(9-29-97)

**[FLUROXYPYR METHYLHEPTYL ESTER]** **Metabolism Study [§85-1]**

EPA Reviewer: Linda L. Taylor, Ph.D.
Reregistration Branch I, formerly Toxicology Branch II (7509C)
Branch Senior Scientist: Whang Phang, Ph.D.
Reregistration Branch I, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - [rat] OPPTS 870.7485 [§85-1)]
DP BARCODE: D232217 SUBMISSION CODE: S515138
P.C. CODE: 128959 TOX. CHEM. NO.: 463-O

TEST MATERIAL (PURITY): Fluroxypyr $^{14}$C-MHE [99%] and $^{14}$C-methylheptanol [97.5%]
SYNONYMS: acetic acid ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)-1-methylheptyl ester [CAS No. 81406-37-3];
1-methyl-1-heptanol [CAS No. 4128-31-8]

CITATION: Domoradzki, J.Y. and Brzak, K.A.. (1996). Fluroxypyr Methylheptyl Ester (Fluroxypyr MHE) and Methylheptanol: Metabolism in Male Fischer 344 Rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company. Project No. HET K-137992-014. June 3, 1996. MRID 44080327. Unpublished.

SPONSOR: The Dow Chemical Company

EXECUTIVE SUMMARY: In a metabolism study (MRID 44080327]), Fluroxypyr $^{14}$C-methylheptyl ester [95.8 % a.i. unlabeled; radiochemical purity 99%; labeled on the methylheptanol portion of the molecule] or $^{14}$C- methylheptanol [98.9% unlabeled; radiochemical purity 97.5%] was administered to 5 [plasma]/3 [balance] male Fischer 344 rats/group in single oral [equimolar] doses of 50 mg Fluroxypyr methylheptyl ester/kg body weight or 17.7 mg Methylheptanol/kg body weight. The total recovery of the administered dose was 105% and 104%, with the principal route of excretion being expired $^{14}CO_2$, which contained ≈61% and 63% of the radioactivity for the fluroxypyr MHE and methylheptanol balance groups, respectively. The urine contained ≈30% and 27% and the feces contained 5% and 7% of the administered dose for the Fluroxypyr MHE and Methylheptanol groups, respectively. At 48 hours post dose, ≈7% of the administered dose was recovered in the blood, carcass, and skin of both groups. The overall rates and routes of elimination were comparable between the groups. Each was extensively absorbed and rapidly eliminated. Approximately 52% and 54% of the administered Fluroxypyr MHE and Methylheptanol, respectively, was absorbed and expired as $^{14}CO_2$ within 12 hours post dose, and an additional 18% of the administered dose was excreted in the urine within 12 hours post dose. Based on the percentage of the dose in the expired $^{14}CO_2$, urine, and tissues, ≈90% of the dose was absorbed by the rats in each case. Once absorbed, both were extensively metabolized [20-22 metabolites] and rapidly expired as $^{14}CO_2$ and eliminated in the urine with a half-life of 6 hours. Fluroxypyr MHE displayed a slower absorption rate than Methylheptanol, but once absorbed, the pharmacokinetic parameters were similar. Peak plasma concentrations of $^{14}$C-radioactivity were attained by 7 and 10 hours post dose, and the half-lives for the elimination phase were ≈18.2 and 17.4 hours for Fluroxypyr MHE and Methylheptanol, respectively. It

1

was stated that the percentage of radioactivity recovered in the tissues and carcass [≈7%] suggests $^{14}C$-incorporation into the carbon pool that may account for the longer half life in plasma as compared to the urinary half-life of 6 hours. Average area under the curve values were 140 μg eq hr/g and 163 μg eq hr/g for the Fluroxypyr MHE and Methylheptanol groups, respectively. Clearance values were comparable for these groups also [2.1 and 1.8 mL/min kg]. These pharmacokinetic parameters indicate no difference in kinetics of Methylheptanol, based on whether it is labeled alone or as part of the Fluroxypyr MHE molecule. Urine profiles were similar and indicated extensive metabolism [20-22 metabolites]. Unchanged Fluroxypyr MHE was not detected in any of the samples, and the author stated that this "is consistent with the majority of the dose metabolized to $CO_2$." The data indicate that the Fluroxypyr MHE bond is readily hydrolyzed and that the methylheptyl ester portion of Fluroxypyr is bioequivalent to Methylheptanol.

This nonguideline metabolism study [§85-1] in the rat is classified **ACCEPTABLE.**

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No Flagging statement was provided.

## I. MATERIALS AND METHODS

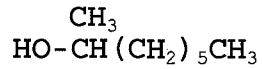
### A. MATERIALS

#### 1. Test Compound

**Radiolabeled Test Material**
(a) Fluroxypyr 1-methylheptyl-1-$^{14}$C-ester; Radiochemical purity: 99%; Specific Activity: 25.3 mCi/mmol; Batch #: B930-96, Inv. No. 1204.
(b) $^{14}$C-Methylheptanol; Radiochemical purity: 97.5%; Specific Activity: 24.2 mCi/mmol; Batch #: B930-93, Inv. No. 1189. Both $^{14}$C-labeled in the same positions on the methylheptanol portion of the molecules.

**Nonradiolabeled Test Material**
Non radioactive Fluroxypyr methylheptyl ester: Purity: 95.8%; CAS No.: 81406-37-3.
[Structure]

Non radioactive Methylheptanol: Purity: 98.9%; CAS No.: 4128-31-8.
[Structure]



#### 2. Vehicle: corn oil

#### 3. Test animals: Species: rat
Strain: CDF Fischer 344
Age and Weight: ≈ 7 and 9 weeks old; 170-250 g
Source: Charles River Breeding Laboratories, Kingston, NY.
Housing: **prior to study**: 2/cage; **study**: individually [apparently] in Roth-type metabolism cages
Diet: Ralston Purina #5002, ad libitum [withheld for ≈16 hours prior to dosing and 4 hours post dose]
Water: municipal tap, ad libitum [withheld for ≈16 hours prior to dosing and 4 hours post dose]
Environmental conditions: standard
Acclimation: ≥ 7 days; acclimated to metabolism cage ≥2 days

4. Preparation of dosing solutions

Fluroxypyr methylheptyl ester [MHE] and methylheptanol radiotracers were diluted with non-labeled compound in corn oil to obtain the targeted dosing volume of 5 g dosing solution/kg body weight. The target dose of Fluroxypyr MHE was 50 mg/kg, and the target dose of methylheptanol was 17.7 mg/kg. The target radioactivity for all dose groups was ≈500 μCi/kg or 100 μCi/rat. The quantity of test material actually administered was determined by weighing the dosing syringe prior to and following dosing. Aliquots of the dosing solutions were analyzed for homogeneity, radioactivity, and methylheptanol [GC with flame ionization Detection (FID)] or Fluroxypyr MHE [high performance liquid chromatography (HPLC) with UV detection] concentration.

B. STUDY DESIGN AND METHODS

1. Animal Assignment

Rats were assigned to treatment groups randomly and acclimated to the glass Roth-type metabolism cages for a period of at least 2 days prior to dosing. Each had an indwelling jugular vein catheter implanted ≈ 1 day prior to test material administration [modified method of Harms and Ojeda, 1974] and was allowed to recover for approximately one day prior to dosing. The selection of rats to be dosed was based on best functioning cannula. There were 3 rats/group for the balance phase and 5 rats/group plasma phase of the study. NOTE: The Methods section does not describe these two phases, but the data tables identify these two phases.

2. Dosing and sample collection

Doses were administered via gavage at a dosing volume of 5 g dosing solution/kg body weight following an ≈16-hour fast. Following dosing, each rat was returned to its Roth-type metabolism cage and air was drawn through the cages at ≈500 mL/min. In order to obtain blood specimens, the lids of the cages were removed to facilitate blood collection.

**Blood** - Blood samples [≈0.1-0.2 mL each] were drawn from the jugular cannula at ≈10, 20, 30, 45 minutes post dose and at ≈1, 1.5, 2, 3, 5, 7, 10, 12, 24, and 48 hours post dose using a syringe. An aliquot of each sample was centrifuged to obtain plasma, which was subsequently weighed and analyzed for radioactivity.

**Urine** - All urine voided during the study were collected in dry-ice cooled traps, which were changed and a cage rinse was performed at 12-hour intervals. Each urine specimen/cage rinse was weighed, and a weighed aliquot was analyzed for radioactivity. Selected samples of urine were pooled and stored frozen at -80°C until evaluated to determine the chemical identity of the radioactivity.

**Feces** - Feces were collected at 24-hour intervals in dry-ice containers. An aqueous homogenate [≈25% w/w] was prepared, and weighed aliquots of



4

these homogenates were placed in scintillation vials, solubilized, and quantitated for radioactivity. Selected fecal specimens were pooled and stored frozen [-80°C] for possible evaluation to determine the chemical identity of the radioactivity. This latter evaluation was not performed since greater than 10% of the dose was not excreted in the feces.

**Charcoal and $^{14}CO_2$ Traps** - The traps were changed at 12-hour intervals. Radioactivity trapped on the charcoal was desorbed with a weighed amount of toluene, and a weighed aliquot of toluene was analyzed for radioactivity. The $CO_2$ trap solutions were weighed and a weighed aliquot was analyzed for radioactivity.

3. Sample analysis

**Profile of Urine Samples** - The 12- and 24-hour urine samples were thawed at room temperature. The individual rat samples were pooled, by dose and time interval, by combining equal volumes of each. Each pooled urine samples was centrifuged and the clear liquid was transferred to another vial. Recovery of urinary radioactivity following separation of the solids was 99-100%. Urine samples were analyzed by High Performance Liquid Chromatography [HPLC] and UV and $^{14}C$ detection. Since the urinary profiles obtained from the 12-hour pooled Fluroxypyr MHE and methylheptanol doses were similar with only 2 minor exceptions [Peaks 6 and 27], hydrolysis work was performed only on the Fluroxypyr MHE pooled urine. Chemical hydrolysis was done by fortifying an aliquot of the 0-12 hour pooled urine with either 5N NaOH or concentrated HCL [10% v/v]. These samples were heated overnight at ≈60°C. An unchanged aliquot was also heated and is referred to as the "60°C thermal control". Prior to analysis by HPLC, the pH of the acid and base hydrolyzed samples was adjusted to 4-7. Enzymatic hydrolysis was also performed only on the 12-hour Fluroxypyr MHE pooled urine. Aliquots of urine were fortified with either glucuronidase [3450 units of Type HP-2 from Helix pomatia] or sulfatase [57 units total of Type VIII: abalone Entrails and Type VI: Aerobacter Aerogenes]. The pH of the glucuronidase samples was adjusted to ≈5. These samples were heated overnight at 37°C. An unchanged urine aliquot was also heated and is referred to as the "37°C thermal control". Prior to analysis by HPLC, no adjustments were made to the pH of these samples.

**$^{14}C$ Analysis** - Radioactivity was quantified in a liquid scintillation spectrometer [Beckman, models LS3801 or LS1801]. Counts per minute [CPM] were corrected for quench and background and converted to disintegrations per minute [DPM]. Two sealed $^{14}C$-standards were counted with each group of samples to monitor the performance of the liquid scintillation counter

4. Data Analysis: Where appropriate, data were expressed as means ± standard deviations. Plasma $^{14}C$-concentration time-course data were used to compare the absorption and elimination of methylheptanol and Fluroxypyr MHE. The concentration time course of $^{14}C$-activity in the plasma was described by a 1-compartment model using the method of residuals and linear regression to estimate the half-life, $t_{½}$. The area under the plasma $^{14}C$-concentration-time curves [AUC] was calculated using the

trapezoidal rule. The volume of distribution was calculated as the dose divided by AUC and the overall rate of elimination [$k_{el}$]. The clearance [Cl] was defined as the dose divided by the AUC. All calculations in the data base were conducted using Microsoft Excel®, full precision.

## II. RESULTS

A. Radiochemical Purity - The radiochemical purity of Fluroxypyr $^{14}$C-MHE was determined to be 99.3±0.08%. The recovery of radioactivity through the liquid chromatography [LC] system was 99.0±4.4%. The limit of detection was 0.2% of the injected radioactivity. The radiochemical purity of $^{14}$C-methylheptanol was determined to be 98.3±0.1%. A limit of detection of 0.5% was calculated. The GC/LRAM $^{14}$C-activity system recovery for the $^{14}$C-2-methylheptanol RC purity determination was 97.6±2.5%.

B. Test Material Administration: All dose solutions were within 10% and 7% of their targeted concentrations and radioactivity, respectively [Table 1]. The average amounts of dose solution, radioactivity, and test material administered is listed in Table 2. The mean 50 mg Fluroxypyr $^{14}$C-MHE/kg dose to male rats was 50.5 mg/kg, and the mean 17.7 mg $^{14}$C-methylheptanol/kg dose to male rats was 16.8 mg/kg. Additionally, the average amount of radioactivity [µCi/rat] administered to the rats ranged from 88 to 92 µCi/rat. The differences between actual and targeted doses of radioactivity and test material were acceptable.

Table 1. Concentration of Radioactivity/Test Material in Dosing Solutions

| Dose Solution | Target $^{14}$C [µCi/g] | Actual $^{14}$C [µCi/g] | Target Dose [mg/g] | Actual Dose [mg/kg] |
|---|---|---|---|---|
| Plasma | | | | |
| 50 mg Fluroxypyr-$^{14}$C-MHE/kg | 100 | 93.4 | 10 | 9.64 (96%) |
| 17.7 mg $^{4}$C-Methylheptanol/kg | 100 | 96.8 | 3.54 | 3.25 (92%) |
| Balance | | | | |
| 50 mg Fluroxypyr-$^{14}$C-MHE/kg | 100 | 95.0 | 10 | 10 (100%) |
| 17.7 mg $^{4}$C-Methylheptanol/kg | 100 | 94.4 | 3.54 | 3.17 (90%) |

data from Table 1, page 35 of the report

Table 2. Dose Administered

| Dose Administered Group | Plasma♦ | | Balance♣ | |
|---|---|---|---|---|
| | Fluroxypyr MHE | Methylheptanol | Fluroxypyr MHE | Methylheptanol |
| Body weight [g] | 182.5±4.9 | 182.9±2.1 | 188.6±5.6 | 183.3±7.2 |
| Dose solution [g] | 0.9567±0.1226 | 0.9516±0.0648 | 0.9257±0.0580 | 0.9706±0.0707 |
| Radioactivity [µCi/rat] | 89.35±11.45 | 92.11±6.27 | 87.97±5.51 | 91.63±6.68 |
| Compound [mg] | 9.2±1.2 | 3.1±0.2 | 9.5±0.6 | 3.1±0.2 |
| Compound [mg/kg] | 50.46±5.64 | 16.90±1.07 | 50.52±2.10 | 16.76±1.42 |

♦ n=5; ♣ n=3; data from Table 2, page 36 of the report

C. Distribution of Radioactivity: **Fluroxypyr MHE**: A total of 95% to 105% of the administered radioactivity was recovered in the plasma and balance

groups [Table 3]. In the balance portion of the study, the principal route of excretion was $CO_2$, which contained ≈61% of the radioactivity. The urine, including urine rinse, contained ≈30% of the administered radioactivity and 7% of the administered radioactivity was recovered in the feces. Less than 8% of the administered radioactivity was recovered in the blood, carcass, and skin after 48 hours post dose. **Methylheptanol**: A total of 104% of the administered radioactivity was recovered in the balance group, with a lower amount [78%] being recovered in the plasma group, which was attributed to not trapping all of the expired $^{14}CO_2$. In the balance portion of the study, the principal route of excretion was expired $CO_2$, which contained 63% of the radioactivity [Table 3]. The urine, including urine rinse, contained 27% of the radioactivity, and the feces contained 5% of the radioactivity. Less than 8% of the administered radioactivity was recovered in the blood, carcass, and skin 48 hours post dose.

Table 3. Distribution of Radioactivity Recovered 48 Hours After Dosing

| Phase Sample | % of Administered Radioactivity | |
|---|---|---|
| | 17.7 mg $^{14}$C-Methylheptanol/kg | 50 mg Fluroxypyr-$^{14}$C-MHE/kg |
| Plasma | | |
| $CO_2$ | 41.38±9.86 | 49.66±3.35 |
| urine | 23.82±5.16 | 25.13±2.25 |
| tissues and carcass♪ | 6.66±1.48 | 11.15±8.65 |
| feces | 4.75±4.04 | 8.07±5.96 |
| final cage wash | 0.54±0.25 | 1.11±0.73 |
| charcoal trap | 1.11±1.05 | 0.11±0.06 |
| Total | 78.26±15.24 | 95.22±2.16 |
| Balance | | |
| $CO_2$ | 62.90±1.92 | 60.66±5.38 |
| urine | 26.88±2.88 | 29.54±3.19 |
| tissues and carcass♫ | 7.24±0.64 | 7.22±0.88 |
| feces | 5.24±0.92 | 6.96±2.33 |
| final cage wash | 0.71±0.51 | 0.56±0.11 |
| charcoal trap | 0.52±0.38 | 0.06±0.01 |
| Total | 103.48±1.38 | 105.01±6.23 |

♪ carcass, tissues, including skin + blood + plasma; ♫ carcass, tissues, including skin + blood; data from Table 3, page 37 of the report

D. Plasma Radioactivity: The average concentrations of radioactivity in the plasma of rats was similar following the oral administration of both test materials. The highest concentration of radioactivity [3.7 μg eq/g plasma] was found in the plasma samples collected 7 hours post dose in the Fluroxypyr MHE rats [Table 4]. Following Methylheptanol exposure, the highest concentration in the plasma was observed at 2 hours [3.5604], although a similar concentrations were attained at 0.5 and 10 hours [3.5043 and 3.5075]. Pharmacokinetic parameters are displayed in Table 5. The absorption half-live was 1.87 hours for Fluroxypyr MHE and 0.42 hour for Methylheptanol. The difference in absorption is attributed to the fact that Fluroxypyr $^{14}$C-MHE may first be hydrolyzed and then absorbed. Overall, the pharmacokinetic parameters that describe the time-course of radioactivity in the plasma for both test materials are very similar. The hale-life for the elimination phase was 18.2 hours for

Fluroxypyr MHE and 17.4 hours for Methylheptanol. Equivalent area under the curve values of ≈140 and 163 µg eq hr/g were calculated for rats administered Fluroxypyr MHE or Methylheptanol, respectively. Additionally, clearance values are 2.1 and 1.8 mL/min kg for Fluroxypyr MHE and Methylheptanol, respectively.

Table 4. Concentration of Radioactivity in Plasma at Various Intervals After Dosing

| Test Material Time [hour] | µg Equivalents/g Plasma | |
|---|---|---|
| | 17.7 mg $^{14}$C-Methylheptanol/kg♪ | 50 mg Fluroxypyr-$^{14}$C-MHE/kg♪ |
| 0.17 | 2.5774±0.7142 | 0.2188±0.0596 |
| 0.33 | 3.2318±0.5537 | 0.4518±0.898 |
| 0.5 | 3.5043±0.4700 | 0.7257±0.1833 |
| 0.75 | 3.3356±0.6485 | 1.0782±0.2391 |
| 1 | 3.3438±0.8108 | 1.4477±0.2100 |
| 1.5 | 3.2749±0.7820 | 1.7944±0.2638 |
| 2 | 3.5604±1.2186 | 1.7415±0.0754 |
| 3 | 3.3708±0.9255 | 2.6515±0.1981 |
| 5 | 3.3050±1.0567 | 3.2021±0.2273 |
| 7 | 3.2537±1.0472 | 3.7207±0.5709 |
| 10 | 3.5075±0.8477 | 3.4378±0.5417 |
| 12 | 3.2108±0.9722 | 2.9883±0.4397 |
| 24 | 1.6844±0.4990 | 1.6717±0.2859 |
| 48 | 0.7707±0.2577 | 0.7979±0.1355 |

♪ mean ± SD for 5 rats; data from Table 4, page 38 of the report

Table 5. Pharmacokinetic Parameters

| Parameter | 17.7 mg $^{14}$C-Methylheptanol/kg | 50 mg Fluroxypyr-$^{14}$C-MHE/kg |
|---|---|---|
| absorption rate constant [$hr^{-1}$] | 1.63 | 0.37 |
| absorption half-life [hr] | 0.42 | 1.87 |
| area under the curve [AUC, 0-48 hr; µg equiv*hr/g] | 163 | 140 |
| clearance [Cl; Cl = dose/AUC; mL/min kg] | 1.80 | 2.1 |
| elimination rate constant [$k_{el}$; $hr^{-1}$] | 0.040 | 0.038 |
| half-life od Beta [$t_{½}\beta$; hr] | 17.39 | 18.16 |
| volume of distribution [Vd; Vd = dose/AUC*$k_{el}$; mL/kg] | 2700 | 3316 |

data from Table 5, page 39 of the report

E. Excretion of Radioactivity: URINE - Following dosing, the time-course of urinary elimination of radiolabel was similar [Table 6], with an average of 15.6% and 14.6% of the administered dose being recovered in the 0-12 hour collection interval followed by an additional 5.2% and 4.1% in the 12-24 hour sample for Fluroxypyr MHE and Methylheptanol, respectively. After 48 hours post dose, 24-25% of the radiolabel was recovered in the urine [including urine rinse] from both groups. The rate of radiolabel excreted in the urine was essentially the same with half-lives of ≈6 hours [Figure 4, appended to file copy of DER].

Table 6. Radiolabel Excreted in Urine [% Administered Dose]

| Test Material Group Sample | Fluroxypyr MHE | | Methylheptanol | |
|---|---|---|---|---|
| | interval | cumulative | interval | cumulative |
| Plasma♦ | | | | |
| rinse | | | | |
| 0-12 | 2.83±1.17 | 2.83±1.17 | 3.12±1.19 | 3.12±1.19 |
| 12-24 | 0.42±0.12 | 3.25±1.28 | 0.51±0.24 | 3.64±1.38 |
| 24-36 | 0.11±0.07 | 3.37±1.23 | 0.15±0.06 | 3.78±1.42 |
| 36-48 | 0.04±0.03 | 3.41±1.20 | 0.10±0.06 | 3.88±1.44 |
| TOTAL | 3.41±1.20 | | 3.88±1.44 | |
| urine | | | | |
| 0-12 | 15.60±2.69 | 15.60±2.69 | 14.59±3.70 | 14.59±3.70 |
| 12-24 | 5.19±1.98 | 20.79±1.90 | 4.11±1.14 | 18.70±3.97 |
| 24-36 | 0.75±0.48 | 21.54±2.32 | 0.98±0.48 | 19.68±4.19 |
| 36-48 | 0.18±0.12 | 21.72±2.42 | 0.26±0.12 | 19.94±4.19 |
| TOTAL | 21.72±2.42 | | 19.94±4.19 | |
| GRAND TOTAL | 25.13±2.25 | | 23.82±5.16 | |
| Balance♣ | | | | |
| rinse | | | | |
| 0-12 | 4.12±3.00 | 4.12±3.00 | 2.28±0.27 | 2.28±0.27 |
| 12-24 | 0.67±0.39 | 4.79±4.02 | 0.46±0.13 | 2.74±1.62 |
| 24-36 | 0.12±0.03 | 4.91±4.09 | 0.14±0.03 | 2.88±1.69 |
| 36-48 | 0.19±0.23 | 5.10±4.32 | 0.06±0.01 | 2.94±1.73 |
| TOTAL | 5.10±3.07 | | 2.94±0.22 | |
| urine | | | | |
| 0-12 | 17.80±5.15 | 17.80±5.15 | 17.70±1.72 | 17.70±1.72 |
| 12-24 | 5.01±1.11 | 22.81±11.81 | 4.88±1.52 | 22.58±12.34 |
| 24-36 | 1.38±0.47 | 24.19±12.63 | 1.13±0.24 | 23.71±12.95 |
| 36-48 | 0.25±0.14 | 24.44±12.74 | 0.22±0.02 | 23.93±13.07 |
| TOTAL | 24.44±5.94 | | 23.93±3.07 | |
| GRAND TOTAL | 29.54±3.19 | | 26.88±2.88 | |

♦ n=5; ♣ n=3; data from Table 6, pages 40-41 of the report

FECES - Approximately 6% of the administered radioactivity was recovered in the 0-24 hour feces sample, with an additional 1% in the 24-48 hour interval in the Fluroxypyr MHE groups [Table 7]. In the Methylheptanol groups, an average of 4% of the administered radioactivity was recovered in the 0-24 hour feces followed by an additional 1% in the 24-48 hour sample. After 48 hours post dose, ≈5-8% of the radiolabel was recovered in the feces from all groups.

Table 7. Radiolabel Excreted in Feces [% Administered Dose]

| Test Material Group Sample | Fluroxypyr MHE | | Methylheptanol | |
|---|---|---|---|---|
| | interval | cumulative | interval | cumulative |
| Plasma♦ | | | | |
| feces | | | | |
| 0-24 | 6.38±4.56 | 6.38±4.56 | 3.90±4.19 | 3.90±4.19 |
| 24-48 | 1.68±1.57 | 8.07±5.96 | 0.85±0.46 | 4.75±3.43 |
| TOTAL | 8.07±5.96 | | 4.75±4.04 | |
| Balance♣ | | | | |
| feces | | | | |
| 0-24 | 6.17±2.01 | 6.17±2.01 | 4.29±1.06 | 4.29±1.06 |
| 24-48 | 0.79±0.34 | 6.96±4.92 | 0.96±0.50 | 5.24±3.01 |
| TOTAL | 6.96±2.33 | | 5.24±0.92 | |

♦ n=5; ♣ n=3; data from Table 8, page 43 of the report

EXPIRED $CO_2$ - The total amount of radiolabel excreted via expired $CO_2$ was 61% for Fluroxypyr MHE and 63% for Methylheptanol. Within the first 12 hours post dose, 52% and 54% of the administered radioactivity was expired as $CO_2$ in the Fluroxypyr MHE and Methylheptanol groups, respectively. Of the amount of expired as $CO_2$, 86% was expired within the first 12-hour interval. An additional 6% of the administered radioactivity was expired during the 12-24 hour interval.

Table 8. Radiolabel Excreted in Expired $CO_2$ [% Administered Dose]

| Test Material Group Sample | Fluroxypyr MHE | | Methylheptanol | |
|---|---|---|---|---|
| | interval | cumulative | interval | cumulative |
| Plasma♦ | | | | |
| $CO_2$ | | | | |
| 0-12 | 39.51±4.57 | 39.51±4.57 | 33.55±7.57 | 33.55±7.57 |
| 12-24 | 8.08±2.08 | 47.59±2.86 | 5.63±1.97 | 39.18±9.45 |
| 24-36 | 1.06±0.96 | 48.65±3.28 | 1.40±0.43 | 40.59±9.74 |
| 36-48 | 1.01±0.76 | 49.66±3.35 | 0.80±0.26 | 41.38±9.86 |
| TOTAL | 49.66±3.35 | | 41.38±9.86 | |
| Balance♣ | | | | |
| $CO_2$ | | | | |
| 0-12 | 51.51±3.38 | 51.51±3.38 | 54.08±2.88 | 54.08±2.88 |
| 12-24 | 6.33±1.66 | 57.84±35.12 | 6.16±0.69 | 60.24±35.51 |
| 24-36 | 2.00±0.42 | 59.84±36.43 | 1.87±0.34 | 62.11±36.47 |
| 36-48 | 0.82±0.11 | 60.66±36.93 | 0.79±0.05 | 62.90±36.91 |
| TOTAL | 60.66±5.38 | | 62.90±1.92 | |

♦ n=5; ♣ n=3; data from Table 9, page 44 of the report

CHARCOAL TRAPS - The amount of radioactivity trapped as volatile organics was ≤0.11% [plasma] in the Fluroxypyr groups and 0.52% [balance] and 1.11% [plasma] for the Methylheptanol groups [Table 9].

Table 9. Radiolabel Excreted in Charcoal Traps [% Administered Dose]

| Test Material Group Sample | Fluroxypyr MHE | | Methylheptanol | |
|---|---|---|---|---|
| | interval | cumulative | interval | cumulative |
| Plasma♦ | | | | |
| CHARCOAL TRAP | | | | |
| 0-12 | 0.03±0.01 | 0.03±0.01 | 0.96±-.96 | 0.96±0.96 |
| 12-24 | 0.05±0.03 | 0.08±0.03 | 0.09±0.06 | 1.05±1.01 |
| 24-36 | 0.02±0.03 | 0.10±0.05 | 0.04±0.03 | 1.09±1.04 |
| 36-48 | 0.01±0.01 | 0.11±0.06 | 0.02±0.02 | 1.11±1.05 |
| TOTAL | 0.11±0.06 | | 1.11±1.05 | |
| Balance♣ | | | | |
| CHARCOAL TRAP | | | | |
| 0-12 | 0.02±0.01 | 0.02±0.01 | 0.45±0.37 | 0.45±0.37 |
| 12-24 | 0.04±0.02 | 0.06±0.03 | 0.05±0.03 | 0.50±0.27 |
| 24-36 | 0.01±0.00 | 0.06±0.04 | 0.01±0.00 | 0.51±0.28 |
| 36-48 | 0.00±0.00 | 0.06±0.04 | 0.01±0.00 | 0.52±0.28 |
| TOTAL | 0.06±0.01 | | 0.52±0.38 | |

♦ n=5; ♣ n=3; data from Table 10, page 45 of the report

TISSUES: Approximately 7% of the administered dose was found in the carcass and ≈0.14% in the blood of all groups [Table 10].

Table 10. Radiolabel in Blood, Carcass, and Skin [% Administered Dose]

| Test Material Group Sample | Fluroxypyr MHE | | Methylheptanol | |
|---|---|---|---|---|
| | plasma♦ | balance♣ | plasma♦ | balance♣ |
| blood | 0.11 | 0.14 | 0.13 | 0.14 |
| carcass | 8.74 | 7.03 | 4.30 | 7.08 |
| skin | 2.24 | 0.04 | 2.16 | 0.02 |

♦ n=5; ♣ n=3; data from Appendix Tables 5-8, page 50-53 of the report

F. Analysis of Pooled Urine Samples: Pooled urine samples [12- and 24-hour] from each test material group were analyzed by HPLC with UV and radiochemical detection to determine the extent of metabolism [Table 11]. The average recovery from the HPLC system for all analyses was 97.5%±2.0%. The urine profiles were similar and indicate extensive metabolism [20-22 metabolites]. No Fluroxypyr MHE was detected in any sample. It is stated that the Fluroxypyr MHE bond is readily hydrolyzed and the methylheptyl ester portion of Fluroxypyr is bioequivalent to methylheptanol.

Table 11. Summary of Urine HPLC Profile Data [% of Dose]

| Peak # | Retention Time [min] | 12-hour | | 24-hour | |
|---|---|---|---|---|---|
| | | Fluroxypyr MHE | Methylheptanol | Fluroxypyr MHE | Methylheptanol |
| 1 | 2.4 | 1.1 | 1.2 | 1.0 | 0.8 |
| 2 | 6.8 | 0.4 | 0.4 | nd | nd |
| 3 | 7.7 | 0.2 | 0.2 | nd | nd |
| 4 | 11.4 | 1.0 | 0.9 | 0.4 | 0.3 |
| 5 | 12.7 | 2.5 | 1.7 | 0.6 | 0.6 |
| 6 | 14.4 | nd | 0.3 | nd | 0.3 |
| 7 | 16 | 0.6 | 0.5 | 0.4 | 0.3 |
| 8 | 16.1 | nd | nd | nd | nd |
| 9 | 17.1 | 1.5 | 1.6 | 0.6 | 0.6 |
| 10 | 19.2 | 0.9 | 0.9 | 0.4 | 0.3 |
| 11 | 18.8 | ** | ** | nd | nd |
| 12 | 22.2 | 0.3 | 0.3 | nd | nd |
| 13 | 27.8 | nd | nd | nd | nd |
| 14 | 29.9 | 0.6 | 0.5 | 0.2 | nd |
| 15 | 30.6 | 1.6 | 1.9 | 0.4 | 0.2 |
| 16 | 32.2 | 0.6 | 0.7 | 0.5 | 0.4 |
| 17 | 32.4 | nd | nd | nd | nd |
| 18 | 34.3 | 0.7 | 0.6 | 0.1 | nd |
| 19 | 35 | 0.6 | 0.5 | nd | nd |
| 20 | 35.9 | 0.6 | 0.6 | 0.1 | nd |
| 21 | 36.4 | 0.2 | 0.2 | nd | nd |
| 22 | 37.6 | nd | nd | nd | nd |
| 23 | 42.3 | 0.3 | 0.3 | 0.3 | 0.2 |
| 24 | 42.8 | 0.4 | 0.2 | 0.1 | nd |
| 25 | 44.1 | 0.1 | 0.1 | nd | nd |
| 26 | 44.6 | 1.1 | 0.9 | 0.1 | nd |
| 27 | 46.3 | nd | 0.1 | nd | nd |

nd = not detected; ** peaks 10 and 11 appear to merge in 12-hour sample; were resolved in hydrolyzed urines;

data from Table 7, page 42 of the report

6. Proposed Metabolic Pathway

No metabolic pathway was proposed. It is stated that, once absorbed, Fluroxypyr MHE and Methylheptanol are extensively metabolized and rapidly expired as $CO_2$ within 12 hours post dose and eliminated in the urine with a half-life of 6 hours. The fluroxypyr MHE bond is said to be readily hydrolyzed and the methylheptyl ester portion of Fluroxypyr is stated to be bioequivalent to Methylheptanol.

## III. DISCUSSION

The objective of this study was to compare the pharmacokinetics and metabolism of the methylheptyl ester portion of Fluroxypyr methylheptyl ester to that of methylheptanol. Each compound was administered as a single oral dose in corn oil at equimolar doses of 17.7 mg $^{14}$C-Methylheptanol/kg body weight and 50 mg Fluroxypyr $^{14}$C-MHE/kg body weight. The overall disposition of each compound was comparable. The total recovery of the administered dose was 105% and 104%, with the principal route of excretion being expired $^{14}CO_2$, which contained ≈61% and 63% of the radioactivity for the fluroxypyr MHE and methylheptanol balance groups, respectively. The urine contained ≈30% and 27% and the feces contained 5% and 7% of the administered dose for the Fluroxypyr MHE and Methylheptanol groups, respectively. At 48 hours post dose, ≈7% of the administered dose was recovered in the blood, carcass, and skin of both groups. The overall rates and routes of elimination were comparable between the groups. Each was extensively absorbed and rapidly eliminated. Approximately 52% and 54% of the administered Fluroxypyr MHE and Methylheptanol, respectively, was absorbed and expired as $^{14}CO_2$ within 12 hours post dose, and an additional 18% of the administered dose was excreted in the urine within 12 hours post dose. Based on the percentage of the dose in the expired $^{14}CO_2$, urine, and tissues, ≈90% of the dose was absorbed by the rats in each case. Once absorbed, both were extensively metabolized [20-22 metabolites] and rapidly expired as $^{14}CO_2$ and eliminated in the urine with a half-life of 6 hours. Fluroxypyr MHE displayed a slower absorption rate than Methylheptanol, but once absorbed, the pharmacokinetic parameters were similar. Peak plasma concentrations of $^{14}$C-radioactivity were attained by 7 and 10 hours post dose, and the half-lives for the elimination phase were ≈18.2 and 17.4 hours for Fluroxypyr MHE and Methylheptanol, respectively. It was stated that the percentage of radioactivity recovered in the tissues and carcass [≈7%] suggests $^{14}$C-incorporation into the carbon pool that may account for the longer half life in plasma as compared to the urinary half-life of 6 hours. Average area under the curve values were 140 μg eq hr/g and 163 μg eq hr/g for the Fluroxypyr MHE and Methylheptanol groups, respectively. Clearance values were comparable for these groups also [2.1 and 1.8 mL/min kg]. These pharmacokinetic parameters indicate no difference in kinetics of Methylheptanol, based on whether it is labeled alone or as part of the Fluroxypyr MHE molecule. Urine profiles were similar and indicated extensive metabolism [20-22 metabolites]. Unchanged Fluroxypyr MHE was not detected in any of the samples, and the author stated that this "is consistent with the majority of the dose metabolized to $CO_2$." The data indicate that the Fluroxypyr MHE bond is

readily hydrolyzed and that the methylheptyl ester portion of Fluroxypyr is bioequivalent to Methylheptanol.

B. Study deficiencies: None that would adversely affect study interpretation. The plasma and balance phases of the study were not described in the Methods section of the report.

**ATTACHMENTS**: Figure 3 [page 29], Figure 4 [page 30], Figure 9 [page 34] of the report

cc: LTaylor [RRB1]
7509C:RRB1:LTaylor:CM#2Rm816C:305-6486:8/19/97
RD1:BChin:9/17/97:ToxTeam: / /97

Sign-off date: 09/29/97
DP Barcode: d232550
HED DOC Number: 012328
Toxicology Branch: tb2

Sign-off date: 09/29/97
DP Barcode: d232217
HED DOC Number: 012328
Toxicology Branch: tb2



16