acceptable

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DATA EVALUATION REPORT

STUDY TYPE: 85-1; Rat General Metabolism

TOX. CHEM NO: 188AAA

MRID NO.: 42374201

TEST MATERIAL: C^{14}-Oxyfluorfen

SYNONYMS: Goal Herbicide

STUDY NUMBER: Report No. 90R-193

SPONSOR: Rohm and Haas Company

TESTING FACILITY: Toxicology Department, Rohm and Haas Co.

TITLE OF REPORT: C^{14}-Oxyfluorfen (Goal Herbicide): Pharmacokinetic Study in Rats

AUTHOR(S): L.J. DiDonato & G.A. Hazleton

REPORT ISSUED: May 26, 1992

CONCLUSION: Groups of 5/sex/dose Sprague-Dawley rats were orally dosed once with C^{14}-oxyfluorfen at three different doses: 4 mg/kg, 320 mg/kg, and, following pretreatment for 2 weeks with 40 ppm Goal Technical, were "pulse" dosed with 4 mg/kg C^{14}-oxyfluorfen. Excreta were collected up to 7 days and analyzed for radiolabel. Groups of rats were sacrificed at 6 hours and 7 days and plasma (whole blood), selected tissues, and carcasses were collected and analyzed for C^{14}-residues. In addition, groups of rats were serially bled over the 7 day period and plasma and whole blood were analyzed for C^{14}-label.

The total recovery of radioactivity was 97-99, 84-91, and 85-86% for the low-, high-, and pulse-dose groups, respectively. Most (82-98%) of the radioactivity was was excreted within 2 days and found predominately in the feces. In contrast to males, the urine of females contained 3-4 times more radiolabel than the urine of males. After 7 days only 0.1-1.4% of the radiolabel remained in

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the carcasses of males and females of all dose groups. Elimination of the radiolabel from the plasma was biphasic in both sexes of the low- and high-dose groups (rapid phase = 9-13 hours; slow phase = 26-32 hours). Radiolabel was higher in all tissues at the 6 hour period than at the 7 day sampling period. At the low- and high-dose and pulse-dose, highest concentrations were found in fat, liver, adrenal, thyroid, kidney, lung and ovaries. Pretreatment with 40 ppm for 2 weeks did not have a remarkable effect on tissue distribution of radiolabel.

Core Classification: Acceptable

REVIEW: Pharmacokinetic Study in Rats (Toxicology Department, Rohm and Haas Co., Report No. 90R-193, May 26, 1992)

Test Material: The following is a list of compounds that were used in the dosing aspect of the study:

1. C^{14}-Oxyfluorfen; Lot No. 602.0015; Specific Activity 9.12 mCi/g; 92.9% a.i.; Tox. Dept. Sample No. 90-122

2. C^{13}-Oxyfluorfen; Lot No. MWS-15-92; 94.9% a.i.; Tox. Dept. Sample No. 90-128

3. Nonradiolabeled oxyfluorfen; Lot No. RPO 8674FP; 99.4% a.i.; Tox. Dept. Sample No. 90-129

4. Nonradiolabeled Goal Technical Herbicide; Lot No. 2-0956; 71.4% a.i.; Tox. Dept. Sample No. 90-001

Methods: The absorption, distribution and excretion of C^{14}-oxyfluorfen was determined in male and female Crl:CD(Sprague-Dawley)BR rats (approximately 125-150 grams) (Charles River Kingston; Stone Ridge, NY). The experimental design for this study included three different treatments of C^{14}-oxyfluorfen: a low dose (4 mg/kg), a high dose (320 mg/kg) and a pulse-dose (dietary treatment with 40 ppm (a.i.) nonradiolabeled Goal Technical Herbicide for 2 weeks followed by a 4 mg/kg radiolabeled dose). Material balance, excretion, plasma/whole blood and tissue data were collected from groups of rats administered either low-, high-, or pulse-doses of C^{14}-oxyfluorfen. A detailed description of the experimental design is shown below:

			Dose C^{14}-oxyfluorfen		Time After C^{14}-oxyfluorfen Administration									
GP	Sx	Rte	mg/kg	n	0hr	1	3	6	10	1 d	2	3	4	7[b]
A	M	Or.	4	5	E					E	E	E	E	E,K
B	F	Or.	4	5	E					E	E	E	E	E,K
C	M	Or.	4	4		B	B	B	B	B	B	B	B	B,K*
D	F	Or.	4	4		B	B	B	B	B	B	B	B	B,K*
E	M	Or.	4	4	E			E,K[d]						
F	F	Or.	4	4	E			E,K[d]						
G	M	Or.	320	5	E					E	E	E	E	E,K
H	F	Or.	320	5	E					E	E	E	E	E,K
I	M	Or.	320	4		B	B	B	B	B	B	B	B	B,K*
J	F	Or.	320	4		B	B	B	B	B	B	B	B	B,K*
K	M	Or.	320	4	E			E,K[d]						
L	F	Or.	320	4	E			E,K[d]						
M[a]	M	Pl.	4	5	E					E	E	E	E	E,K
N[a]	F	Pl.	4	5	E					E	E	E	E	E,K

Footnotes for Study Design

E: Collect urine, urine funnel wash, and feces over dry ice for C^{14}-analysis; store remaining excreta samples frozen for metabolite identification and analysis.

B: Collect whole blood and plasma for C_{14}-analysis.

K: Kill and collect whole blood, liver, fat, kidney, bone marrow, heart, lungs, brain, testes (males), ovaries (females), muscle, spleen, adrenals, thyroids, and remaining carcass for C_{14}-analysis. Store remaining samples frozen for possible metabolite identificaton and analysis.

K*: After blood collection, animals were killed and carcasses were stored frozen.

a: These animals received 40 ppm (ai) nonradiolabeled Goal Technical Herbicide in the diet for two weeks prior to receiving a single pulse dose (oral gavage) of 4 mg/kg C_{14}-oxyfluorfen.

b: The 7 day excreta collection was a pooled sample consisting of 5, 6, and 7 day excreta.

c: All animals were dosed orally by gavage at 5 ml/kg (corn oil).

d: Animals in Groups E, F, K, and L were killed when peak C^{14}-concentrations occurred in plasma, pending the results of Groups C, D, I, and J. Whole blood and other tissues (described in item "K") plus excreta were collected and analyzed for C_{14}-label, and then stored frozen for possible identification and analysis.

The C^{14}-metabolite analysis will be conducted by the Residue Metabolism and Environmental Fate Department of the Rohm and Haas Company and will be presented in a separate report.

The dose solution (0.8 mg/ml) for the low-, and pulse-dose groups (Groups A, B, C, D, E, F, M, and N) was prepared by dissolving 1 part C^{14}-oxyfluorfen and 1 part C^{13}-oxyfluorfen in acetone. Subsequently, the acetone was evaporated under nitrogen, and a known volume of corn oil was added.

The dose solution (64 mg/ml) for the high-dose groups (Groups G, H, I, J, K, and L) was prepared by dissolving 1 part C^{14}-oxyfluorfen and 5 parts C^{13}-oxyfluorfen* and 4 parts nonradiolabeled analytically pure oxyfluorfen in acetone. Subsequently, the acetone was evaporated and the correct amount of corn oil was added. Both dosing solutions were warmed to 37° C prior to dosing. The 0.8 mg/ml and 64 mg/ml dose solutions were used to dose the 4 mg/kg and 320 mg/kg dose groups, respectively.

The diet, used for the two-week pretreatment of pulse-dose Groups M and N, was prepared by dissolving nonradioactive Goal Technical Herbicide (71.4% a.i.) in acetone and mixing with a small amount of feed. This premix was then brought to an appropriate weight with additional untreated feed. The diet was analyzed for concentration and was found to be 96.7% of the target dietary concentration of 40 ppm a.i. Over the 2 week feeding period the average compound intake for males and females was 3-5 mg a.i. per kg per day.

* C^{13}-oxyfluorfen was included in the dose preparation to assist in the metabolite identification phase of the project. The results of the metabolite identification and analysis will be submitted as an addendum to this pharmacokinetic study.

The C^{14}-oxyfluorfen dose solutions were administered orally by gavage (5 ml/kg) to 6 groups of rats (males, Groups A, C, E; and females, Groups B, D, F) at 4 mg/kg and 6 groups of rats (males, G, I, K; and females, Groups H, J, L) at 320 mg/kg. Two additional groups of rats (males Group M; and females Group N) received nonradiolabeled Goal Technical in the diet at 40 ppm for 2 weeks prior to receiving a "pulse" oral dose (5 ml/kg) of 4 mg/kg C^{14}-oxyfluorfen.

For Groups A, B, G, H, M, and N, urine and feces were collected at intervals up to 7 days after dose administration and analyzed for C^{14}-label. All rats in these groups were killed after 7 days and whole blood (plasma), liver, fat, kidney, bone marrow, heart, lungs, brain, testes (males), ovaries (female), muscle, spleen, adrenals, and thyroids were removed and analyzed for C^{14}-label. In addition, the remaining carcasses were collected for C^{14}-analysis. For Groups C, D, I, and J, whole blood and plasma were collected at intervals up to and including 7 days after dose administration and analyzed for C^{14}-label. All rats in these groups wre killed after 7 days and tissues and carcass were discarded. Rats in Groups E, F, K, and L were killed at 6 hours after dose administration when plasma C^{14}-concentrations were near or at peak levels. In these animals, tissues (previously described) and remaining carcasses were collected and analyzed for C^{14}-label.

The half-lives of elimination of C^{14}-label from whole blood and plasma were calculated using the equation: half-life ($t_{1/2}$ = ln $2/k_{el}$. The rate constants of elimination (k_{el}), were designated α (for rapid phase) and β (for slow phase), and were determined by linear regression analysis on time course data (i.e., ln (ppm) plotted against time).

RESULTS: There were no treatment-related deaths or toxic signs during the study. The table below shows the material balance for recovery of C^{14}-label

7-Day Recovery of C^{14}-Label from Rats Given a Single Oral Dose or Pulse-Dose of C^{14}-Oxyfluorfen*

Dose(mg/kg)	4 M	4 F	320 M	320 F	4 M Pl	4 F Pl
Urine	10.27	24.71	5.11	25.11	9.94	18.61
UFW	0.96	2.09	0.76	1.90	0.77	1.38
Feces	87.00	68.63	77.49	63.31	71.37	63.59
Cage Wash	0.07	0.08	0.10	0.12	0.07	0.10
Whole Blood	0.07	0.06	0.02	0.02	0.04	0.01
Tissues	0.45	0.40	0.18	0.12	0.77	0.43
Carcass	0.76	0.70	0.68	0.45	1.38	0.50
Total	99.58	96.71	84.34	91.02	85.40	86.10

* values represent percent of administered dose

UFW = Urine Funnel Wash

Pl = pulse-dose

The overall recovery of radioactivity in both low-dose sexes were comparable (99.6% and 96.7% for males ans females, respectively) with the most recovery in the excreta after 7 days (feces, urine and UFW). The overall recovery in the high-dose was 84.3% in male and 91.0% in females with the C^{14}-label located in the excreta. There was only small amounts of radiolabel in the tissues or carcass (0.12-0.45% in tissues and 0.45-0.76% in carcasses). Similarly, in the pulse-dose, recovery in males and females was 85.4% and 86.1% and most of the radiolabel was found in the excreta, with minor amounts found in the tissues collected (.4-.8%) and remaining carcass (0.5-1.5%). In both the low- and high-dose, and pulse-dose groups, 82-95% of the excreted dose was eliminated in the first 2 days.

Although the data are not tabulated in the review, the report states that in the low- and high-dose groups, the highest C^{14}-concentrations in plasma occurred at 6 and 6-24 hours, respectively, and declined thereafter. Elimination of the C^{14}-label from the plasma was biphasic in both sexes of the low- and high-dose groups (rapid phase = 9-13 hours; slow phase = 26-32 hours). The following table from the report shows the half-lives in plasma and whole blood.

Dose (mg/kg)	Sex	$T_{1/2}$ (hr)* Plasma Rapid phase	Plasma Slow phase	Whole Blood Rapid phase	Whole Blood Slow phase
4	M	12.5	31.9	13.9	78.9
4	F	8.5	29.2	12.3	63.0
320	M	13.1	26.1	13.9	45.9
320	F	10.0	32.4	12.3	79.4

* Half life ($t_{1/2}$) for rapid phase of elimination = $\ln 2/\alpha$
  Half life ($t_{1/2}$) for slow phase of elimination = $\ln 2/\beta$

Tissue concentrations of C^{14}-label were higher at the 6 hour sampling period than at 7 days in the low- and high-dose groups. A total of 4-6 and 3% of the administered dose was present in the tissues collected at 6 hour in the low- and high-dose groups, respectively. At the end of 7 days, 0.4-0.5 and 0.1-0.2% of the administered dose was observed in the tissues from the low- and high-dose groups, respectively. In males and females of the pulse-dose group, 0.4-0.8% of the administered dose was observed in tissues at 7 days. In the table shown below, the tissue distribution of C^{14}-label in males and females at 7 days is presented.

7 Day Tissue C^{14}-Concentration in Rats Given a Single Oral or Pulse Dose of C^{14}-Oxyfluorfen*

Dose(mg/kg)	4 M	4 F	320 M	320 F	4 M PL	4 F PL
Liver	.277	.271	7.034	4.266	.290	.225
Kidney	.174	.103	6.949	2.938	.167	.105
Heart	.021	.017	1.138	1.108	.097	.054
Lung	.136	.149	2.808	2.581	.601	.616
Testes	.022	-	0.748	-	.020	-
Ovaries	-	.157	-	6.620	-	.227
Fat	.267	.373	25.728	23.820	.820	.356
Brain	.010	.006	.396	.551	.020	.016
Muscle	.002	.000	.273	.507	.010	.001
Spleen	.022	.022	.977	.832	.039	.039
Adrenals	1.181	.340	4.550	4.923	.406	.174
Thyroid	.169	.252	3.878	2.590	.126	.071
Bone Marrow	.044	.057	0.859	.780	.029	.007

* = Values represent ppm (μg equivalent per gram wet weight tissue)

PL = pulse-dose

At the low- and high-dose and pulse-dose, highest levels were found in the adrenals, fat, ovaries, thyroid, liver, kidney and lung.

Lowest levels were found in the brain, muscle, spleen, bone marrow, heart, and testes.

It can be seen from a comparison of the low-dose with the pulse-dose that the overall distibution of C^{14}-label in tissues was not significantly altered by pre-dosing the rats for 2 weeks with 40 ppm (a.i.) Goal Technical Herbicide in their diet.

There were signed and dated statements of Quality Assurance and Good Laboratory Practice Compliance.