FOR DU PONT USE ONLY

Copies to: [redacted]

E. I. du Pont de Nemours and Co., Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P. O. Box 50,
Newark, Delaware 19711

HASKELL LABORATORY REPORT NO. 61-82 MR NO. [redacted]

Material Tested	Haskell No.	Other Codes
Octanoic acid, pentadecafluoro-, ammonium salt (carbonyl ^{14}C-labelled)	14,129	None

Study Initiated/Completed
10/15/81-11/13/81

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

PLACENTAL TRANSFER OF ^{14}C-LABELLED C-8 IN THE RAT

Summary: Radioactive ^{14}C-labelled perfluorooctanoate (C-8) was transferred from maternal blood to the fetuses of pregnant rats. A single 10 mg/kg dose of ^{14}C-labelled C-8 was administered orally by gavage to the pregnant dams on the 19th day of gestation. Maternal blood and placental levels of ^{14}C-labelled C-8 increased between 2 and 4 hours after dosing then decreased between 4 and 8 hours after dosing. The µg equivalents of ^{14}C-labelled C-8 per mL of maternal blood were approximately 12 µg/mL at 2 hours, 20 µg/mL at 4 hours and 12 µg/mL at 8 hours after dosing. The fetal levels were 0.7 µg/g tissue at 2 hours, 3 µg/g tissue at 4 hours and approximately 3 µg/g tissue at 8 hours after dosing. All other tissues from the pregnant dams were examined for ^{14}C activity and exhibited trends similar to maternal blood, increasing between 2 and 4 hours and decreasing between 4 and 8 hours after dosing. The data reflected only minimal impedence for transfer of ^{14}C-labelled C-8 from maternal blood to the fetuses.

Introduction: The study was designed to evaluate placental transfer of ^{14}C-labelled C-8 in the rat. Data regarding placental transfer of C-8 may be useful for evaluating data from teratological studies.

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 uCi/mg. The compound was 70 percent straight chained C-8 and 30 percent branched isomers. The radiolabelled compound was readily water soluble, therefore water was used as the dosing vehicle. The dose was formulated immediately prior to dosing. The pregnant female rats

received a single 10 mg/kg dose of ^{14}C-labelled C-8 orally by gavage on the 19th day of gestation. The rats were individually placed in glass metabolism units immediately after dosing. Two rats were sacrificed at each time interval of 2, 4, and 8 hours after dosing.

Rats were sacrificed by exposure to chloroform. Blood was drawn by cardiac puncture at sacrifice and refrigerated in heparinized tubes. The placentas, umbilical cords and fetuses were then removed and dissected from each other and weighed. The umbilical cords and placentas were individually placed into paper combustion cones and fetuses stored frozen. The following organs and tissues were also excised, weighed, and frozen: heart, lungs, liver, spleen, kidneys, G. I. tract, amnionic sac, brain, and fat, skin, and muscle samples. The carcasses were also weighed and frozen. Urine and fecal samples excreted between dosing and sacrifice were collected and frozen. The metabolism units were washed successively with dilute detergent, water, and acetone. The washes were collected and stored in Nalgene® bottles.

The placentas, umbilical cords and fetuses were oxidized in their entirety using a Packard Model 306 Sample Oxidizer. Samples of the maternal tissues, carcass and feces were also oxidized and analyzed for ^{14}C activity by liquid scintillation counting with an Intertechnique SL4000 Scintillation Counter. The urine and cage washes were analyzed directly by liquid scintillation counting.

Results: The data in Table 1 were expressed as µg equivalents of ^{14}C-labelled C-8 per gram wet weight of tissue for the placentas and fetuses. The µg equivalent levels in the placentas increased between the 2- and 4-hour sacrifice points and then decreased between the 4- and 8-hour sacrifice points. The placental values were higher than the corresponding fetal values at each time point, however, the magnitude of the difference was much greater at the 2-hour point than at the 4- and 8-hour points. The fetal levels were approximately 0.7 µg equivalents/gram wet weight at the 2-hour point, then increased substantially (4 fold increase) by the 4-hour point to an approximate average value of 3 µg equivalents per gram wet weight. The fetal values remained constant between the 4- and 8-hour points. The number of viable fetuses per animal had no effect on the µg equivalents observed.

The average values for the placental and fetal µg equivalents were compared to the corresponding maternal blood values. The data in Table 2 show the maternal µg equivalent levels increasing from 14 to approximately 22 µg equivalents/mL between the 2- and 4-hour sacrifice points. The blood levels then decreased to approximately 12 µg equivalents/mL between the 4- and 8-hour time points. The most revealing data were the maternal blood/fetal ratios for each animal at the different time points. The ratio dropped substantially from an average of 22 to 8 between the 2- and 4-hour sacrifice points. These data reflected the greater fold increase in the fetal µg equivalent concentrations compared to the increase observed in the maternal blood. The ratio also diminished somewhat between the 4- and 8-hour time points reflecting the decrease in maternal blood levels while fetal levels remained unchanged.

The fetal and placental µg equivalent concentrations were also compared in Table 3 to other tissue levels. The kidneys and liver had the highest µg equivalent level regardless of the time point. The ug equivalent levels in all tissues and organs tended to increase between 2 and 4 hours then decreased between 4 and 8 hours. The fetal levels were lower at the 2-hour sacrifice than other tissues presented in Table 3. By the 4-hour sacrifice the fetal concentrations were similar to the concentrations observed in the spleen, heart, and fat. The fetal levels were similar to the heart and lungs at the eight-hour sacrifice. The magnitude of the µg equivalent concentration increase was far greater in the fetal tissue than any other organ or tissue examined.

Conclusion: Placental transfer of ^{14}C-labelled C-8 was shown to occur after administration of a single oral dose of ^{14}C-labelled C-8. The comparison of fetal levels of C-8 at 2 and 4 hours relative to the concentrations observed in the maternal blood, placenta and other organs revealed evidence of resistance to placental transfer of C-8. However, by 4 hours the fetal concentrations of C-8 increased substantially more than all other organs and tissues examined. In contrast to other tissues examined, C-8 levels in the fetuses did not decrease between 4 and 8 hours. The peak fetal C-8 concentrations were similar in magnitude to the levels observed in the spleen, heart, lungs and fat. Significant quantities of C-8 can therefore be transferred from the placenta to the fetus with the placental barrier offering minimal resistance to transfer.

---

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

Contaminants:
- o [redacted]
- o [redacted]

Purity: [redacted]

CAS Registry No.: 3825-26-1

Report by: Stephen Hundley
Stephen G. Hundley
Research Biochemist

Approved by: R W Hartgrove Jr.
Ralph W. Hartgrove
Section Supervisor
Biochemical Toxicology

SGH:tac:WF:3.2
Date Issued: May 18, 1982
[redacted]
Report No. 61-82

TABLE 1

^{14}C-Labelled C-8 Concentrations in Placentas and Fetuses from Pregnant Rats Dosed Once Orally with [^{14}C] C-8

Rat# and Time Point		µg Equivalents Per Gram Wet Weight* Placentas (Ave. + S.D.)	Fetuses (Ave. + S.D.)
Rat #1	2 hours	4.8 ± 0.5 (12)[a]	0.6 ± 0.1 (13)
Rat #2	2 hours	6.1 ± 0.5 (4)	0.7 ± 0.1 (4)
Rat #1	4 hours	10.1 ± 0.6 (6)	3.6 ± 0.4 (6)
Rat #2	4 hours	7.0 ± 0.5 (8)	2.4 ± 0.1 (9)
Rat #1	8 hours	5.1 ± 0.6 (11)	3.5 ± 0.4 (11)
Rat #2	8 hours	4.9 ± 0.4 (13)	2.5 ± 0.2 (13)

* µg Equivalents were based on 1.1×10^6 DPM/mg as the specific ^{14}C activity for [^{14}C] C-8.

[a] Numbers in parentheses indicate the number of placentas or fetuses.

TABLE 2

Comparison of the µg Equivalents of ^{14}C-Labelled C-8 in the Maternal Blood, Placenta and Fetus

Rat & Time Point	µg Equivalents/g (mL) Maternal Blood	Placenta*	Fetus	Maternal Blood/ Fetal Ratio
Rat #1 2 hours	14.7	4.8	0.6	23
Rat #2 2 hours	14.2	6.1	0.7	21
Rat #1 4 hours	25.3	10.1	3.6	7
Rat #2 4 hours	19.4	7.0	2.4	8
Rat #1 8 hours	13.4	5.1	3.5	4
Rat #2 8 hours	11.7	4.9	2.5	5

* The placenta and fetus values are the averages from the total number of placentas and fetuses in each animal.

TABLE 3

Internal Distribution of ^{14}C-Labelled C-8 in Pregnant Female Rats Following a Single Oral Dose

μg Equivalents [^{14}C] C-8 Per Gram Wet Weight[a]

Tissue	2 Hours		4 Hours		8 Hours	
	Rat #1	Rat #2	Rat #1	Rat #2	Rat #1	Rat #2
Liver	17.5	14.3	21.9	13.3	9.5	8.5
Kidneys	20.2	22.8	40.1	21.2	17.0	14.6
Heart	3.9	4.6	5.5	3.9	3.1	2.8
Lungs	5.8	5.4	9.8	7.0	3.9	3.0
Skin	3.3	3.7	7.1	4.8	2.8	1.9
Spleen	2.0	1.8	3.2	2.0	1.3	1.3
Fat	0.9	1.9	5.1	2.0	2.8	0.6
Placenta*	4.8	6.1	10.1	7.0	5.1	4.9
Fetus*	0.6	0.7	3.6	2.4	3.5	2.5

---

a The μg equivalents were based upon the specific activity of ^{14}C-labelled C-8, 1.1×10^6 DPM/mg.

* The values for the placenta and fetus are averages from the total number of placentas and fetuses found in each pregnant rat.