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HASKELL LABORATORY REPORT NO. 62-82 [redacted]

Material Tested*	Haskell No.	Other Codes
Octanoic acid, pentadecafluoro-, ammonium salt (carbonyl ^{14}C-labelled)	14,129	[redacted]

Study Initiated/Completed
6/23/81-9/27/81

Material Submitted by
[redacted]
Polymer Products Department
D-11070

EXCRETION AND DISPOSITION OF ^{14}C-AMMONIUM PERFLUOROOCTANOATE IN MALE AND FEMALE RATS, MICE, HAMSTERS, AND RABBITS

Summary: Sex and species differences in the excretion and disposition of ^{14}C-labelled ammonium perfluorooctanoate (C-8) were observed in the present study. Substantial sex differences in rats and hamsters were observed in the excretion of ^{14}C activity following a single oral dose of ^{14}C-labelled C-8. The female rat and the male hamster excreted over 99 percent of the original ^{14}C activity by 120 hours after dosing, conversely the male rat and the female hamster excreted 39 and 60 percent of the original ^{14}C activity, respectively, by 120 hours post-dosing. Both sexes of rabbits excreted the ^{14}C activity as rapidly and completely as the female rat and the male hamster. The male and female mice excreted only 21 percent of the original ^{14}C activity by 120 hours post-dosing.

The rapid excretors (female rat, male hamster, and male and female rabbit) contained negligible amounts of ^{14}C in organs and tissues at sacrifice. The slow excretors exhibited the highest ^{14}C concentrations in the blood and liver with substantial levels in the kidneys, lungs and skin.

Introduction: The excretion of perfluorooctanoate (C-8) has been shown to differ substantially between male and female rats (1). Female rats excreted over 90 percent of a single dose by 24 hours after dosing. Male rats excreted only 50 percent of the dose by 4 days after dosing and 15 percent of the dose was still in male rats 32 days after dosing. The purpose of the present study was to make a preliminary examination of the excretion and

disposition of ^{14}C-labelled C-8 after administration to male and female rats, mice, hamsters and rabbits. The results should indicate whether sex differences for the excretion and disposition of C-8 occur in species other than the rat.

Procedures: The ^{14}C-labelled C-8 was obtained from 3M Company as the ammonium salt. The compound was labelled on the carbonyl position and had a specific activity of 0.5 μ Ci/mg. The compound was 70 percent straight-chained C-8 and 30 percent branched C-8 isomers. The radiolabelled compound was readily water soluble, therefore water was used as the dosing vehicle.

A male and a female of each species received a single 10 mg/kg oral gavage dose of ^{14}C-labelled C-8. The rats, mice and hamsters were housed individually in glass metabolism units immediately after dosing. House vacuum was used to generate a 500 mL/min/airflow through the metabolism units. The incoming air was passed initially through successive Drierite®- and Ascarite®-filled glass columns to remove water and CO_2, respectively. The air leaving the metabolism unit was passed successively through two gas scrubbing bottles, each containing 250 mL (150 mL for mice) 2N NaOH for trapping expired CO_2. The 2N NaOH solutions were changed 12, 24, 48, 72, 96 and 120 hours after dosing. Urine and feces were collected at the same time intervals.

The male and female rabbits were individually housed in stainless steel metabolism cages immediately after dosing. Urine and feces were collected 24, 48, 72, 96, 120, 144 and 168 hours after dosing. Expired CO_2 was not trapped from the rabbits. Blood was withdrawn from the rabbits by cardiac puncture 168 hours after dosing. The rabbits were sacrificed in a CO_2 chamber following cardiac puncture. The rabbit blood was heparinized and refrigerated in small Nalgene® bottles.

The rats, mice and hamsters were all sacrificed 120 hours after dosing by chloroform exposure. Blood was drawn by heart puncture upon sacrifice and refrigerated in heparinized tubes. All animals were dissected with the following tissues excised, weighed and frozen: heart, lungs, liver, kidneys, spleen, testes or ovaries, brain, G. I. tract, and muscle, skin and fat samples. The carcasses were then weighed and frozen. Metabolism units (glass and stainless steel) were washed in succession with dilute detergent, water, and acetone. The cage washes were collected in Nalgene® bottles and refrigerated.

Urine, CO_2-trapping solutions, and cage washes were analyzed directly for ^{14}C radioactivity using an Intertechnique SL4000 liquid scintillation counter. Blood, feces, tissue, organ and homogenized carcass samples were analyzed for ^{14}C content by tissue oxidation using a Packard Model 306 Tissue Oxidizer and liquid scintillation counter. Rabbit carcasses were not analyzed for ^{14}C content.

Results: The distribution data of ^{14}C activity are presented in Table 1. The male rat, female hamster, and both sexes of mice retained substantial amounts of the total administered radioactivity in their tissues at the time of sacrifice. In contrast, the female rat, the male hamster and both sexes of rabbit contained only a fraction of a percent of the original dose in their tissues at sacrifice. Urine was the primary route of excretion in all species except the mouse. The percent of dose excreted as ^{14}C-labelled CO_2 ranged from 1.3 to 5.2 percent in both sexes of rat, mouse and hamster.

The total urinary and fecal excretion of ^{14}C activity was expressed as a cumulative percent of the total dose and plotted against collection time. The profiles for rats and hamsters are presented in Figure 1 and reveal striking sex differences. The male rat and the female hamster exhibited a slow steady increment for excretion over the 120 hour post-dosing period. The female rat and the male hamster exhibited a rapid rate for excretion. By 48 hours the female rat had excreted almost the entire dose in the urine and feces and the male hamster excreted over 95 percent of the original dose in the same time span.

Substantial species differences for excretion of ^{14}C activity are reflected in Figure 2 which compares the cumulative urine and feces excretion between mice and rabbits. The mice excreted only 11 percent of the total dose in the urine and feces by 120 hours after dosing. By 24 hours the male and the female rabbit had excreted 78 and 86 percent of the dose, respectively, in the urine and feces. After 48 hours post-dosing the increment of increase in the rabbit urine and feces was negligible. The profiles presented in Figures 1 and 2 depict the animals as either rapid or slow excretors. The female rat, the male hamster and both sexes of rabbit would be in the former category while the male rat, the female hamster and both sexes of mice occupy the latter category.

Tissue distribution of ^{14}C activity was determined and expressed as µg equivalents of ^{14}C-labelled C-8 per gram (mL) tissue. These data are presented in Table 2 and reflect negligible tissue levels in the rapid excretors. The slow excretors exhibited the highest tissue levels in the liver and blood with measureable levels present in all other tissues. Preferential sequestering of ^{14}C-labelled C-8 in the fat was not observed in any of the animals on study. The lowest limit of accurate detection was 0.1 µg equivalent per gram of tissue due to the low specific radioactivity of ^{14}C-labelled C-8.

Conclusion: The data indicated substantial sex or species differences with regard to C-8 excretion and disposition. In general the animals on study can be classified as either slow or rapid excretors of C-8. Mathematical evaluations of the excretion rate were not performed because only one animal of each sex and species was used in the study. However, the observed differences were very substantial and indicative of the sex and species differences which can occur for C-8 excretion. Clearly, the excretion rate for C-8 cannot be predicted for either sex of an unexamined species. The biochemical mechanism(s) for the observed sex and species differences in elimination and disposition of C-8 remain to be elucidated.

Reference:

1. Dow Chemical Company (personal communication).

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* Synonyms: o Ammonium perfluorooctanoate
o C-8
[redacted]

Contaminants: [redacted]

Purity: [redacted]

CAS Registry No.: [redacted]

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TABLE 1

Distribution of ^{14}C Activity Following ^{14}C-Labelled C-8 Administration to Both Sexes of Rats, Mice, Hamsters and Rabbits

Percent of Original Dose[(a)]

	Rat		Mouse		Hamster		Rabbit	
Sample	Male	Female	Male	Female	Male	Female	Male	Female
Urine	25.6	73.9	3.4	6.7	90.3	45.3	76.8	87.9
Feces	9.2	27.8	8.3	5.4	8.2	9.3	4.2	4.6
Tissues	59.6	0.6	73.6	50.0	0.7	26.5	<0.1	0.3
CO_2	3.5	1.5	5.2	4.	1.3	2.9	(b)	-
Cage Wash	0.6	0.8	4.9	4.9	0.6	2.1	0.5	4.8

(a) Each animal received a single 10 mg/kg oral gavage dose of ^{14}C-labelled C-8. The rats, mice, and hamsters were held 120 hours and the rabbits 169 hours after dosing.

(b) Expired CO_2 was not collected for the rabbits.

TABLE 2

Tissue Distribution of ^{14}C-Radioactivity From Both Sexes of Rats, Mice, Hamsters and Rabbits Dosed With ^{14}C-Labelled C-8[a]

µg Equivalent per g(mL) Wet Weight[b]

	Rat		Mouse		Hamster		Rabbit	
Sample	Male	Female	Male	Female	Male	Female	Male	Female
Blood	23.5	<0.1	13.8	10.1	0.1	8.8	<0.1	0.1
Liver	40.0	<0.1	43.2	45.3	0.3	7.3	0.1	1.5
Kidneys	24.0	<0.1	2.9*	2.2*	0.2	7.1	0.1	0.4
Lungs	6.7	<0.1	1.4*	1.3*	<0.1	3.8	<0.1	0.1
Heart	6.4	<0.1	1.2*	0.6*	<0.1	2.9	<0.1	<0.1
Skin	4.8	<0.1	3.5	3.2	<0.1	3.4	<0.1	<0.1
Testes	3.2	-	0.9*	-	<0.1	-	<0.1	-
Muscle	1.9	<0.1	1.1	0.5	<0.1	0.9	<0.1	<0.1
Fat	1.7	<0.1	1.6	1.3	<0.1	1.5	<0.1	<0.1
Brain	0.6	<0.1	0.2*	0.8*	<0.1	0.3	<0.1	<0.1

(a) The rabbits were sacrificed 168 hours after dosing, all other animals were sacrificed 120 hours after dosing.

(b) The µg equivalent calculations were based upon the specific activity of ^{14}C-labelled C-8 which was 1.1×10^6 DPM/mg. The µg equivalent per g wet weight could not accurately be determined below 0.1 µg/g.

* Represents the µg equivalents for the entire organ.

FIGURE 1

Cumulative Urinary and Fecal
Excretion of ^{14}C Radioactivity in Rats and Hamsters

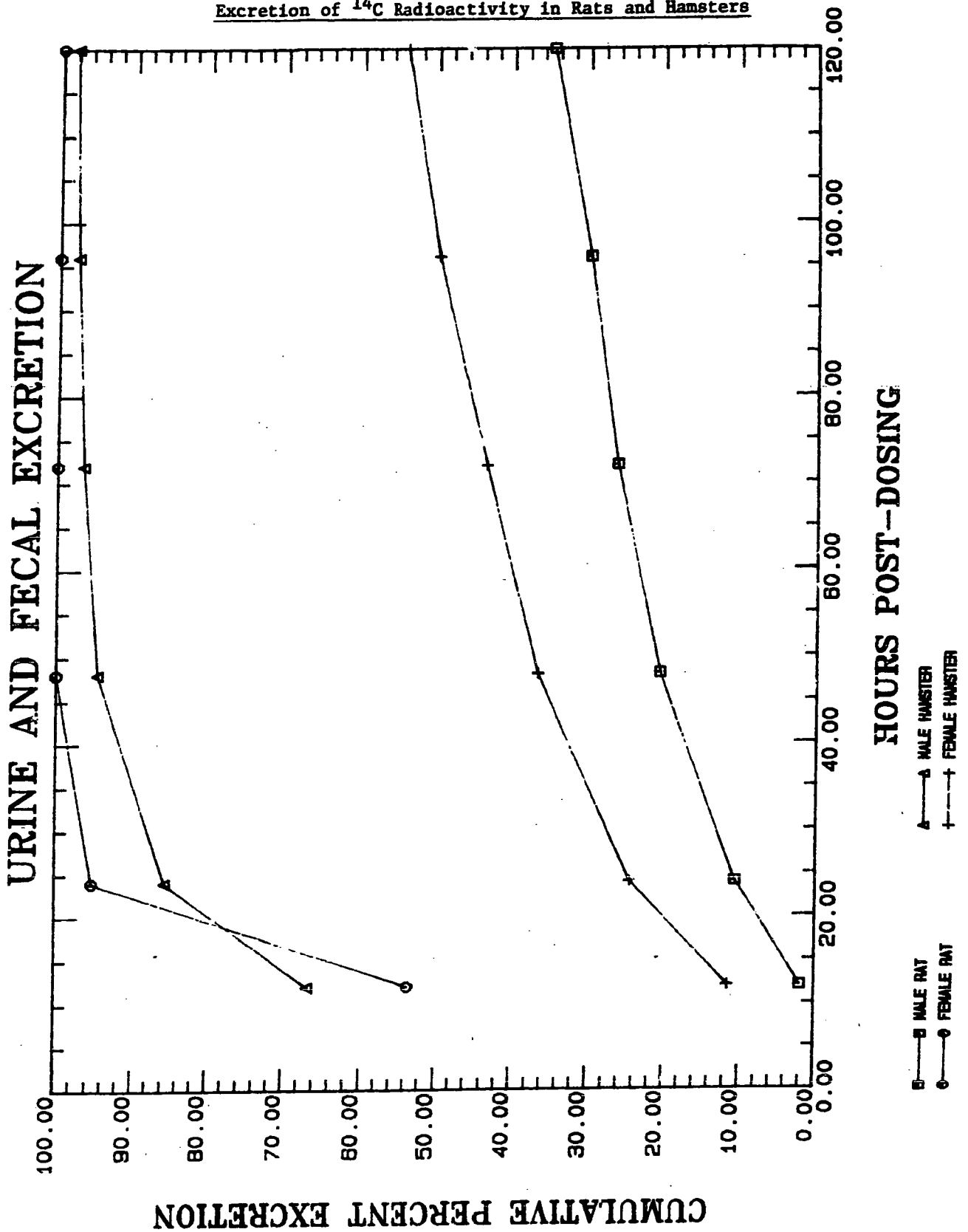

FIGURE 2

Cumulative Urinary and Fecal
Excretion of ^{14}C Radioactivity in Mice and Rabbits