance:

Results of urinary and fecal excretion of ^{14}C-residues and tissue distribution of radioactivity in the study are found in the previous metabolism study intitled "Absorption, distribution and excretion of FMC 54800 in the rat." Feb. 14, 1986 (F2RATM02)

Analysis of ^{14}C-residues in feces

Extraction and fractionation of the alcohol-and acid-^{14}C residues at the two dose levels indicated that 51.3-57.8% and 55.3-[illegible]% of the administered dose was located in the acetonitrile fraction (I), 2.2-3.4% and 2.9-7.0% were located in the hexane fraction (II) and 11.7 -13.7% and 10.7-13.7% were found residues (III, post extraction solids) for both labels respectively.
After HPLC, GC/MS and NMR spectroscopy analysis, results are

tabulated on appended page 11. The predominant excretory product in feces is the parent compound FMC 54800. The standards and their structures are on appended page 12-15. Lesser metabolites are listed on appended page 11.

Analysis of ^{14}C residues in urine:

Data on urinary ^{14}C metabolites are on appended pages 16-21 for female rats dosed with alcohol ^{14}C FMC 54800 the predominant metabolites in the urine were hydrolytic such as biphenyl acid and biphenyl alcohol, as well as oxidative hydolytic products, such as hydroxybiphenyl alcohol, hydroxybiphenyl acid, biphenyl acid, methyl ester and monomethyl catechol biphenyl alcohol.

Discussion:

The majority of radioactivity excreted in the feces was the parent compound and its intact hydroxylated metabolites. Much of the radioactivity excreted in urine was hydrolytic and hydrolytic/oxidative degradation products of the parent compound.

Bifenthrin

PIN 4688-96

Page_____ is not included in this copy.

Pages 110 through 130 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Marcia Van Gemert, Ph.D. M. VanGemert 2/3/87
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Theodore M. Farber, Ph.D.
Chief, Tox. Branch (TS-769C)

005731

DATA EVALUATION REPORT

005731

STUDY TYPE: 1-year dog study

TOX. CHEM. NO.: 463F

ACCESSION NUMBER: 264637

MRID NO.: ?

TEST MATERIAL: talstar, bitenthrin

SYNONYMS: FMC 54800, technical

STUDY NUMBER(S): A83-821

SPONSOR: FMC Corp.

TESTING FACILITY: Hazleton Laboratories America, 9200 Leesburg Pike, Vienna Va. 22180

TITLE OF REPORT: 52-week chronic oral toxicity study in dogs

AUTHOR(S): D.G. Serota

REPORT ISSUED: June 17, 1985

CONCLUSIONS: Tremors were noted in groups 4 (3 mg/kg/day) and 5 (5 mg/kg/day). Sodium levels were increased in group 4 and 5 males at 52 weeks and chloride levels were increased at 52 weeks in group 5 males. Creatinine phosphokinase (C.P.) levels appeared to drop in females in groups 3, 4 and 5 at week 52. There was some indication that this was occurring at week 26 however one animal in the control group was extremely high. There was a significant increase in platelets at 52 weeks in group 5 males. No other treatment-related effects were noted.

NOEL = 0.75 mg/kg
LEL = 1.5 mg/kg based on the increased C.P. at 52 weeks.

Classification: core--Minimum

Special Review Criteria (40 CFR 154.7)

005731

A. MATERIALS:

1. Test compound: FMC-54800 technical, Description Brown solid, Batch #E2392-105, Purity 88.35%,
Samples were taken at weeks 14, 16, 24, 32, 40 and 52 and were sent to the sponsor for stability testing.

2. Test animals: Species: dogs, Strain: Beagles, Age: 23-29 weeks old at initiation of the experiment.
Weight: males 7.2-11.2 kg, females 6.2-10.8 kg.
Source: Hazleton Research Animals Inc.
Reston Va.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned stratified by weight and assigned to groups using a table of random permutations of nine.

Test Group	Dose in diet (mg/kg/d)	Main Study 12 months male	female
1 Cont.	0	4	4
2	0.75	4	4
3	1.5	4	4
4	3.0	4	4
5	5.0	4	4

2. Test Article:

Test diet was analyzed periodically for heavy metals, antibiotics aflatoxins, and on a retrospective basis for microorganisms, pesticides, heavy metals, alkalinity and halogens.
Test article was administered in gelatin capsules once/day 7 days/week. Controls received only an empty capsule.
Dosages were adjusted weekly according to body weight of previous week. Dosing occurred between 6:00 AM and 11:00 AM.

3. Animals received food (Purina Lab Chow Canine Diet No. 5006) and water ad libitum.

4. Statistics - The procedures utilized are on appended pages 1, 2, and 3 from the study text.

5. Quality assurance statement was enclosed in the study and dated 6/18/85.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected daily before initiation of experiment for appearance, behavior, appetite and fecal elimination and twice daily for signs of toxicity and mortality.

Toxicity

The findings of note include tremors in groups 4 and 5. The study text details tremors in group 4 as being intermittant in one male and 2 females between weeks 16 and 23. All group 5 dogs displayed tremors between weeks 15 and 29. Males appeared to display a greater incidence of tremors. The study text notes that in two group 4 and 5 group 5 animals tremors were noted prior to the daily dosing which would indicate a long-acting effect. Tremors did not persist past week 29. No other treatment-related effects were noted. Appended page 4 details the clinical signs seen and their median time of onset.

2. Body weight

Animals were weighed once/week prior to study initiation on the day prior to the study initiation (week 0) and then weekly thereafter starting week 16.

Results: After week 11 group 5 males appeared not to continue to gain weight. However, at no time were the differences statistically significant. No effects were seen in females concerning body weights.

3. Food consumption and compound intake

Consumption was determined weekly starting with week 1 and thereafter on the same schedule as body weights were taken and mean daily diet consumption was calculated.

Results: No treatment-related effects were seen in food consumption.

005731

4. Ophthalmological examinations

Performed on all dogs prior to study initiation and during week 52 using an indirect ophthalmoscope. Topicamide ophthalmic solution was used as a mydriatic according to the study text.

Results:

No treatment-related ophthalmological effects were seen.

5. Blood was collected before treatment and at weeks 26 and 52 for hematology and clinical analysis from all animals. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*		Mean corpuscular HGB conc. (MCHC)
X	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
X	Platelet count*		Reticulocyte count
	Blood Clotting Measurements	X	Differential and erythrocyte morphology
	(Thromboplastin time)		
	(Clotting time		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results: There was a slight non-significant decrease in RBC and HGB at 26 and 52 weeks in group 5 males and females. There was also a significant increase in platelets at 52 weeks in group 5 males. Data are appended on pg. 5 from the study text for reference. No other treatment-related effects were seen.

13

005731

b. Clinical Chemistry

X	Electrolytes·	X	Other.
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphate* (inorganic)	X	Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
	Alkaline phosphatase	X	Total Serum Protein*
	Cholinesterase#		Triglycerides
X	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

There was a significant increase in sodium levels in group 4 and 5 males at week 52 and chloride levels were increased at week 52 in group 5 males. Female sodium and chloride levels were slightly increased also, but not to a statistically significant extent. Data from the study text are on appended page 6 for reference. Glucose levels were higher than control values at week 52 in groups 3 and 5 in males and at 26 weeks in groups 4 and 5 in females. Data are presented on appended page 7 for reference. Creatinine phosphokinase levels appeared to drop in females with increasing dose, and were significantly decreased at week 52 in groups 3 and 5. The raw data numbers appeared to be all over the place for both control and low dose animals, and it is hard to interpret data of this sort with so few animals on test. However, there still appears to be a treatment-related effect. At week 26 in females there was an extremely high reading in the control group, (animal # 22117 had 797 iU/L). The other three animals in this group had lower values (76, 92 and 71 iU/L). If this extraneous number were eliminated from the control group, it would appear that there was also a treatment-related effect on C.P. Summary data are appended on page 8 and individual data for week 52 are appended on pages 9 and 10 for reference.

6. Urinalysis°

Urine was collected from fasted animals prior to study initiation and at 13, 26 and 52 weeks. The CHECKED (X) parameters were examined.

X		X	
X	Appearance*	X	Glucose*
X	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
X	Sediment (microscopic)*		Nitrate
X	Protein*		Urobilinogen
		X	Reducing substances

* Required for chronic studies
° Not required for subchronic studies

Results: No treatment-related effects were noted.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	X	.Aorta*	XX	.Brain*† #
X	.Salivary glands*	XX	.Heart*		Periph. nerve*
X	.Esophagus*	X	.Bone marrow*	X	Spinal cord (3 levels)*
X	.Stomach*	X	.Lymph nodes*	XX	.Pituitary* #
X	.Duodenum*	X	.Spleen*	X	Eyes (optic n.)*
X	.Jejunum*	X	.Thymus*		Glandular
X	.Ileum*		Urogenital	XX	.Adrenals*
X	.Cecum*	XX	.Kidneys*†		Lacrimal gland
X	.Colon*		X.Urinary bladder*	X	Mammary gland*
X	.Rectum*	XX	.Testes*† weighed w	XX	.Parathyroids*†† weighed w
XX	.Liver*† weighed w	X	Epididymides		.Thyroids*††
	Gall bladder*	X	Prostate		Other
X	.Pancreas*		Seminal vesicle		Bone*
	Respiratory	XX	Ovaries*†	X	Skeletal muscle* ∃
X	.Trachea*	X	.Uterus*	X	Skin*
X	.Lung*			X	All gross lesions and masses*

* Required for subchronic and chronic studies
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies
# weighed with grain stem and pituitary
∃ weighed and sectioned with sciatic nerve

a. Organ weight results: No treatment-related effects were seen in absolute or relative organ weights.

0057

b. Gross pathology results: No treatment-related effects were seen in gross pathology of the animals.

c. Microscopic pathology

1) Non-neoplastic and neoplastic: Spontaneous disease lesions occurred but couldn't be ascribed to compound administration. No treatment-related histopathological findings were noted.

Discussion:

Tremors were noted in groups 4 and 5, however, they seemed to disappear by week 29. Sodium levels were increased in group 4 and 5 males at 52 weeks and chloride levels were also increased in group 5 males at 52 weeks. Glucose levels were higher than controls at week 52 in groups 3 and 5 in males and at 26 weeks in group 4 and 5 females. Creatinine phosphokinase levels appeared todrop in females with increasing dose both at 26 and 52 weeks. At 52 weeks there was a significant drop in groups 3 and 5 females. There was also a significant increase in platelets at 52 weeks in group 5 males. No other treatment-related effects were noted.

NOEL = 0.75 mg/kg
LEL = 1.5 mg/kg based on the increased C.P. at 52 weeks.

Core Classification: Minimum

Bifenthrin

RW 4688-96

Page_____ is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

__✓__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
