

TRADE SECRET

Study Title

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

Laboratory Project ID: DuPont-2924

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STUDY COMPLETED ON: August 3, 2000

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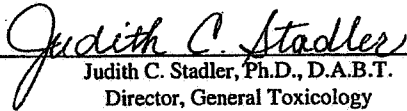
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CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

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STUDY INFORMATION

TEST SUBSTANCE:

Substance Tested: [REDACTED]

Synonyms/Codes: H-24001
[REDACTED]

Haskell Number: 24001

Composition: [REDACTED]

Known Impurities: Unknown

POSITIVE CONTROL:

Substance Tested: [REDACTED]

Synonyms/Codes: H-24019
[REDACTED]

Haskell Number: 24019

Composition: [REDACTED]

Known Impurities: Unknown

POSITIVE CONTROL:

Substance Tested: [REDACTED]

Synonyms/Codes: • H-24020

Haskell Number: 24020

Composition: [REDACTED]

Known Impurities: Unknown

Sponsor: E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Initiated/Completed: April 30, 1999 / (see report cover page)

In-Life Initiated/Completed: May 30, 1999 / August 30, 1999

STUDY PERSONNEL

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SUMMARY

The objective of this study was to evaluate the potential for H-24001, when administered by gavage, to be absorbed and to accumulate in a mammalian system. Six groups of 5 male Crl:CD[®](SD)IGS BR rats each were exposed to 1000 mg/kg/day of H-24001. The test substance was administered to one group of five rats for 5 consecutive days and to 5 groups for 10 days. Approximately two hours after the first dose, blood was collected from the orbital sinus of each rat from the 5-dose group. On selected days (5, 10, 13, 24, 52, 93/94) 5 rats per group were euthanized and the blood and livers were collected. Body weights and clinical signs were recorded on each day of dosing and then approximately every other week during the recovery period. Additionally, 2 negative controls, corn oil and corn oil/acetone (80:20), and 2 positive controls, H-24019 (10 mg/kg/day) and H-24020 (20 mg/kg/day), were tested as described for H-24001.

No deaths occurred during the study. No compound-related clinical signs of toxicity were observed in the rats dosed with H-24001. Rats dosed with a positive control material, H-24019, exhibited diarrhea, salivation, alopecia, black ocular discharge, and staining of various parts of the body during the dosing period. Rats dosed with H-24020, the other positive control substance, exhibited wet perineum and diarrhea during the dosing period. Alopecia was observed during the recovery period for rats dosed with H-24001, H-24019, and H-24020. The negative control rats exhibited no clinical signs during the study.

Comparison of body weights was complicated by a difference in age on test day 1 between the rats dosed with the test substance and those dosed with the positive or negative controls. Accounting for the age difference at study start and the expected rate of body weight gain, the mean body weights and mean body weight gains of the rats dosed with H-24001 were comparable to the negative controls and equal to or greater than the positive controls.

A steady-state for fluorine levels in whole blood was not achieved during 10 consecutive days of dosing with 1000 mg/kg H-24001. An area under the curve (estimated to infinity) was calculated and normalized for fluorine content for the test substance and each positive control. The AUCINF/D for the fluorine component of H-24001 was 1750, compared to AUCINF/D values of 566,479.1 and 70,789.6 for H-24019 and H-24020, respectively.

Under the conditions of this study, administration of H-24001 to male rats for 10 consecutive days resulted in limited absorption and retention of fluorine in the blood. Dose-adjusted areas under the curve (AUCINF/D) for positive controls, H-24019 and H-24020, were approximately 320x and 40x the AUCINF/D for the test substance.

INTRODUCTION

The objective of this study was to define the potential of H-24001 to be absorbed and to bioaccumulate in a mammalian system, as indicated by analytical determination of total fluorine in blood and liver. The test substance was compared to two positive controls that were materials previously shown to bioaccumulate in mammals.

The daily dosage for the test substance was selected based on available toxicity data and the results of a rangefinding study. In the rangefinding study, a group of 5 male rats was dosed by oral gavage with H-24001 at a dosage of 2000 mg/kg for 5 consecutive days. A group of 5 male rats was dosed with deionized water for 5 consecutive days and served as controls. The rats dosed with H-24001 experienced an overall mean body weight gain of 13 grams. The control group had an overall mean body weight gain of 27 grams.

A dosage of 1000 mg/kg was selected for the limit dosage for this project. The limit dosage of 1000 mg/kg was chosen for the main study and was expected to produce less than a 10% difference in mean body weight over 10 days when compared to controls.

All blood samples were analyzed for total fluorine content. This report contains the results of those analyses. Results from analyses of selected liver samples will be presented in a supplemental report.

MATERIALS AND METHODS

A. Test Substance and Positive Control

The test substance, H-24001, was supplied by the sponsor as an amber-brown liquid. The positive controls, H-24019 and H-24020, were supplied by the sponsor as white solids. The test substance and positive controls appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

B. Test Species

Male Crl:CD[®](SD)IGS BR rats were received from Charles River Laboratories, Inc., Raleigh, North Carolina. The Crl:CD[®](SD)IGS BR rat was selected on the basis of extensive experience with this strain and its suitability with respect to longevity, hardiness, sensitivity, and low incidence of spontaneous diseases.

C. Animal Husbandry

1. Housing Environment

Rats were housed singly in stainless steel, wire-mesh cages suspended above cage boards. Animal rooms were maintained on an approximate 12-hour light/dark cycle (fluorescent light) and at a temperature of $23 \pm 1^\circ\text{C}$ and a relative humidity of $50 \pm 10\%$. Occasional excursions outside the accepted ranges were minor and did not affect the study.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI Nutrition International, Inc. Certified Rodent LabDiet® 5002 chow. The feed is guaranteed by the manufacturer to meet specified nutritional requirements and to be free of specified contaminants.

3. Identification

Prior to assignment to groups, each rat was temporarily identified by cage identification. After assignment to groups, an individual identification number was marked or tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number assigned to each rat.

4. Animal Health Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to assure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian.

D. Quarantine and Pretest

Upon arrival at Haskell Laboratory, the rats were removed from shipping cartons and quarantined for 6 days. The rats were weighed 3 times during the pretest period and examined daily for any clinically apparent signs of disease or injury. The rats were observed daily for mortality and signs of illness, injury, or abnormal behavior.

On the bases of acceptable body weight gains and freedom from clinically apparent signs of disease or injury, the rats were released from quarantine by the laboratory animal veterinarian or designee.

E. Study Design

Substance	Vehicle	Dosage (mg/kg)	Number of Animals
Negative Controls	Not applicable		
Corn oil		0	30
Corn oil:acetone		0	30
Positive Controls	Corn oil: acetone		
H-24019		10	30
H-24020		20	30
Test Substance	None		
H-24001		1000	30

F. Assignment to Groups and Study Start

After the quarantine period, the rats were selected on the bases of adequate body weight gain, freedom from any clinical signs of disease or injury, and a body weight within $\pm 20\%$ of the mean. The selected rats were divided by computerized, stratified randomization into 6 groups of 5 rats, so that there were no statistically significant differences among group body weight means.

After assignment to groups, each rat was housed individually. The last 3 digits of the animal number was marked or tattooed on the tail of each rat. The rats were between 7 and 9 weeks of age at the time of dosing. Dosing began on test day 1.

Rats that were not assigned to the study were released for other laboratory purposes, or were sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation.

G. Dosing Material Preparation and Administration

1. Test Substance

H-24001 was dosed as received. The amount of test substance each rat received was based on the body weight collected on each day of dosing and the test substance density of 1150 mg/mL. The test substance was stirred on a magnetic stir plate throughout the dosing procedure.

2. Positive Controls

The solid positive control materials were suspended as emulsions in their respective vehicles. Corn oil was used as the vehicle for H-24020. It was necessary to dissolve H-24019 in acetone before suspending it in corn oil. The ratio of acetone to corn oil was 20:80. The amount each rat received was based on the body weight collected on each day of dosing and the suspension concentration. The dose volumes did not exceed 1 mL/100 g of body weight. The dosing suspensions were stirred on a magnetic stir plate throughout the dosing procedure to maintain homogeneity.

3. Negative Controls

Corn oil and corn oil:acetone (80:20) were chosen as the negative controls because they were the vehicles for the positive controls. Each negative control rat received 1 mL of corn oil or corn oil:acetone. These rats were dosed in a separate room from the rats dosed with the test substance or positive controls.

H. Body Weights

The rats were weighed on each day of dosing and then weekly or every other week during the recovery period.

I. Mortality and Clinical Observations

Cage-site examinations to detect moribund or dead rats and abnormal behavior and appearance among rats were conducted at least once daily throughout the study. At every weighing, each rat were individually handled and examined for abnormal behavior and appearance.

J. Collection and Analysis of Blood and Livers

Approximately 2 hours after the first dose, 1-2 mL of blood was collected into EDTA tubes from the orbital sinus of each rat from Group I. At all other selected time points, 5 rats/group were euthanized by carbon dioxide anesthesia and exsanguination and blood and livers were collected according to the following schedules:

Group	Dosing Days	Tissue Collected	Sampling Time
I	1-5	Blood	Test day 1 (2 hours post dosing)
I	1-5	Blood and Liver	Test day 5 at sacrifice (2 hours post dosing)
II	1-10	Blood and Liver	Test day 10 (2 hours post dosing)
III	1-10	Blood and Liver	Test day 13
IV	1-10	Blood and Liver	Test day 24
V	1-10	Blood and Liver	Test day 52
VI	1-10	Blood and Liver	Test day 94

Five to 10 mL of blood was collected into EDTA tubes at sacrifice. The livers were weighed. The blood from all rats was refrigerated, and the livers were frozen. The blood was appropriately packaged and shipped refrigerated to Jackson Laboratory, Deepwater, New Jersey where it was analyzed for total fluorine.

The total fluorine content of the blood samples was determined by using a Wickbold torch combustion method, followed by analysis with a fluoride ion selective electrode. The liquid blood was decomposed or volatilized in the presence of wet oxygen and swept through an oxy-hydrogen flame in a closed quartz apparatus. The combustion products were collected in an aqueous absorbing solution and analyzed using a fluoride ion selective electrode. The analytical data (ppm F in each sample) was supplied to Haskell Laboratory for evaluation of fluorine biopersistence.

K. Treatment of Fluoride Data

Noncompartmental analysis was conducted on blood fluorine data derived from rats dosed with H-24001 by using WinNonlin Version 3.0 software (Pharsight Corp, Mountain View, CA). WinNonlin software provided a means of computing derived pharmacokinetic parameters from data files including area under the curve (AUCINF), C_{max} and terminal half-life (T_{1/2}). The AUCINF (concentration x time) represents the area under the blood concentration curve from the time of dosing extrapolated to infinity. The maximum observed concentration was C_{max} (concentration). The points included in determination of the terminal half-life were selected manually and given in units of time. Since the dosages and fluorine content for each positive control and the test material varied, all doses were normalized to 0.1 mmole/kg for comparative purposes. The accumulation index (AI, $1/(1-e^{-kt})$) and bioaccumulation index (BI, C_{max} x AI) were calculated and reported but not further use.

H-24019 and H-24020 were used as positive controls. Dosing diluents were used as negative controls, but because of variability and limited sensitivity of the analytical method, the background was set at 0.2 ppm fluorine. Since 0.2 ppm was the fluoride concentration limit of detection, any values listed as <0.2 ppm were excluded from further treatment.

The percent of fluorine and molecular weight of the test substance and positive controls were used as provided by the sponsor. The measurements resulting from analysis of total blood fluorine were used as received (ppm F) from Jackson Laboratory. Fluoride ion was converted to micromolar (μM) equivalents of active component for further comparisons. The data and descriptions of data manipulation and presentation are provided in Appendix C.

RESULTS AND DISCUSSION

A. In-Life Toxicology (Tables 1 and 2; Figure 1, Appendices A and B)

No deaths occurred during the study.

No compound-related clinical signs of toxicity were observed in the rats dosed with H-24001. Rats dosed with H-24019 exhibited diarrhea, salivation, alopecia, black ocular discharge, and staining of various parts of the body during the dosing period. Rats dosed with H-24020 exhibited wet perineum and diarrhea during the dosing period. Alopecia was observed during the recovery period for rats dosed with H-24001, H-24019, and H-24020. The negative control rats exhibited no clinical signs during the study.

Comparison of body weights was complicated by the fact that there was a difference in age on test day 1 between the rats dosed with the test substance and those dosed with the positive or negative controls. This difference resulted in differences in mean body weights on test day 1. The rats dosed with the test substance, H-24001, were older and heavier in weight than the corn oil negative control and H-24020 positive control rats, but younger and lighter in weight than the corn oil/acetone negative control and H-24019 positive control rats. Accounting for the age difference at study start and the expected rate of body weight gain, the mean body weights and mean body weight gains of the rats dosed with H-24001 was comparable to the negative controls and equal to or greater than the positive controls.

B. Fluorine Data (Tables 3 and 4; Figures 2 and 3; Appendix C)

1. Factors Influencing Interpretation of Analysis

The data used in the kinetic analysis were derived from a limited screen, and therefore several caveats and considerations are important. A couple of considerations of particular importance are (1) a single dose was used and kinetics may or may not be linear, (2) the kinetics apply only to blood, (3) steady-state may not have been achieved, and (4) the sample size is low and may impact calculation of the terminal half-life. A more complete list of considerations is shown in Appendix C.

2. Positive Controls

The positive controls were H-24019 and H-24020. The H-24019 normalized μM equivalents in rat blood continued to rise throughout the dosing period and may not have reached steady-state (Figure 2A). The C_{max} for H-24019 was 989.85 ± 116.90 ppm (Mean $\pm$ SD) with a terminal half-life of 40.5 days. The H-24019 AI was 59.0 and the BI was 58382.2. The H-24020 normalized μM equivalents in rat blood peaked after 5 days of dosing and then decreased throughout the dosing period (Figure 2B). The C_{max} for H-24020 was 518.12 ± 44.89 ppm (Mean $\pm$ SD) with a terminal half-life of 8.3 days. The H-24020 AI was 12.5 and the BI was

6497.5. For each of the positive controls, blood was sampled at seven time points throughout the study, with only four of them occurring post-dose. The small sample size and analytical variability should be taken into account when using the derived terminal half-life for comparative purposes. The total internal exposure resulting from a normalized dose was described by AUCINF/D and was the basis for comparison between positive controls and the test material. The AUCINF/D for the fluorine component was 566,479.1 for H-24019 and 70,789.6 for H-24020.

3. Test Substance

The H-24001 normalized μM equivalents in rat blood continued to rise throughout the dosing period and did not reach steady-state (Figure 2C). The C_{max} for H-24001 was 9.188 ± 1.917 ppm (Mean $\pm$ SD) with a terminal half-life of 46.9 days. Blood was sampled at seven time points throughout the study, with only four of those occurring post-dose. The small sample size and analytical variability should be taken into account when using the derived terminal half-life for comparative purposes. The H-24001 AI was 68.1 and the BI was 625.4. The total internal exposure resulting from a normalized dose was described by AUCINF/D and was the basis for comparison between H-24001 and positive controls. The AUCINF/D for the fluorine component of H-24001 was 1750 as compared to AUCINF/D values of 566,479.1 and 70,789.6 for H-24019 and H-24020, respectively. The data, calculations and equations are shown in Appendix C.

CONCLUSIONS

Rats dosed for 10 consecutive days with 1000 mg/kg H-24001 exhibited no mortality or clinical signs of toxicity and had mean body weight gains that were comparable to the negative control rats. A steady state for fluorine in the blood was not achieved for H-24001 during the 10-day dosing period.

Under the conditions of this study, administration of H-24001 to male rats for 10 consecutive days resulted in limited absorption and retention of fluorine in the blood. Dose-adjusted areas under the curve (AUCINF/D) for positive controls, H-24019 and H-24020, were approximately 320x and 40x the AUCINF/D for the test substance.

RECORDS AND SAMPLE STORAGE

Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

TABLES

TABLE 1
MEAN BODY WEIGHTS (g)

Test Days	<u>Negative Controls</u>		<u>Positive Controls</u>		<u>Test Substance</u>
	Corn Oil	Corn Oil:Acetone	H-24019	H-24020	H-24001
1	229.8	297.6	291.5	227.5	245.3
2	234.1	299.6	291.5	232.4	251.4
3	241.4	309.4	298.3	242.0	260.4
4	250.4	314.3	304.1	248.9	267.9
5	259.3	321.5	308.6	252.4	277.6
6	266.8	326.0	312.7	259.8	286.3
7	271.2	334.9	317.5	263.3	291.1
8	281.9	339.2	317.3	269.8	298.6
9	285.2	345.2	318.4	278.5	305.5
10	295.9	351.7	318.9	283.9	309.4
13	321.1	350.7	329.1	289.1	321.3
20	350.5	369.8	359.7	311.3	-
24	378.3	401.0	387.9	340.9	388.5
27	-	-	393.9	-	-
34	407.8	411.4	416.9	402.9	416.8
41	434.5	-	-	425.0	-
47	454.9	-	-	438.2	-
48	-	-	-	-	466.4
52	464.7	527.6	438.1	465.6	483.2
55	487.0	-	-	452.3	-
61	505.1	-	-	465.8	-
62	-	-	523.4	-	506.8
68	515.4	-	-	470.9	-
69	-	-	-	-	517.6
75	-	-	-	-	533.2
76	-	539.0	563.4	-	-
80	-	-	570.7	-	-
81	-	-	-	499.2	-
89	-	-	-	-	543.5
90	556.2	562.2	585.3	527.8	-
93	-	-	-	-	570.5 ^a
94	566.9	567.8	597.9	538.7	-

- a The rats were sacrificed a day early because of a laboratory event on test day 94.
- Indicates that the animal was not weighed.

TABLE 2

MEAN BODY WEIGHT GAINS (g)

Test Days	<u>Negative Controls</u>		<u>Positive Controls</u>		<u>Test Substance</u>
	Corn Oil	Corn Oil:Acetone	H-24019	H-24020	H-24001
1-5	29.5	23.9	17.1	24.9	32.3
1-10	66.1	54.1	27.4	56.4	64.1
10-13	25.2	-1.0	10.2	5.2	11.9
10-24	82.4	49.3	69.0	57.0	79.1
10-52	168.8	175.9	119.2	181.7	173.8
10-93/94	271.0	216.1	279.0	254.8	261.1

TABLE 3
MEAN BLOOD FLUORINE LEVELS

Test Days	<u>Negative Controls</u>		<u>Positive Controls</u>		<u>Test Substance</u>
	Corn Oil ppm	Corn Oil:Acetone ppm	H-24019 ppm	H-24020 ppm	H-24001 ppm
1	<0.2	<0.2	2.1 (0.9)	62.6 (3.2)	4.1 (0.7)
5	<0.2	<0.2	48.8 (17.6)	71.7 (6.2)	13.4 ^e (1.5)
10	<0.2	0.3 ^a (0.1) ^b	61.7 (2.8)	54.2 (7.8)	19.5 (4.0)
13	0.2 ^a (0.1)	0.6 ^c (0.6)	64.5 (7.6)	26.6 (11.4)	6.3 (1.0)
24	<0.2	0.2 ^d	42.2 (2.8)	10.5 (3.0)	2.6 (0.2)
52	0.3 ^a (0.1)	<0.2	26.9 (2.6)	0.9 (0.2)	1.8 (0.2)
93/94	0.3 ^a (0.1)	<0.2	13.2 (2.1)	0.2 ^c (0.1)	1.1 (0.2)

- a Mean of 4 of the 5 values. One of the values was below the LOD.
b Standard deviation is in parentheses.
c Mean of 3 of the 5 values. Two of the values were below the LOD.
d One value. Four of the values were below the LOD.
e Mean of 4 of 5 values. Tube of blood for one rat was missing or broken.

TABLE 4
MEAN BLOOD FLUORINE CONCENTRATION
NORMALIZED TO DOSE

Test Days	<u>Positive Controls</u>		<u>Test Substance</u>
	H-24019 $\mu\text{M F}$ Equivalents	H-24020 $\mu\text{M F}$ Equivalents	H-24001 $\mu\text{M F}$ Equivalents
1	28.92 (13.3) ^a	89.28 (23.4)	1.85 (0.3)
5	747.69 (271.5)	518.12 (44.9)	6.28 ^b (0.7)
10	945.85 (43.5)	391.01 (56.8)	9.19 (1.9)
13	989.85 (116.9)	191.45 (82.7)	2.88 (0.5)
24	645.54 (42.9)	74.35 (22.1)	1.16 (0.1)
52	411.38 (40.6)	4.64 (1.1)	0.74 (0.1)
93/94	195.38 (32.5)	0.24 (0.4)	0.41 (0.1)

a Standard deviation is in parentheses.

b Mean of 4 of the 5 values. No data for one rat.

FIGURES

FIGURE 1

MEAN BODY WEIGHTS (g)

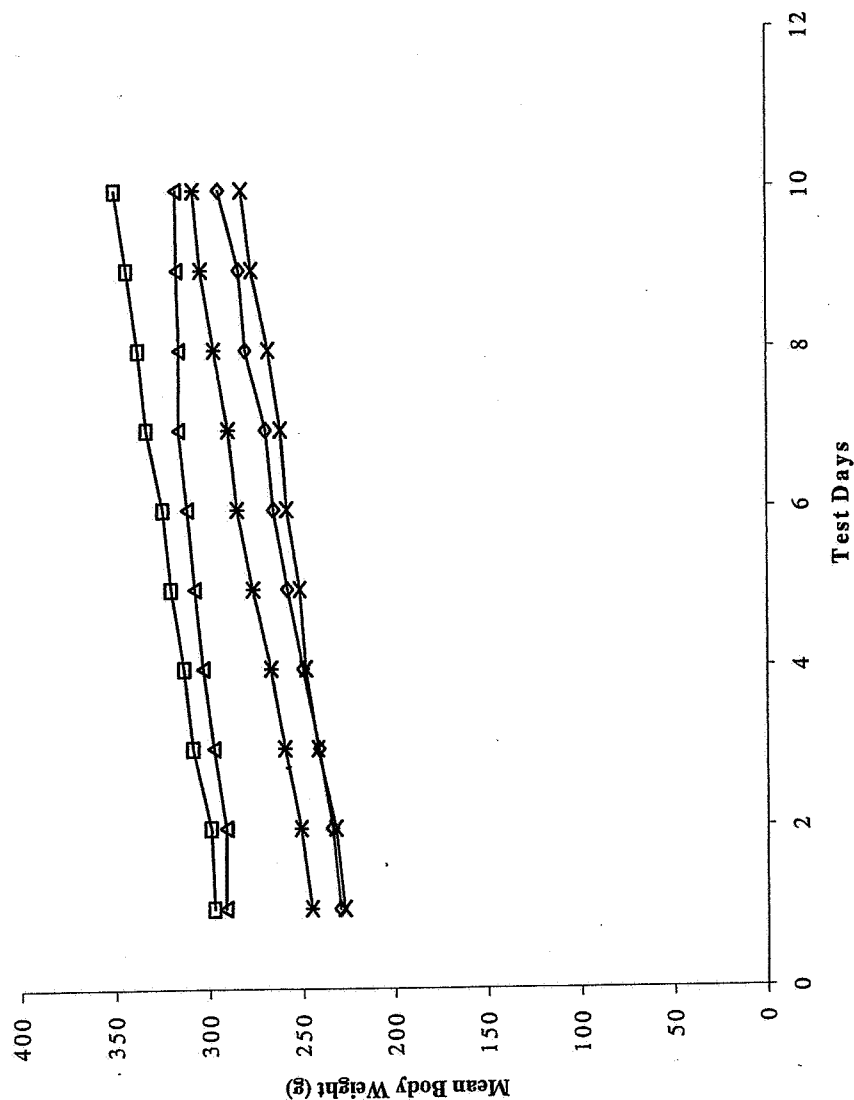
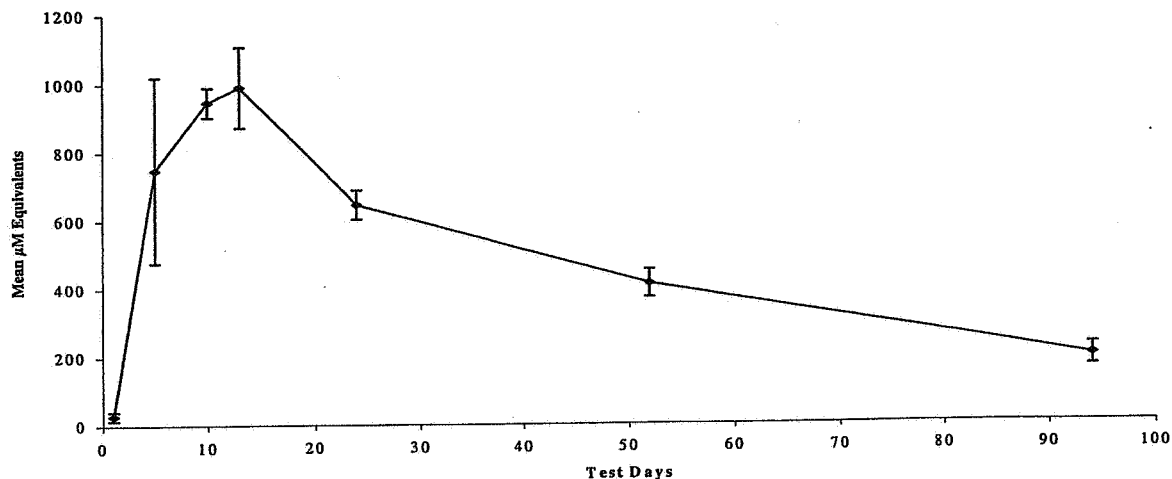


FIGURE 2

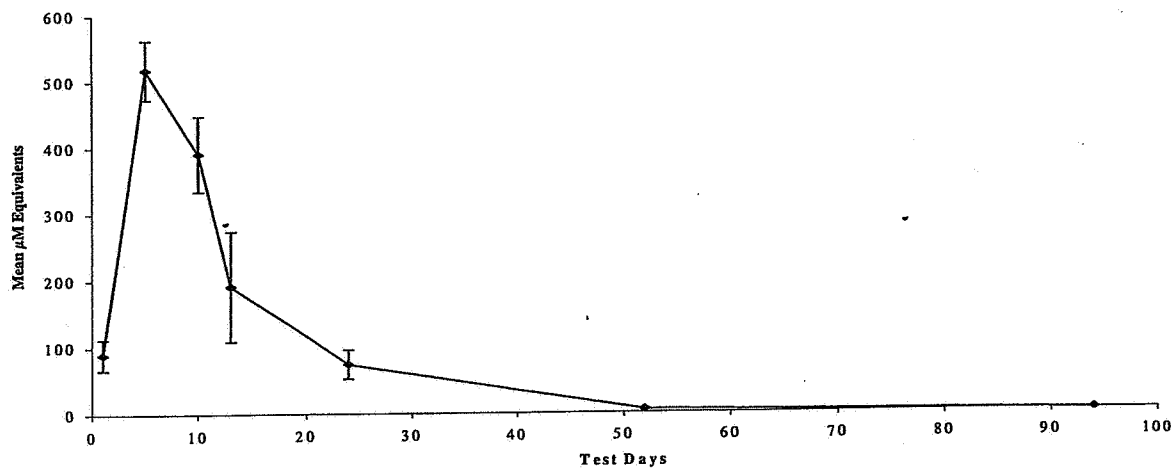
MICROMOLAR EQUIVALENTS IN RAT BLOOD

A. Normalized Rat Blood H-24019 μM Equivalents Resulting from a 10-Day Oral Gavage



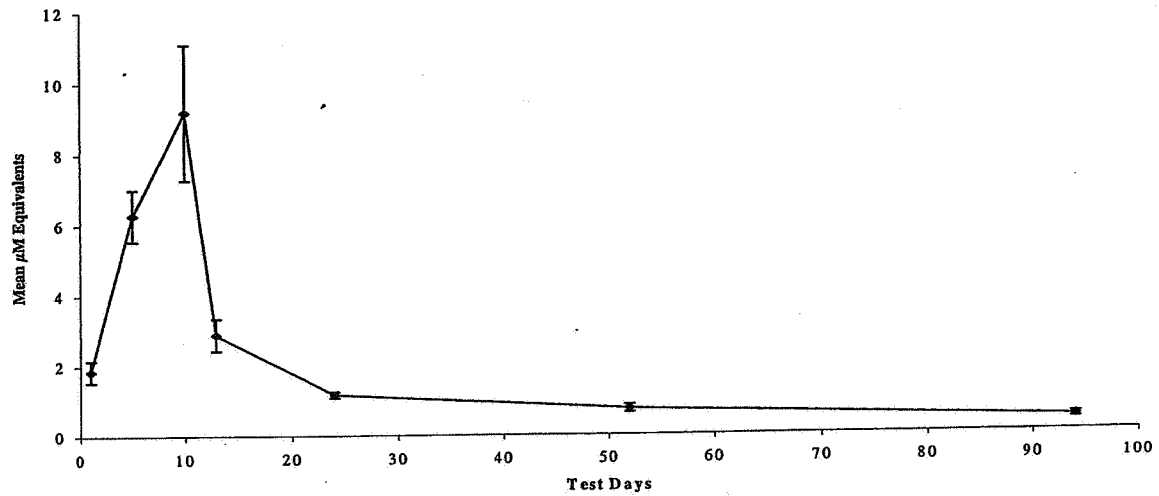
Micromolar (μM) equivalents of H-24019 (positive control) in rat blood resulting from a 10-day oral gavage exposure. Values are means and error bars are standard deviation.

B. Normalized Rat Blood H-24020 μM Equivalents Resulting from a 10-Day Oral Gavage



Micromolar (μM) equivalents of H-24020 (positive control) in rat blood resulting from a 10-day oral gavage exposure. Values are means and error bars are standard deviation.

C. Normalized Rat Blood H-24001 μ M Equivalents Resulting from a 10-Day Oral Gavage

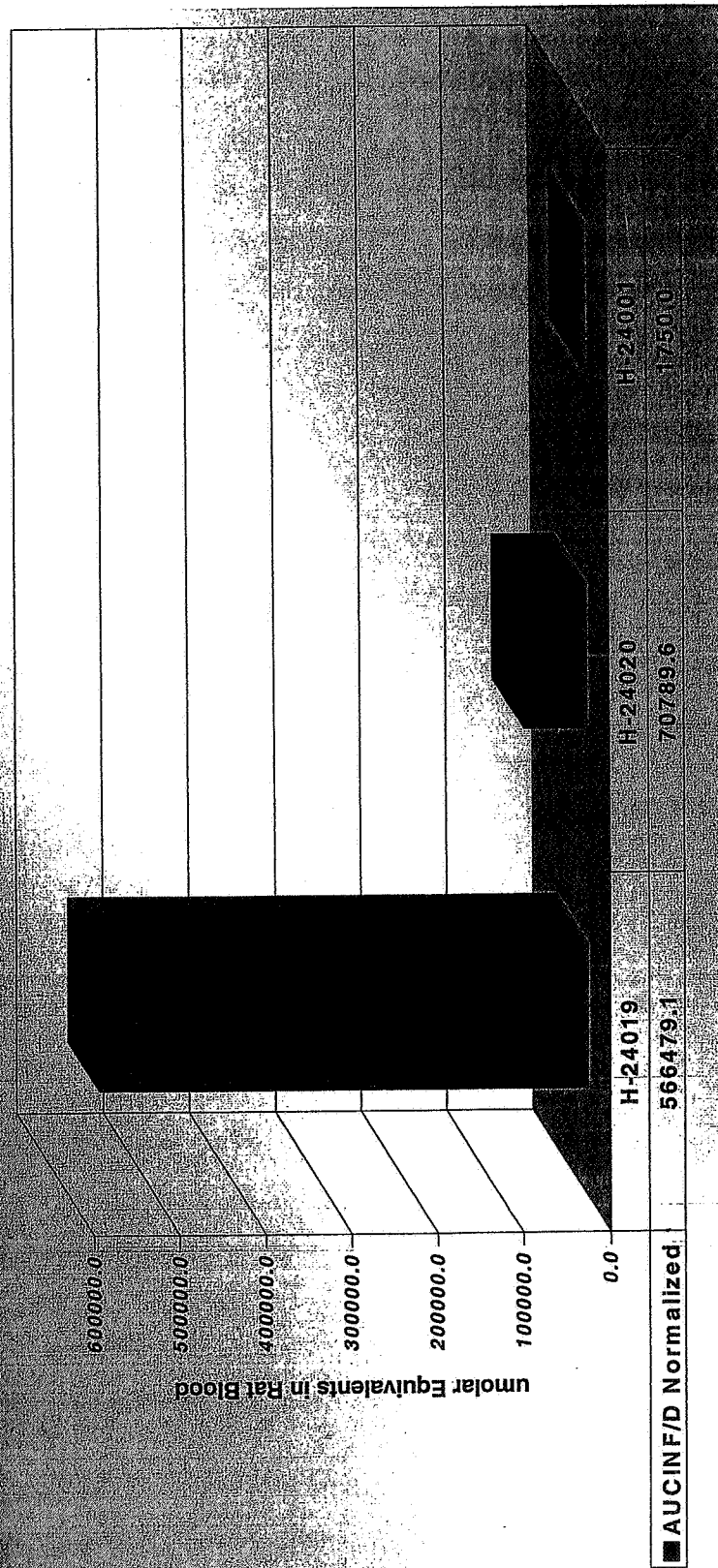


Micromolar (μ M) equivalents of H-24001 (test substance) in rat blood resulting from a 10-day oral gavage exposure. Values are means and error bars are standard deviation.

FIGURE 3

MICROMOLAR EQUIVALENTS IN TEST COMPOUND AND POSITIVE CONTROLS

H-24001 and Positive Control Normalized Blood AUCINF/D in Rats Resulting from 10-day Oral Gavage



APPENDICES

APPENDIX A

Individual Body Weights

INDIVIDUAL BODY WEIGHTS

EXPLANATORY NOTES

ABBREVIATIONS:

SD - sacrificed by design

CORN OIL (NEGATIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP I

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	
627789	222.6	220.7	223.5	236.9	247.7	SD test day 5
627801	215.9	209.1	223.5	233.5	240.1	SD test day 5
627805	249.4	250.1	263.3	273.6	283.7	SD test day 5
627810	230.5	231.6	241.9	254.4	265.0	SD test day 5
627818	229.7	228.6	239.1	252.4	260.2	SD test day 5

CORN OIL (NEGATIVE CONTROL)

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627793	214.8	224.4	232.1	243.1	249.9	257.0	262.0
627797	239.9	245.9	257.3	267.5	280.7	288.0	290.9
627799	228.9	231.4	242.3	246.2	258.9	261.5	266.4
627800	246.9	252.8	265.2	279.3	283.6	295.5	300.1
627808	235.6	241.6	250.1	262.1	270.4	284.1	287.4

ANIMAL NUMBER	DAY 8	DAY 9	TEST DAYS DAY 10
1	1	1	1
2	1	1	1
3	1	1	1
4	1	1	1
5	1	1	1
6	1	1	1
7	1	1	1
8	1	1	1
9	1	1	1
10	1	1	1
11	1	1	1
12	1	1	1
13	1	1	1
14	1	1	1
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21	1	1	1
22	1	1	1
23	1	1	1
24	1	1	1
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27	1	1	1
28	1	1	1
29	1	1	1
30	1	1	1
31	1	1	1
32	1	1	1
33	1	1	1
34	1	1	1
35	1	1	1
36	1	1	1
37	1	1	1
38	1	1	1
39	1	1	1
40	1	1	1
41	1	1	1
42	1	1	1
43	1	1	1
44	1	1	1
45	1	1	1
46	1	1	1
47	1	1	1
48	1	1	1
49	1	1	1
50	1	1	1
51	1	1	1
52	1	1	1
53	1	1	1
54	1	1	1
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87	1	1	1
88	1	1	1
89	1	1	1
90	1	1	1
91	1	1	1
92	1	1	1
93	1	1	1
94	1	1	1
95	1	1	1
96	1	1	1
97	1	1	1
98	1	1	1
99	1	1	1
100	1	1	1

Run	Time	SD	Test day
627793	270.6	274.9	283.5
627797	303.9	305.1	324.2
627799	380.2	284.3	294.7
627800	312.0	315.4	331.3
627808	303.6	305.7	321.8

CORN OIL (NEGATIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP III

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627796	239.8	249.7	253.6	252.5	267.7	277.2	289.8
627806	227.3	234.2	239.4	242.9	258.5	270.4	275.2
627807	221.5	225.9	237.1	244.1	254.9	257.7	260.3
627809	234.2	240.4	252.5	260.3	272.8	277.9	282.6
627816	235.0	238.6	250.0	258.9	265.1	274.5	278.6

ANIMAL NUMBER	TEST DAYS		
	DAY 8	DAY 9	DAY 10

627796	285.9	290.1	300.0	322.7	SD	test	day 13
627806	282.8	285.8	302.8	320.3	SD	test	day 13
627807	270.7	274.7	280.7	305.2	SD	test	day 13
627809	297.9	300.2	311.9	336.2	SD	test	day 13
627816	291.8	296.4	305.7	330.2	SD	test	day 13

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

CORN OIL (NEGATIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP IV

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627791	231.1	235.4	241.2	246.8	255.9	262.6	268.4
627794	224.4	233.0	238.1	247.8	260.0	267.4	270.1
627804	224.7	228.8	230.6	243.0	251.7	252.9	259.5
627812	221.9	231.5	236.3	245.7	255.5	264.9	269.5
627817	233.5	231.3	229.0	244.8	255.4	266.4	270.0

ANIMAL NUMBER	TEST DAYS			
	DAY 8	DAY 9	DAY 10	DAY 13

627791	274.0	279.1	285.0	- ^a	334.4	365.6	SD test day 24
627794	286.1	289.5	295.4	- ^a	377.4	416.7	SD test day 24
627804	267.2	270.6	278.1	- ^a	345.8	378.1	SD test day 24
627812	278.2	282.7	294.3	- ^a	356.5	388.4	SD test day 24
627817	277.8	280.4	294.6	- ^a	368.7	407.3	SD test day 24

a Rat was not weighed.

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

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CORN OIL (NEGATIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP V

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627792	235.8	240.8	244.3	247.9	252.5	264.4	268.1
627798	241.1	253.4	257.6	266.1	272.9	281.9	286.2
627813	214.8	219.2	220.5	233.2	239.8	243.2	246.8
627814	217.5	220.5	223.7	225.2	233.8	236.7	240.6
627815	230.1	242.2	243.8	255.7	265.0	270.0	274.1

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 34
627792	282.4	286.4	295.2	- ^a	360.0	389.2	426.1
627798	294.3	296.3	315.7	- ^a	380.2	403.5	443.1
627813	258.7	259.2	267.9	- ^a	323.6	342.3	367.9
627814	248.0	250.7	257.3	- ^a	299.3	319.4	343.7
627815	289.2	293.4	303.3	- ^a	368.3	396.5	434.9

ANIMAL NUMBER	TEST DAYS		
	DAY 41	DAY 47	DAY 52
627792	456.5	482.3	496.8 SD test day 52
627798	470.7	496.9	517.3 SD test day 52
627813	395.0	407.2	416.8 SD test day 52
627814	358.7	372.7	386.9 SD test day 52
627815	462.6	487.3	505.9 SD test day 52

a Rat was not weighed.

CORN OIL (NEGATIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS
GROUP VI

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627795	218.0	219.5	225.3	234.3	239.4	246.2	250.1
627811	228.6	226.3	236.7	246.1	251.5	259.6	263.6
627819	248.8	255.3	264.9	274.4	280.4	288.0	290.3
627820	225.5	228.9	239.2	247.9	255.6	261.3	265.3
627821	227.5	233.2	240.7	246.1	251.2	259.8	263.9

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 34
627795	261.4	265.0	270.7	- ^a	308.0	329.8	362.0
627811	273.0	276.7	285.6	- ^a	337.8	360.6	396.4
627819	304.5	308.0	324.3	- ^a	399.7	431.2	472.5
627820	281.3	282.9	292.4	- ^a	367.2	393.0	445.5
627821	272.6	275.3	281.8	- ^a	330.1	352.9	385.6

ANIMAL NUMBER	TEST DAYS						
	DAY 41	DAY 47	DAY 52	DAY 55	DAY 61	DAY 68	
627795	384.2	398.0	- ^a	411.1	435.7	440.7	
627811	422.0	439.3	- ^a	455.4	463.0	473.6	
627819	505.9	534.9	- ^a	551.7	574.4	588.6	
627820	478.0	504.1	- ^a	529.7	547.1	558.6	
627821	411.8	426.1	- ^a	439.1	459.0	463.3	

a Rat was not weighed.

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

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		CORN OIL (NEGATIVE CONTROL)	
		INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS	
		GROUP VI	
ANIMAL NUMBER	TEST DAYS		
	DAY 90	DAY 94	
627795	474.6	485.0	SD test day 94
627811	503.6	511.6	SD test day 94
627819	638.1	653.1	SD test day 94
627820	608.6	618.0	SD test day 94
627821	509.0	521.5	SD test day 94

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

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CORN OIL:ACETONE (NEGATIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP I

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	
625361	322.6	325.0	337.6	340.3	349.7	SD test day 5
625363	273.7	271.4	278.4	281.7	286.7	SD test day 5
625364	291.1	290.9	299.9	306.0	312.0	SD test day 5
625380	289.4	286.2	291.5	300.1	305.5	SD test day 5
625383	304.7	299.7	302.7	310.7	313.1	SD test day 5

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

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CORN OIL:ACETONE (NEGATIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP II

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625355	280.0	282.0	293.0	297.9	306.1	311.2	315.7
625362	290.3	294.1	303.5	308.9	313.8	315.8	323.8
625367	301.5	307.8	315.6	320.1	327.7	333.7	345.6
625368	312.3	318.0	326.0	336.4	343.7	347.5	360.8
625378	309.6	306.4	327.3	328.4	333.7	336.6	346.9

ANIMAL NUMBER	TEST DAYS	
	DAY 8	DAY 9
625355	321.7	320.9
625362	323.9	332.3
625367	349.1	352.4
625368	364.2	380.8
625378	350.1	354.2

	TEST DAYS	
	DAY 10	DAY 10
	333.6	SD test day 10
	332.9	SD test day 10
	363.8	SD test day 10
	386.7	SD test day 10
	365.4	SD test day 10

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

CORN OIL:ACETONE (NEGATIVE Control)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP III

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625357	311.9	308.8	320.3	328.4	340.5	343.3	361.1
625358	285.7	286.3	295.5	296.4	306.0	302.7	309.2
625370	307.9	316.7	329.5	337.9	346.9	349.8	364.1
625384	294.2	300.0	312.0	309.3	316.3	314.1	321.4
625385	297.6	304.6	313.0	320.4	331.9	334.0	345.4

ANIMAL NUMBER	TEST DAYS		
	DAY 8	DAY 9	DAY 10

625357	364.2	370.3	376.9	405.6	SD test day 13
625358	319.8	321.6	320.3	340.7	SD test day 13
625370	373.4	374.7	385.6	407.0	SD test day 13
625384	325.6	331.0	340.6	357.1	SD test day 13
625385	347.0	349.5	358.9	377.6	SD test day 13

CORN OIL:ACETONE (NEGATIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP IV

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625354	303.0	304.1	310.5	312.2	319.3	324.7	331.2
625365	327.7	328.7	337.9	343.6	357.7	357.2	364.3
625371	294.5	299.0	313.4	318.3	321.8	329.6	338.5
625376	289.7	289.9	302.2	304.9	313.2	317.0	322.8
625381	297.8	297.5	301.7	305.6	314.4	314.4	321.0

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	
625354	336.2	337.0	348.8	355.8	377.7	396.1	SD test day 24
625365	370.5	379.3	381.2	407.1	438.2	459.6	SD test day 24
625371	340.3	345.9	351.2	372.6	413.0	447.3	SD test day 24
625376	331.5	339.0	345.2	363.2	399.7	432.9	SD test day 24
625381	321.6	329.1	331.6	341.2	358.2	381.8	SD test day 24

CORN OIL:ACETONE (NEGATIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP V

ANIMAL NUMBER	DAY 1	DAY 2	TEST DAYS				DAY 5	DAY 6	DAY 7
			DAY 3	DAY 4	DAY 5	DAY 6			
625356	291.7	291.2	304.5	307.0	316.9	319.8	319.8	323.9	323.9
625359	297.9	303.3	314.0	315.0	323.5	323.5	323.5	333.9	333.9
625360	296.8	300.7	308.5	312.7	319.1	332.2	332.2	339.5	339.5
625372	294.8	298.8	310.6	317.4	324.0	329.0	329.0	335.6	335.6
625374	295.9	302.2	312.1	321.7	323.4	328.3	328.3	337.2	337.2

ANIMAL NUMBER	DAY 8	DAY 9	TEST DAYS				DAY 20	DAY 24	DAY 27
			DAY 10	DAY 13	DAY 20	DAY 24			
625356	328.8	334.7	341.3	361.9	396.7	- ^a	- ^a	431.3	431.3
625359	339.1	346.2	353.6	372.9	410.0	- ^a	- ^a	440.9	440.9
625360	347.9	354.3	363.4	381.7	419.8	- ^a	- ^a	465.9	465.9
625372	344.7	348.8	355.1	373.1	395.1	- ^a	- ^a	432.1	432.1
625374	338.0	344.6	350.8	371.5	401.3	- ^a	- ^a	447.2	447.2

ANIMAL NUMBER	DAY 34	DAY 52	TEST DAYS	
			SD	test day 52
625356	466.2	533.7	SD	test day 52
625359	467.7	530.3	SD	test day 52
625360	484.1	555.4	SD	test day 52
625372	454.7	506.2	SD	test day 52
625374	466.8	512.3	SD	test day 52

a Rat was not weighed.

CORN OIL:ACETONE (NEGATIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP VI

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625353	305.9	307.3	316.8	325.0	331.7	330.1	342.5
625369	281.7	279.9	289.7	286.9	292.8	295.3	303.8
625373	294.6	301.3	312.7	317.0	325.4	329.0	334.6
625375	289.1	291.0	298.0	307.0	309.6	314.2	323.5
625377	293.9	294.8	302.9	312.0	318.0	317.4	325.0

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 27
625353	344.7	352.7	358.1	371.7	399.1	- ^a	427.7
625369	307.3	311.9	317.2	331.1	347.6	- ^a	374.9
625373	340.6	348.2	352.6	371.5	402.3	- ^a	444.6
625375	324.7	336.0	336.9	350.1	387.9	- ^a	432.3
625377	325.0	333.7	340.7	353.5	376.3	- ^a	405.2

ANIMAL NUMBER	TEST DAYS						
	DAY 34	DAY 52	DAY 76	DAY 90	DAY 94		
625353	453.3	- ^a	544.9	562.8	565.3	SD test day 94	
625369	388.2	- ^a	483.8	505.3	514.8	SD test day 94	
625373	477.1	- ^a	628.8	661.3	673.7	SD test day 94	
625375	455.6	- ^a	567.3	589.8	588.8	SD test day 94	
625377	419.1	- ^a	470.3	492.0	496.6	SD test day 94	

a Rat was not weighed.

H-24019 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP I

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	
625322	290.3	283.7	291.5	298.9	298.0	SD test day 5
625323	285.0	285.5	290.2	290.9	294.0	SD test day 5
625336	316.5	313.5	320.1	327.1	329.0	SD test day 5
625343	288.2	281.9	286.8	291.0	293.7	SD test day 5
625349	303.6	295.9	308.2	310.1	318.1	SD test day 5

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

H-24019 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP II

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625320	279.3	283.0	287.7	288.4	295.9	299.4	300.6
625330	286.7	286.1	291.1	296.5	304.0	302.3	306.7
625332	300.0	295.9	304.1	308.8	315.0	322.4	320.7
625341	304.9	309.0	317.5	320.0	325.1	327.5	327.4
625350	257.1	268.5	267.3	272.2	272.6	276.3	283.6

ANIMAL NUMBER	TEST DAYS	
	DAY 8	DAY 9

625320	308.5	306.3	312.1	SD test day 10
625330	314.0	312.6	310.1	SD test day 10
625332	324.1	321.8	318.3	SD test day 10
625341	332.4	320.3	325.6	SD test day 10
625350	279.8	282.5	284.3	SD test day 10

H-24019 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP III

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625321	307.0	307.8	311.4	319.6	322.3	328.4	335.2
625327	311.4	306.6	312.5	317.8	318.3	319.3	327.6
625342	273.7	275.5	282.3	285.8	290.8	294.2	326.6
625345	291.2	291.7	297.3	303.3	306.4	310.4	316.1
625348	265.5	258.6	268.0	275.2	280.1	285.2	290.6

TEST DAYS

ANIMAL NUMBER	TEST DAYS			
	DAY 8	DAY 9	DAY 10	DAY 13
625321	337.8	339.6	346.1	371.2 SD test day 13
625327	334.3	337.0	336.3	355.3 SD test day 13
625342	304.3	305.9	307.8	324.4 SD test day 13
625345	317.3	312.9	315.0	336.9 SD test day 13
625348	302.7	306.5	309.7	336.4 SD test day 13

H-24019 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP IV

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625325	282.8	285.9	291.7	295.5	303.2	309.2	308.3
625328	315.6	315.2	323.9	327.7	335.0	340.4	340.1
625338	264.6	261.9	268.5	272.6	275.7	281.9	284.4
625340	304.0	309.2	316.9	326.0	329.8	334.1	338.4
625352	285.5	283.9	289.1	299.6	307.9	308.2	312.4

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	
625325	318.6	321.9	327.4	331.6	355.8	381.3	SD test day 24
625328	352.0	351.7	357.5	367.4	400.2	423.9	SD test day 24
625338	287.4	291.3	290.2	291.1	320.4	339.9	SD test day 24
625340	347.0	352.2	359.2	368.1	389.3	419.0	SD test day 24
625352	316.9	322.3	321.0	329.6	355.7	375.3	SD test day 24

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

H-24019 (POSITIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

ANIMAL NUMBER	GROUP V						
	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625324	303.0	298.5	305.8	312.1	320.1	322.8	326.8
625329	318.9	316.3	326.5	335.4	338.3	346.7	351.6
625333	292.4	291.2	297.8	304.1	307.7	312.0	313.5
625334	274.6	277.0	286.4	290.6	292.0	300.1	304.2
625344	262.9	262.2	269.0	273.5	274.5	284.1	-

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 27
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 27
625324	332.5	337.9	336.1	299.6	336.0	- ^a	380.3
625329	352.5	360.1	357.0	364.3	396.4	- ^a	423.3
625333	315.8	316.7	319.3	325.8	349.2	- ^a	375.2
625334	292.6	302.2	305.8	312.0	338.6	- ^a	368.8
625344	280.7	285.2	289.3	295.8	309.7	- ^a	330.4

ANIMAL NUMBER	TEST DAYS						
	DAY 34	DAY 52	SD	test	day	52	
	DAY 34	DAY 52	SD	test	day	52	
625324	397.3	447.4	447.4	SD	test	day	52
625329	442.7	498.1	498.1	SD	test	day	52
625333	384.6	427.4	427.4	SD	test	day	52
625334	384.2	426.5	426.5	SD	test	day	52
625344	348.3	391.0	391.0	SD	test	day	52

a Rat was not weighed.

H-24019 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP VI

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
625326	313.2	317.1	325.5	330.9	336.2	336.0	-
625335	301.0	303.6	302.3	310.4	315.1	299.6	293.6
625346	290.2	293.4	300.2	309.5	313.5	318.6	326.0
625347	266.0	275.6	287.7	300.0	308.5	316.6	326.9
625351	310.6	310.9	321.1	329.6	338.2	341.6	340.7

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 27
625326	311.5	308.9	297.5	274.2	335.4	- ^a	390.7
625335	294.2	285.3	274.0	266.3	340.1	- ^a	393.8
625346	292.9	290.8	288.4	296.9	352.5	- ^a	388.2
625347	330.5	330.1	333.0	355.7	402.1	- ^a	436.2
625351	351.1	357.8	350.5	380.0	413.7	- ^a	452.4

ANIMAL NUMBER	TEST DAYS						
	DAY 34	DAY 52	DAY 62	DAY 76	DAY 80	DAY 90	DAY 94
625326	427.5	- ^a	497.5	540.0	547.9	565.2	577.5 SD test day 94
625335	427.0	- ^a	506.0	538.6	547.7	562.1	579.5 SD test day 94
625346	407.4	- ^a	485.8	523.7	532.8	542.4	556.9 SD test day 94
625347	466.4	- ^a	568.6	617.8	618.1	632.6	638.9 SD test day 94
625351	483.3	- ^a	559.0	596.8	607.2	624.0	636.8 SD test day 94

a Rat was not weighed.

H-24020 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP I

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	
627756	227.2	226.4	233.4	238.6	237.5	SD test day 5
627767	227.0	231.8	237.9	245.8	248.6	SD test day 5
627771	219.5	214.7	226.1	233.5	239.6	SD test day 5
627773	246.8	244.4	252.7	263.8	262.3	SD test day 5
627777	225.4	221.4	232.9	239.4	236.0	SD test day 5

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H-24020 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP II

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627768	236.9	244.1	245.2	256.5	256.2	265.5	271.4
627774	258.6	261.6	275.8	283.4	289.3	301.5	303.2
627776	212.0	216.3	223.7	226.6	229.6	233.7	236.9
627782	221.6	228.3	237.3	239.0	238.8	244.7	246.7
627785	220.3	221.7	234.7	238.4	241.8	250.5	255.6

ANIMAL NUMBER	TEST DAYS	
	DAY 8	DAY 10

627768	272.3	293.5
627774	319.8	338.2
627776	246.1	254.4
627782	251.0	268.2
627785	260.7	267.9

SD test day 10	SD test day 10
SD test day 10	SD test day 10
SD test day 10	SD test day 10
SD test day 10	SD test day 10
SD test day 10	SD test day 10

H-24020 (POSITIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP III

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627758	235.1	240.3	248.6	255.8	261.2	272.0	276.1
627763	212.1	218.3	226.5	234.3	230.8	235.5	238.0
627764	230.0	235.0	246.1	251.3	254.8	261.7	264.7
627787	235.1	241.0	250.1	257.2	258.6	237.6	240.3
627788	219.4	222.3	232.2	239.6	247.6	256.7	257.9

ANIMAL NUMBER	TEST DAYS			
	DAY 8	DAY 9	DAY 10	DAY 13
627758	280.6	283.6	295.8	308.7 SD test day 13
627763	255.2	261.2	272.5	285.8 SD test day 13
627764	275.8	281.9	288.0	306.7 SD test day 13
627787	221.7	235.7	234.7	234.9 SD test day 13
627788	274.1	276.9	284.8	309.4 SD test day 13

H-24020 (POSITIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP IV

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627759	226.6	232.9	241.4	250.9	254.2	262.1	265.4
627761	240.7	247.4	257.1	262.5	266.7	259.2	262.6
627770	235.6	244.3	253.6	260.1	267.7	277.3	279.8
627779	231.5	237.9	252.6	261.4	262.3	273.8	277.5
627786	211.6	218.2	222.5	230.4	230.6	240.6	244.1

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	
627759	277.8	284.9	288.0	- ^a	348.0	380.1	SD test day 24
627761	240.1	257.4	266.9	- ^a	335.7	359.4	SD test day 24
627770	291.4	301.3	306.4	- ^a	355.8	379.8	SD test day 24
627779	289.0	293.4	301.0	- ^a	374.4	406.2	SD test day 24
627786	251.3	255.8	257.0	- ^a	304.4	326.1	SD test day 24

a Rat was not weighed.

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

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H-24020 (POSITIVE CONTROL)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP V

ANIMAL NUMBER	TEST DAYS						
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
627757	221.2	225.4	236.3	241.1	247.9	252.2	254.4
627760	226.2	232.0	244.4	251.7	260.2	254.5	258.3
627765	228.3	235.3	247.1	251.6	256.4	261.1	264.7
627772	245.2	256.4	266.2	277.0	276.9	285.0	291.0
627781	219.0	226.3	236.5	242.9	247.2	251.6	256.1

ANIMAL NUMBER	TEST DAYS						
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 34
627757	269.1	276.7	279.7	- ^a	324.3	343.0	372.3
627760	262.6	280.3	287.3	- ^a	348.6	379.9	419.4
627765	271.5	282.4	288.1	- ^a	349.8	382.7	400.9
627772	300.9	307.5	317.0	- ^a	375.5	404.0	446.9
627781	258.1	266.8	271.2	- ^a	315.1	338.8	372.0

ANIMAL NUMBER	TEST DAYS		
	DAY 41	DAY 47	DAY 52
627757	402.8	419.7	436.7 SD test day 52
627760	437.7	448.9	456.5 SD test day 52
627765	422.9	444.8	455.6 SD test day 52
627772	478.4	494.3	513.5 SD test day 52
627781	389.9	408.2	421.0 SD test day 52

a Rat was not weighed.

H-24020 (POSITIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP VI

ANIMAL NUMBER	TEST DAYS									
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10
627762	227.2	235.0	248.7	257.3	263.0	275.1	279.7			
627769	231.1	241.1	255.9	264.2	272.3	286.3	289.9			
627775	224.7	235.7	246.8	254.7	265.7	276.7	280.2			
627778	213.1	217.4	221.3	225.5	230.1	236.9	240.4			
627783	216.4	218.2	226.6	232.0	238.0	243.9	247.6			
ANIMAL NUMBER	TEST DAYS									
	DAY 8	DAY 9	DAY 10	DAY 13	DAY 20	DAY 24	DAY 34	DAY 41	DAY 47	DAY 52
627762	285.9	299.1	301.5	- ^a	356.5	381.5	419.6			
627769	302.0	309.6	312.5	- ^a	386.6	414.4	456.5			
627775	286.6	296.0	304.5	- ^a	353.3	377.4	413.9			
627778	244.8	250.8	255.1	- ^a	294.0	320.0	347.1			
627783	256.6	259.2	264.3	- ^a	311.3	340.9	380.0			
ANIMAL NUMBER	TEST DAYS									
	DAY 41	DAY 47	DAY 52	DAY 55	DAY 61	DAY 68	DAY 74	DAY 81	DAY 88	DAY 95
627762	438.7	439.9	- ^a	453.5	473.0	471.6				
627769	479.7	474.6	- ^a	512.2	511.4	531.4				
627775	433.2	451.1	- ^a	460.8	477.4	478.6				
627778	356.8	373.5	- ^a	386.0	393.3	398.3				
627783	409.6	426.9	- ^a	449.0	473.8	474.8				

a Rat was not weighed.

H-24020 (POSITIVE CONTROL)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP VI

ANIMAL NUMBER	TEST DAYS	
	DAY 81	DAY 90
627762	500.3	523.3
627769	566.2	603.2
627775	510.4	537.5
627778	410.1	436.5
627783	508.8	538.5
	528.6	557.2
	SD test day 94	SD test day 94
	609.6	SD test day 94
	552.8	SD test day 94
	445.3	SD test day 94
	557.2	SD test day 94

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H-24001 (TEST SUBSTANCE)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP I

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	
626904	265.0	265.1	279.7	286.5	300.9	SD test day 5
626905	232.8	241.6	249.0	258.5	274.2	SD test day 5
626915	249.6	249.4	260.5	265.6	275.4	SD test day 5
626923	255.6	261.0	265.6	273.5	280.5	SD test day 5
626930	234.7	239.3	245.9	252.8	258.8	SD test day 5

H-24001 (TEST SUBSTANCE)
INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP II

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
626900	251.0	259.5	270.3	276.1	288.6	294.3	302.0
626909	231.0	234.8	244.5	252.1	262.2	270.9	278.1
626912	245.6	255.7	262.4	274.6	281.3	293.7	298.1
626919	242.9	248.5	260.9	267.2	278.7	288.7	291.8
626921	260.1	271.0	284.5	292.6	303.4	307.8	316.8

ANIMAL NUMBER	DAY 8	DAY 9	DAY 10
626900	312.1	320.0	331.0
626909	287.5	295.2	298.2
626912	309.5	316.1	322.2
626919	298.2	306.2	307.6
626921	323.2	329.4	335.5

H-24001: Biopersistence Screening
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H-24001 (TEST SUBSTANCE)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP III

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
626901	235.1	239.7	254.3	254.8	264.9	268.4	274.5
626907	248.7	254.0	268.0	272.2	289.3	300.6	299.0
626910	257.0	260.3	267.3	279.4	288.8	293.8	297.4
626913	225.7	229.5	235.2	241.9	250.9	255.1	258.4
626914	240.0	246.2	257.1	266.6	280.7	288.2	295.0

ANIMAL NUMBER	DAY 8	DAY 9	DAY 10	DAY 13	DAY 24	DAY 34	DAY 48
626901	280.5	292.4	294.3	301.9	SD test day 13		
626907	313.1	320.1	321.4	345.5	SD test day 13		
626910	305.8	310.2	318.3	334.4	SD test day 13		
626913	266.5	269.7	272.8	282.7	SD test day 13		
626914	305.9	314.4	319.4	342.1	SD test day 13		

H-24001 (TEST SUBSTANCE)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP IV

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
626897	234.4	238.9	247.4	254.9	261.7	271.7	283.0
626903	249.3	253.4	261.7	273.6	286.9	296.3	305.8
626916	245.1	256.4	259.5	272.1	282.2	289.1	294.5
626925	230.2	239.0	249.9	258.0	268.8	275.3	282.8
626926	262.7	265.6	279.3	281.0	292.8	299.5	301.5

ANIMAL NUMBER	DAY 8	DAY 9	DAY 10	DAY 13	DAY 24	DAY 34	DAY 48
626897	283.4	295.4	303.0	- ^a	379.3	SD test day 24	SD test day 24
626903	312.4	318.8	321.3	- ^a	404.0	SD test day 24	SD test day 24
626916	298.7	303.5	310.5	- ^a	382.7	SD test day 24	SD test day 24
626925	294.5	296.2	303.8	- ^a	390.7	SD test day 24	SD test day 24
626926	305.8	311.6	319.4	- ^a	385.7	SD test day 24	SD test day 24

a Rat was not weighed.

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

H-24001 (TEST SUBSTANCE)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP V

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
626898	251.4	261.5	266.3	274.8	283.7	294.6	296.4
626902	268.6	276.7	286.4	290.9	301.5	307.3	310.0
626908	250.7	256.9	266.2	276.1	285.7	294.3	298.9
626918	232.6	235.8	243.4	249.1	252.8	263.9	261.4
626922	227.3	234.1	240.4	249.0	253.3	261.5	265.5

ANIMAL NUMBER	DAY 8	DAY 9	DAY 10	DAY 13	DAY 24	DAY 34	DAY 48
626898	300.3	307.7	310.2	- ^a	- ^a	406.6	450.2
626902	316.8	322.1	322.4	- ^a	- ^a	436.3	486.3
626908	308.7	312.6	319.0	- ^a	- ^a	452.4	503.5
626918	265.6	279.8	276.3	- ^a	- ^a	369.6	418.5
626922	271.9	283.2	279.4	- ^a	- ^a	381.9	422.4

ANIMAL NUMBER	DAY 52	DAY 62	DAY 69	DAY 75	DAY 83	DAY 89	DAY 93
626898	467.6	SD test day 52					
626902	500.1	SD test day 52					
626908	523.4	SD test day 52					
626918	433.2	SD test day 52					
626922	433.6	SD test day 52					

a Rat was not weighed.

H-24001: Biopersistence Screening
10-Dose Oral Gavage Study in Rats

DuPont-2924

H-24001 (TEST SUBSTANCE)

INDIVIDUAL BODY WEIGHTS (g) OF MALE RATS

GROUP VI

ANIMAL NUMBER	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
626906	260.8	262.7	274.7	282.9	290.4	305.6	311.8
626911	229.5	238.1	246.2	248.5	257.9	271.7	271.4
626920	239.0	246.9	250.9	260.5	267.4	280.3	282.5
626924	244.4	255.0	260.8	271.6	280.6	289.5	296.8
626927	257.1	265.9	274.5	280.3	283.5	295.2	303.3
ANIMAL NUMBER	DAY 8	DAY 9	DAY 10	DAY 13	DAY 24	DAY 34	DAY 48
626906	313.9	323.5	326.6	- ^a	- ^a	484.4	550.4
626911	280.6	286.3	286.6	- ^a	- ^a	381.7	429.9
626920	292.9	298.4	295.4	- ^a	- ^a	397.8	448.8
626924	303.4	310.8	322.6	- ^a	- ^a	433.9	478.6
626927	313.1	312.7	318.4	- ^a	- ^a	422.9	475.5
ANIMAL NUMBER	DAY 52	DAY 62	DAY 69	DAY 75	DAY 83	DAY 89	DAY 93
626906	572.8	597.0	613.8	627.4	645.0	659.1	674.6
626911	439.6	446.3	455.2	475.8	479.0	500.1	506.9
626920	467.9	471.0	484.7	493.1	501.8	521.5	527.1
626924	494.7	503.8	516.8	527.5	531.4	540.6	549.5
626927	499.2	516.1	-	542.4	560.1	578.9	594.5

a Rat was not weighed.

APPENDIX B

Individual Clinical Observations

CORN OIL (NEGATIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP I

Animal Number	Observation	Test Day
627789	No abnormalities detected	1-5
627801	No abnormalities detected	1-5
627805	No abnormalities detected	1-5
627810	No abnormalities detected	1-5
627818	No abnormalities detected	1-5

GROUP II

Animal Number	Observation	Test Day
627793	No abnormalities detected	1-10
627797	No abnormalities detected	1-10
627799	No abnormalities detected	1-10
627800	No abnormalities detected	1-10
627808	No abnormalities detected	1-10

GROUP III

Animal Number	Observation	Test Day
627796	No abnormalities detected	1-13
627806	No abnormalities detected	1-13
627807	No abnormalities detected	1-13
627809	No abnormalities detected	1-13
627816	No abnormalities detected	1-13

CORN OIL (NEGATIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP IV

Animal Number	Observation	Test Day
627791	No abnormalities detected	1-24
627794	No abnormalities detected	1-24
627804	No abnormalities detected	1-24
627812	No abnormalities detected	1-24
627817	No abnormalities detected	1-24

GROUP V

Animal Number	Observation	Test Day
627792	No abnormalities detected	1-52
627798	No abnormalities detected	1-52
627813	No abnormalities detected	1-52
627814	No abnormalities detected	1-52
627815	No abnormalities detected	1-52

GROUP VI

Animal Number	Observation	Test Day
627795	No abnormalities detected	1-94
627811	No abnormalities detected	1-94
627819	No abnormalities detected	1-94
627820	No abnormalities detected	1-94
627821	No abnormalities detected	1-94

CORN OIL:ACETONE (NEGATIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP I

Animal Number	Observation	Test Day
625361	No abnormalities detected	1-5
625363	No abnormalities detected	1-5
625364	No abnormalities detected	1-5
625380	No abnormalities detected	1-5
625383	No abnormalities detected	1-5

GROUP II

Animal Number	Observation	Test Day
625355	No abnormalities detected	1-10
625362	No abnormalities detected	1-10
625367	No abnormalities detected	1-10
625368	No abnormalities detected	1-10
625378	No abnormalities detected	1-10

GROUP III

Animal Number	Observation	Test Day
625357	No abnormalities detected	1-13
625358	No abnormalities detected	1-13
625370	No abnormalities detected	1-13
625384	No abnormalities detected	1-13
625385	No abnormalities detected	1-13

CORN OIL:ACETONE (NEGATIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP IV

Animal Number	Observation	Test Day
625354	No abnormalities detected	1-24
625365	No abnormalities detected	1-24
625371	No abnormalities detected	1-24
625376	No abnormalities detected	1-24
625381	No abnormalities detected	1-24

GROUP V

Animal Number	Observation	Test Day
625356	No abnormalities detected	1-52
625359	No abnormalities detected	1-52
625360	No abnormalities detected	1-52
625372	No abnormalities detected	1-52
625374	No abnormalities detected	1-52

GROUP VI

Animal Number	Observation	Test Day
625353	No abnormalities detected	1-94
625369	No abnormalities detected	1-94
625373	No abnormalities detected	1-94
625375	No abnormalities detected	1-94
625377	No abnormalities detected	1-94

H-24019 (POSITIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP I

Animal Number	Observation	Test Day
625322	No abnormalities detected	1-5
625323	No abnormalities detected	1-5
625336	No abnormalities detected	1-5
625343	No abnormalities detected	1-5
625349	No abnormalities detected	1-5

GROUP II

Animal Number	Observation	Test Day
625320	No abnormalities detected	1-10
625330	No abnormalities detected	1-10
625332	No abnormalities detected	1-10
625341	No abnormalities detected	1-4, 6-10
	Diarrhea	5
625350	No abnormalities detected	1-10

GROUP III

Animal Number	Observation	Test Day
625321	No abnormalities detected	1-4, 6-13
	Diarrhea	5
625327	No abnormalities detected	1-13
625342	No abnormalities detected	1-13
625345	No abnormalities detected	1-13
625348	No abnormalities detected	1-13

H-24019 (POSITIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP IV

Animal Number	Observation	Test Day
625325	No abnormalities detected	1-24
625328	No abnormalities detected	1-24
625338	No abnormalities detected	1-6, 8-24
	Salivation	7
625340	No abnormalities detected	1-24
625352	No abnormalities detected	1-24

GROUP V

Animal Number	Observation	Test Day
625324	No abnormalities detected	1-52
625329	No abnormalities detected	1-6, 8-52
	Salivation	7
625333	No abnormalities detected	1-6, 8-52
	Salivation	7
625334	No abnormalities detected	1-52
625344	No abnormalities detected	1-52

GROUP VI

Animal Number	Observation	Test Day
625326	No abnormalities detected	1-6, 9-76, 77-94
	Salivation	7-8
	Alopecia both front legs	76
625335	Alopecia abdomen	7, 8, 9, 10, 13, 20, 27
625346	No abnormalities detected	1-6, 11-94
	Salivation	7-8
	Black ocular discharge	8
	Yellow-stained perineum	8
	Red-stained chin	8
	Brown-stained chin	9-10
625347	No abnormalities detected	1-94
625351	No abnormalities detected	1-6, 8-94
	Salivation	7

H-24020 (POSITIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP I

Animal Number	Observation	Test Day
627756	No abnormalities detected	1-5
627767	No abnormalities detected	1-5
627771	No abnormalities detected	1-5
627773	No abnormalities detected	1-5
627777	No abnormalities detected	1-5

GROUP II

Animal Number	Observation	Test Day
627768	No abnormalities detected	1-10
627774	No abnormalities detected	1-10
627776	No abnormalities detected	1-10
627782	No abnormalities detected	1-10
627785	No abnormalities detected	1-10

GROUP III

Animal Number	Observation	Test Day
627758	No abnormalities detected	1-13
627763	No abnormalities detected	1-13
627764	No abnormalities detected	1-13
627787	No abnormalities detected	1-5, 7-13
	Wet perineum	6
627788	No abnormalities detected	1-8, 10-13
	Diarrhea	9

H-24020 (POSITIVE CONTROL)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP IV

Animal Number	Observation	Test Day
627759	No abnormalities detected	1-24
627761	No abnormalities detected	1-24
627770	No abnormalities detected	1-24
627779	No abnormalities detected	1-24
627786	No abnormalities detected	1-24

GROUP V

Animal Number	Observation	Test Day
627757	No abnormalities detected	1-52
627760	No abnormalities detected	1-52
627765	No abnormalities detected	1, 3-52
	Wet perineum	2
627772	No abnormalities detected	1, 3-52
	Wet perineum	2
627781	No abnormalities detected	1-52

GROUP VI

Animal Number	Observation	Test Day
627762	No abnormalities detected	1-8, 10-94
	Diarrhea	9
627769	No abnormalities detected	1-94
627775	No abnormalities detected	1-94
627778	Alopecia perineum	81, 90, 94
627783	No abnormalities detected	1-23, 94
	Alopecia both front paws	24, 34, 41, 47,
		55, 61,
	Alopecia right front leg	74, 81, 90

H-24001 (TEST SUBSTANCE)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP I

Animal Number	Observation	Test Day
626904	No abnormalities detected	1-5
626905	No abnormalities detected	1-5
626915	No abnormalities detected	1-5
626923	No abnormalities detected	1-5
626930	No abnormalities detected	1-5

GROUP II

Animal Number	Observation	Test Day
626900	No abnormalities detected	1-10
626909	No abnormalities detected	1-10
626912	No abnormalities detected	1-10
626919	No abnormalities detected	1-10
626921	No abnormalities detected	1-10

GROUP III

Animal Number	Observation	Test Day
626901	No abnormalities detected	1-13
626907	No abnormalities detected	1-13
626910	No abnormalities detected	1-13
626913	No abnormalities detected	1-13
626914	No abnormalities detected	1-13

H-24001 (TEST SUBSTANCE)

INDIVIDUAL CLINICAL OBSERVATIONS IN MALE RATS

GROUP IV

Animal Number	Observation	Test Day
626897	No abnormalities detected	1-24
626903	No abnormalities detected	1-24
626916	No abnormalities detected	1-24
626925	No abnormalities detected	1-24
626926	No abnormalities detected	1-24

GROUP V

Animal Number	Observation	Test Day
626898	No abnormalities detected	1-52
626902	No abnormalities detected	1-52
626908	No abnormalities detected	1-52
626918	No abnormalities detected	1-52
626922	No abnormalities detected	1-52

GROUP VI

Animal Number	Observation	Test Day
626906	No abnormalities detected	1-93
626911	No abnormalities detected	1-48
	Alopecia perineum	52
	Alopecia both front paws	62, 69, 75
	Alopecia both front legs	89, 93
626920	No abnormalities detected	1-93
626924	No abnormalities detected	1-93
626927	No abnormalities detected	1-24
	Alopecia underbody	34, 48, 52, 62
	Alopecia chest	69, 75, 83
	Alopecia right side	89, 93

APPENDIX C

Analysis of Blood Fluoride Data

Terms and Calculations

Terms:

Active

% Active

Mol Wt Active

Formulation Dose

% F in Active

Mol Wt F

The molecular weight of fluorine g/mol

Compound Calculations:

Dose Active (mg/kg) The mg of fluorine containing compound administered per kg of animal body weight.
$$= (\% \text{ active}/100) * \text{Formulation Dose}$$

Dose Active (mmole/kg) The mmole of fluorine containing compound administered per kg of animal body weight
$$= \text{dose [mg/kg]} / \text{Mol Wt Active [mg/mmol]}$$

Dose F (mg/kg) The mg Fluorine administered per kg of animal body weight
$$= (\% \text{ F in active}/100) * \text{Dose Active [mg/kg]}$$

Dose F (mmol/kg) The mmole of fluorine administered per kg of animal body weight
$$= \text{Dose F [mg/kg]} / \text{Mol Wt F [mg/mmol]}$$

Molar Ratio (Active/F) The moles of fluorine containing compound per mole of fluorine
$$= \text{Dose Active [mmol/kg]} / \text{Dose F [mmol/kg]}$$

Formulation Dose
Normalization Factor The formulation dose that would be required to administer the amount of active needed to achieve the normalized dose
$$= (\text{Normalized dose of Active [mmol/kg]} / \text{Dose Active [mmol/kg]}) * \text{Formulation Dose}$$

Individual Animal Measurement:

ppm F in blood The ppm fluoride measured in blood

Individual Animal Calculations:

**ppm F in Blood minus
Bkg 0.2 ppm** The ppm fluoride measured in plasma minus the background
fluoride measured in control animal blood. In this case the value
was established at 0.2 ppm.

**ppm F in Blood
normalized to 0.1 mmol/kg
Dose** The ppm fluoride minus background that would be expected if the
active dose was 0.1 mmol/kg instead of the actual active dose. This
assumes linearity between administered dose and blood fluorine
levels, but is needed because different doses of active were used in
the study.
$$= (0.1 \text{ [mmol/kg]} / \text{Active dose [mmol/kg]}) * (\text{ppm F in blood} \\ \text{minus background})$$

**μmolar equivalents of
active in blood** The μmolar [μmol/L] concentration of fluorine containing
compound in plasma based on the ppm fluorine in plasma
normalized to 0.1 mmol/kg active dose. This assumes that all
plasma fluorine is derived from the fluorine-containing component
in the formulation. Note: 1 ppm – 1 mg/L
$$= (\text{Normalized ppm [mg/L] fluorine in blood} / \text{Mol Wt F} \\ \text{[mg/mmol]}) * \text{molar ratio active/F [mmol active/mmol F]} * \\ 1000 \text{ μmol/mmol}$$

Factors Influencing Interpretation of Kinetic Analysis

Considerations:

- The data used for kinetic analysis was from a limited screen and extrapolation should be done cautiously.
- Sample size is low
- Analytical data used without validation
- Steady-state not reached
- Terminal phase may not be reached
- Some compounds are mixtures of fluorinated compounds
- Different active and formulation doses were used
- Different vehicles were used to deliver formulations
- The kinetics apply only to plasma, not to specific tissues or the whole body
- Each compound may have very different potency for producing toxicity

Assumptions: (May or may not be justified in all cases)

- Plasma fluorine concentrations are linear with respect to dose
- Analytical method is appropriate for all types of compounds
- Elimination kinetics can be determined based on total fluorine rather than on concentrations of individual components
- Background plasma Fluoride is 0.2 ppm
- % F data is the % Fluorine of the active (Fluorine containing component(s) in the formulation
- Molecular weight is the molecular weight of the active component in the formulation

Data for H- 24019

Given:

Mol Wt. Active (g/mole):	497	% F in Active:	65
Formulation Dose (mg/kg):	10	Mol Wt. F (g/mol):	19
% Active (F Containing) in Formulation:	100		

Calculated Values:

Dose Active (mg/kg):	10	Dose F (mmol/kg):	0.342
Dose Active (mmole/kg):	0.020	Molar Ratio (Active/F):	0.059
Formulation Dose Normalization Factor:	49.7	Dose F (mg/kg):	6.5

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μmolar equivalents of active in blood
Group I					
625322	1	1.0	0.8	3.98	12.31
625323	1	1.3	1.1	5.47	16.92
625336	1	2.6	2.4	11.93	36.92
625343	1	2.6	2.4	11.93	36.92
625349	1	2.9	2.7	13.42	41.54
Group I					
625322	5	51.7	51.5	255.96	792.31
625323	5	38.0	37.8	187.87	581.54
625336	5	38.7	38.5	191.35	592.31
625343	5	78.5	78.3	389.15	1204.62
625349	5	37.1	36.9	183.39	567.69
Group II					
625320	10	65.6	65.4	325.04	1006.15
625330	10	61.1	60.9	302.67	936.92
625332	10	60.5	60.3	299.69	927.69
625341	10	63.1	62.9	312.61	967.69
625350	10	58.1	57.9	287.76	890.77

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μmolar equivalents of active in blood
Group III					
625321	13	77.2	77.0	382.69	1184.62
625327	13	61.5	61.3	304.66	943.08
625342	13	64.6	64.4	320.07	990.77
625345	13	57.0	56.8	282.30	873.85
625348	13	62.4	62.2	309.13	956.92
Group IV					
625325	24	40.3	40.1	199.30	616.92
625328	24	46.3	46.1	229.12	709.23
625338	24	43.2	43.0	213.71	661.54
625340	24	39.1	38.9	193.33	598.46
625352	24	41.9	41.7	207.25	641.54
Group V					
625324	52	24.7	24.5	121.77	376.92
625329	52	29.8	29.6	147.11	455.38
625333	52	27.3	27.1	134.69	416.92
625334	52	29.1	28.9	143.63	444.62
625344	52	23.8	23.6	117.29	363.08
Group VI					
625326	94	12.4	12.2	60.63	187.69
625335	94	16.4	16.2	80.51	249.23
625346	94	13.1	12.9	64.11	198.46
625347	94	11.0	10.8	53.68	166.15
625351	94	11.6	11.4	56.66	175.38

Data for H- 24020

Given:

Mol Wt. Active (g/mole):	426	% F in Active:	69
Formulation Dose (mg/kg):	20	Mol Wt. F (g/mol):	19
% Active (F Containing) in Formulation:	100		

Calculated Values:

Dose Active (mg/kg):	20	Dose F (mmol/kg):	0.726
Dose Active (mmole/kg):	0.047	Molar Ratio (Active/F):	0.065
Formulation Dose Normalization Factor:	42.6	Dose F (mg/kg):	13.8

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μmolar equivalents of active in blood
Group I					
627773	1	13.2	13.0	27.69	94.20
627771	1	8.1	7.9	16.83	57.25
627767	1	16.5	16.3	34.72	118.12
627756	1	14.1	13.9	29.61	100.72
627777	1	10.7	10.5	22.37	76.09
Group I					
627773	5	75.3	75.1	159.96	544.20
627771	5	66.8	66.6	141.86	482.61
627767	5	64.8	64.6	137.60	468.12
627756	5	80.0	79.8	169.97	578.26
627777	5	71.6	71.4	152.08	517.39
Group II					
627768	10	56.3	56.1	119.49	406.52
627774	10	51.0	50.8	108.20	368.12
627776	10	54.8	54.6	116.30	395.65
627782	10	43.6	43.4	92.44	314.49
627785	10	65.1	64.9	138.24	470.29

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μmolar equivalents of active in blood
Group III					
627758	13	43.5	43.3	92.23	313.77
627764	13	20.7	20.5	43.67	148.55
627787	13	13.2	13.0	27.69	94.20
627763	13	30.8	30.6	65.18	221.74
627788	13	24.9	24.7	52.61	178.99
Group IV					
627759	24	9.2	9.0	19.17	65.22
627779	24	14.9	14.7	31.31	106.52
627770	24	11.6	11.4	24.28	82.61
627761	24	9.9	9.7	20.66	70.29
627786	24	6.7	6.5	13.85	47.10
Group V					
627757	52	0.9	0.7	1.49	5.07
627781	52	0.6	0.4	0.85	2.90
627760	52	1.0	0.8	1.70	5.80
627765	52	0.9	0.7	1.49	5.07
627772	52	0.8	0.6	1.28	4.35
Group VI					
627778	94	0.3	0.1	0.21	0.72
627783	94	<0.2	*	*	*
627762	94	0.2	0.0	0.00	0.00
627775	94	0.2	0.0	0.00	0.00
627769	94	<0.2	*	*	*

* = Below LOD (Level of Detection)

Data for H- 24001

Given:

Mol Wt. Active (g/mole):	60	% F in Active:	60
Formulation Dose (mg/kg):	1000	Mol Wt. F (g/mol):	19
% Active (F Containing) in Formulation:	35		

Calculated Values:

Dose Active (mg/kg):	350	Dose F (mmol/kg):	11.053
Dose Active (mmole/kg):	0.583	Molar Ratio (Active/F):	0.053
Formulation Dose Normalization Factor:	171.4	Dose F (mg/kg):	210

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μmolar equivalents of active in blood
Group I					
626904	1	3.3	3.1	0.53	1.48
626905	1	4.2	4.0	0.69	1.90
626915	1	3.9	3.7	0.63	1.76
626923	1	3.9	3.7	0.63	1.76
626930	1	5.1	4.9	0.84	2.33
Group I					
626904	5	12.8	12.6	2.16	6.00
626905	5	13.3	13.1	2.25	6.24
626915	5	11.9	11.7	2.01	5.57
626923	5	#	#	#	#
626930	5	15.5	15.3	2.62	7.29
Group II					
626900	10	15.2	15.0	2.57	7.14
626909	10	18.5	18.3	3.14	8.71
626912	10	20.8	20.6	3.53	9.81
626919	10	25.7	25.5	4.37	12.14
626921	10	17.3	17.1	2.93	8.14

Rat #	Test Day Sample	ppm F in blood	ppm F in blood minus Bkg 0.2 ppm	ppm F in blood Normalized to 0.1 mmoles/Kg Dose	μ molar equivalents of active in blood
Group III					
626901	13	7.7	7.5	1.29	3.57
626907	13	5.5	5.3	0.91	2.52
626910	13	6.8	6.6	1.13	3.14
626913	13	5.7	5.5	0.94	2.62
626914	13	5.6	5.4	0.93	2.57
Group IV					
626897	24	2.4	2.2	0.38	1.05
626903	24	2.8	2.6	0.45	1.24
626916	24	2.7	2.5	0.43	1.19
626925	24	2.5	2.3	0.39	1.10
626926	24	2.8	2.6	0.45	1.24
Group V					
626898	52	1.8	1.6	0.27	0.76
626902	52	2.0	1.8	0.31	0.86
626908	52	1.4	1.2	0.21	0.57
626918	52	1.7	1.5	0.26	0.71
626922	52	1.9	1.7	0.29	0.81
Group VI					
626906	94	0.8	0.6	0.10	0.29
626911	94	1.0	0.8	0.14	0.38
626920	94	1.2	1.0	0.17	0.48
626924	94	1.2	1.0	0.17	0.48
626927	94	1.1	0.9	0.15	0.43

= Tube of blood for this rat was missing or broken.