ADME NTP Study S0192 Ferrocene

The contract laboratory abbreviation for the test article is FCN.
Species: young adult male F344 rats.
Vehicles: intravenous, Emulphor EL-620:ethanol:phosphate buffered saline 15:5:80 (v/v); inhalation, conditioned room air.

CASRN 102-54-5

This study had two separate study protocols and reports. The first used [^{14}C]FCN as the radiolabel; the second, later report used [^{55}Fe]FCN.
Radiolabeled with carbon-14 in the ring; Ferrocene, [U-cyclopentadienyl-^{14}C]-
Radiolabeled with iron-55; [^{55}Fe]Ferrocene.

Ferrocene Studies Performed:

- 1 mg/kg [^{14}C]FCN single intravenous administration with sacrifice at 72 hours postdose.

- 5 ng/mL [^{14}C]FCN 6-hour nose-only inhalation exposure divided into two groups: sacrifice at 72 hours post 6-hour exposure (Group A) and at 0 hour immediately after 6-hour exposure (Group B).

- 25 ng/mL [^{14}C]FCN 6-hour nose-only inhalation exposure divided into two groups: sacrifice at 72 hours post 6-hour exposure (Group A) and at 0 hour immediately after 6-hour exposure (Group B).

- 1 mg/kg [^{55}Fe]FCN single intravenous administration with sacrifice at 72 hours postdose.

- 5 ng/mL [^{55}Fe]FCN 6-hour nose-only inhalation exposure divided into two groups: sacrifice at 72 hours post 6-hour exposure (Group A) and at 0 hour immediately after 6-hour exposure (Group B).

- 25 ng/mL [^{55}Fe]FCN 6-hour nose-only inhalation exposure divided into two groups: sacrifice at 72 hours post 6-hour exposure (Group A) and at 0 hour immediately after 6-hour exposure (Group B).

For toxicokinetic studies, a second group of three rats was added to the above treatments for blood sampling. In addition, a blood-only intravenous study was done:

- 1 mg/kg [^{14}C]FCN single intravenous administration with sacrifice at 145 hours postdose.

Toxicokinetic parameters:

Best fits of ferrocene blood concentrations following a single intravenous dose in the rat were obtained using a mammillary 3-compartment system. Simultaneous solution of the differential equations yielded estimates for K12, K21, K13, K31, and V, the volume of the central compartment. These parameters were subsequently employed in a 7-compartment model with clearance metabolically from the central compartment by metabolism to iron-containing metabolite(s) (Fe_{met}) with clearance CL_{Fe} and metabolism to ferrocenyl glucuronide (FCN-Gluc) with subsequent excretion into the urine (clearance CL_{out}).

Estimates of the amount of Fe-metabolite(s) in plasma (volume V_p) and erythrocytes (volume V_B) were obtained by subtracting the concentration of parent ferrocene in whole blood from the amount of total iron (^{55}Fe) in plasma and erythrocytes (assuming that parent ferrocene was distributed homogenously throughout whole blood). The Fe-metabolite(s) were cleared from the plasma compartment into the erythrocyte compartment (clearance CL_D) or into the feces (CL_{feces}). Differential equations for the model were solved simultaneously using PCNONLIN (SCI Software, Lexington, KY). Dat were weighted as C^{-1}.

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Table 1

Cumulative Excretion of Total ^{14}C by F344-M Rats after Administration of [^{14}C]FCN by Intravenous or Inhalation Exposure[a]

Route		IV		Inhalation			
Dose		1.0 mg FCN/kg body weight		25 ng FCN/mL air		5 ng FCN/mL air	
Excreta	Time (h)	μg-eq FCN	(% recovered)[b]	μg-eq FCN	(% recovered)[b]	μg-eq FCN	(% recovered)[b]
Urine	24	125 ± 5	(61.1 ± 2.6)	491 ± 69[c]	(64.9 ± 9.3)[c]	138 ± 30[c]	(76.7 ± 2.4)[c]
	48	150 ± 6	(73.6 ± 2.5)	615 ± 34	(81.2 ± 3.5)	152 ± 33	(84.2 ± 1.6)
	72	158 ± 7	(77.6 ± 2.7)	646 ± 23	(85.3 ± 1.6)	156 ± 33	(86.6 ± 1.2)
Feces	24	19 ± 2	(9.2 ± 0.3)	38 ± 9[d]	(5.0 ± 1.1)[d]	7 ± 3[d]	(4.0 ± 2.1)[d]
	48	29 ± 3	(13.8 ± 0.7)	64 ± 6	(8.4 ± 0.4)	12 ± 2	(7.1 ± 1.6)
	72	35 ± 6	(17.0 ± 2.2)	69 ± 6	(9.1 ± 0.5)	14 ± 2	(8.1 ± 1.9)
Breath	24	3 ± 1	(1.5 ± 0.2)	18 ± 4	(2.4 ± 0.6)	5 ± 3	(2.9 ± 0.8)
(Volatiles)	48	4 ± 1	(1.7 ± 0.4)	20 ± 4	(2.7 ± 0.6)	6 ± 3	(3.1 ± 0.8)
	72	4 ± 1	(2.0 ± 0.5)	22 ± 5	(2.9 ± 0.7)	6 ± 2	(3.2 ± 0.8)
Breath	24	3 ± 0	(1.4 ± 0.1)	4 ± 1	(0.6 ± 0.1)	1 ± 0	(0.5 ± 0.1)
(CO_2)	48	3 ± 0	(1.6 ± 0.1)	6 ± 1	(0.8 ± 0.2)	1 ± 0	(0.6 ± 0.1)
	72	4 ± 1	(1.7 ± 0.1)	6 ± 2	(0.8 ± 0.3)	1 ± 1	(0.8 ± 0.1)
Total		201 ± 11	(98.3 ± 0.7)[e]	743 ± 23	(98.1 ± 0.7)	177 ± 35	(98.6 ± 0.2)

[a] Values are mean ± SD for three rats.
[b] Values are percent of total ^{14}C recovered in excreta and tissues.
[c] Value includes urine collected during the exposure period.
[d] Value includes feces collected during the exposure period.
[e] Value is 88.3 ± 1.4 percent of the administered ^{14}C.

Table 2

Cumulative Excretion of Total ^{55}Fe by F-344 Male Rats after Administration of [^{55}Fe]FCN by Intravenous or Inhalation Exposure[a]

Route		IV	Inhalation	
Dose		1.0 mg FCN/kg body weight	25 ng FCN/mL air	5 ng FCN/mL air
Excreta	End of Collection Period (h)[b]	(% of Recovered Dose)[c]	(% of Recovered Dose)[c]	(% of Recovered Dose)[c]
Urine	6	10.4 ± 1.6	7.9 ± 3.5[d]	15.4 ± 3.4[d]
	12	19.4 ± 1.4	15.0 ± 1.3	24.2 ± 4.7
	24	29.3 ± 1.5	23.5 ± 1.9	33.1 ± 2.1
	48	37.6 ± 2.4	31.0 ± 2.2	36.7 ± 2.1
	72	39.8 ± 2.5	33.4 ± 1.7[c]	38.0 ± 1.8[e]
Feces	24	5.1 ± 1.1	8.4 ± 2.5[f]	4.3 ± 3.7[f]
	48	10.9 ± 2.0	12.8 ± 0.8	10.3 ± 1.0
	72	13.0 ± 2.2	18.3 ± 0.9	12.8 ± 1.8[e]
Breath	6	0.3 ± 0.1	15.0 ± 0.3	8.3 ± 1.5
(Volatiles)	12	0.5 ± 0.1	16.5 ± 0.2	9.0 ± 1.5
	24	0.5 ± 0.1	17.1 ± 0.1	9.3 ± 1.6
	48	0.6 ± 0.1	17.4 ± 0.1	9.5 ± 1.6
	72	0.6 ± 0.1	17.5 ± 0.2	9.6 ± 1.7[e]
Total		53.4 ± 0.89[g]	69.2 ± 1.7	60.4 ± 0.9

a Values are mean ± SD for three rats.
b Time points are referenced to time of iv dosing or to the end of 6 h inhalation exposure.
c Values are percent of total ^{55}Fe recovered in excreta, tissues, blood and residual carcass.
d Value includes urine collected during the exposure period.
e Value includes excreta collected after 66 h, when all animals in this group were found dead.
f Values includes feces collected during the exposure period.
g Total recovery following iv dosing was 91.4 ± 1.8% of the administered ^{55}Fe.

Table 3

Concentration of ^{14}C in Tissues of F344-M Rats Immediately following Inhalation Exposure of [^{14}C]FCN[a]

Concentration	25 ng FCN/mL air			5 ng FCN/mL air		
Tissue Name	ng-eq cmpd per g Tssue	Tissue Blood Ratio	Percent of Recovered ^{14}C in Total Tissue[b]	ng-eq cmpd per g Tissue	Tissue Blood Ratio	Percent of Recovered ^{14}C in Total Tissue[b]
Adipose	8490 ± 1340	23.1 ± 2.1	20.9 ± 1.9	1150 ± 80	13.7 ± 1.9	14.2 ± 2.1
Bladder	7500 ± 1930	20.3 ± 3.2	0.08 ± 0.02	741 ± 124	8.9 ± 2.3	0.04 ± 0.02
Blood	367 ± 35	unity	0.68 ± 0.02	84 ± 7	unity	0.77 ± 0.01
Brain	507 ± 38	1.4 ± 0.1	0.13 ± 0.02	101 ± 4	1.2 ± 0.1	0.12 ± 0.01
Cecum[c]	5170 ± 4540	14.7 ± 13.7	0.39 ± 0.35	859 ± 524	9.9 ± 5.8	0.30 ± 0.17
Heart	526 ± 12	1.4 ± 0.1	0.06 ± .00	114 ± 4	1.4 ± 0.1	0.06 ± 0.01
Intestine, large[c]	2490 ± 890	7.0 ± 3.0	0.30 ± 0.15	489 ± 200	5.7 ± 2.1	0.23 ± 0.07
Intestine, small[c]	12000 ± 5900	32.1 ± 12.6	3.13 ± 1.23	3410 ± 30	40.6 ± 3.4	4.09 ± 0.34
Kidney	26100 ± 6500	72.6 ± 23.8	6.72 ± 2.19	5000 ± 610	59.8 ± 12.1	6.46 ± 0.79
Liver	4130 ± 280	11.3 ± 0.7	5.34 ± 0.96	896 ± 76	10.6 ± 0.8	5.68 ± 0.41
Lung	1650 ± 110	4.5 ± 0.5	0.22 ± 0.03	382 ± 21	4.5 ± 0.5	0.24 ± 0.04
Muscle	444 ± 85	1.2 ± 0.3	7.7 ± 2.2	73 ± 4	0.9 ± 0.1	6.23 ± 1.01
Nasopharynx	4230 ± 1230	11.6 ± 3.6	0.81 ± 0.15	1370 ± 250	16.4 ± 4.2	1.75 ± 0.12
Plasma	386 ± 51	1.0 ± 0.0	0.37 ± 0.01	76 ± 6	0.9 ± 0.0	0.36 ± 0.01
Skin	1410 ± 410	3.8 ± 0.7	8.3 ± 1.4	149 ± 36	1.8 ± 0.4	4.45 ± 0.98
Spleen	558 ± 150	1.5 ± 0.4	0.03 ± 0.01	81 ± 3	1.0 ± 0.1	0.02 ± 0.00
Testis	342 ± 54	0.9 ± 0.1	0.13 ± 0.02	69 ± 1	0.8 ± 0.1	0.12 ± 0.01
Trachea	18000 ± 2700	49.5 ± 8.7	0.16 ± 0.05	2350 ± 530	28.4 ± 9.1	0.15 ± 0.12

a Values are mean ± SD for three rats.

b Percent of recovered ^{14}C was based on the total radioactivity in the urine and feces plus the radioactivity present in tissues. Adipose assumed to be 7.0% of body weight; blood = 5.2%; muscle = 48%; skin = 17%; plasma = 52% of blood.

c Intestinal contents were removed before analysis. The combined small intestine, large intestine and cecum contents contained 19.8 ± 2.2 (25 ng/mL) and 22.0 ± 1.4 (5 ng/mL) percent of the recovered ^{14}C, respectively.

Table 4

Summary of ^{55}Fe in Tissues of F-344 Male Rats Sacrificed Immediately Following Cessation of 6 h Inhalation Exposure to [^{55}Fe]FCN[a]

Concentration	25 ng FCN/mL Air			5 ng FCN/mL Air		
Tissue Name	µg-eq cmpd per g Tissue	Tissue to Blood Ratio	Percent of Recovered ^{55}Fe in Total Tissue[b]	µg-eq cmpd per g Tissue	Tissue to Blood Ratio	Percent of Recovered ^{55}Fe in Total Tissue[b]
Adipose	9190 ± 1360	40.9 ± 24.4	33.9 ± 5.3	1410 ± 240	7.72 ± 2.45	9.23 ± 0.35
Bladder	4760 ± 3870	20.2 ± 14.7	0.1 ± 0.1	1050 ± 790	6.62 ± 7.12	0.07 ± 0.06
Blood	260 ± 90	unity	0.5 ± 0.2	200 ± 80	unity	0.95 ± 0.28
Brain	470 ± 140	2.2 ± 1.6	0.1 ± c	70 ± 20	0.40 ± 0.15	0.06 ± 0.01
Heart	570 ± 160	2.6 ± 1.8	0.1 ± c	120 ± 30	0.65 ± 0.11	0.04 ± 0.01
Kidney	29940 ± 1580	126.2 ± 50.5	9.2 ± 0.4	8790 ± 460	49.26 ± 18.26	7.48 ± 1.36
Liver	7260 ± 370	30.5 ± 11.6	11.5 ± 1.4	2700 ± 220	14.86 ± 4.66	12.08 ± 1.52
Lung	4720 ± 680	20.3 ± 9.8	0.6 ± 0.1	4680 ± 420	25.94 ± 9.04	1.62 ± 0.22
Muscle	880 ± 790	4.8 ± 5.9	16.6 ± 15.2	70 ± 40	0.39 ± 0.18	3.16 ± 1.35
Nasopharyngeal	8570 ± 3160	40.4 ± 32.7	1.5 ± 0.4	11790 ± 1300	65.41 ± 21.66	4.65 ± 0.74
Skin	1470 ± 390	6.0 ± 1.9	9.7 ± 2.5	310 ± 140	1.57 ± 0.22	0.06 ± 0.01
Spleen	630 ± 100	2.7 ± 1.1	c ± c	450 ± 210	2.45 ± 1.22	6.97 ± 2.36
Testis	360 ± 60	1.6 ± 1.0	0.1 ± c	80 ± 30	0.41 ± 0.12	0.08 ± 0.02
Trachea	16880 ± 3940	76.4 ± 50.6	0.2 ± 0.1	7430 ± 950	40.49 ± 11.25	0.54 ± 0.09
Carcass[d]	620 ± 10	2.7 ± 1.2	67.4 ± 2.5	240 ± 40	1.35 ± 0.52	66.54 ± 1.73

a Values are mean ± SD for three rats.

b Percent of recovered ^{55}Fe was based on the total radioactivity in the urine and feces plus the radioactivity present in tissues. Adipose assumed to be 7.0% of body weight; blood = 5.2%; muscle = 48%; skin = 17%; plasma = 52% of blood.

c Value is less than 0.05.

d Includes intestinal contents.

Table 5

Concentration of ^{14}C in Tissues of F344-M Rats 72 h after Administration of [^{14}C]FCN by Intravenous or Inhalation Exposure[a]

Route	iv			Inhalation					
Dose	1.0 mg FCN/kg body weight			25 ng FCN/mL air			5 ng FCN/mL air		
Tissue Name	ng-eq cmpd per g Tissue	Tissue Blood Ratio	% of Recovered ^{14}C in Total Tissue	ng-eq cmpd per g Tissue	Tissue to Blood Ratio	% of Recovered ^{14}C in Total Tissue	ng-eq cmpd per g Tissue	Tissue Blood Ratio	% of Recovered ^{14}C in Total Tissue
Adipose	35 ± 6	3.3 ± 1.4	0.22 ± 0.04	194 ± 134	3.2 ± 1.7	0.42 ± 0.30	16 ± 16	1.6 ± 1.7	0.16 ± 0.16
Bladder	38 ± 5	3.5 ± 0.8	0.00 ± 0.00	95 ± 30	1.6 ± 0.4	0.00 ± 0.00	39 ± 17	3.3 ± 1.3	0.00 ± 0.00
Blood	12 ± 3	unity	0.05 ± 0.01	60 ± 15	unity	0.10 ± 0.02	12 ± 2	unity	0.08 ± 0.02
Brain	4 ± 1	0.4 ± 0.1	0.00 ± 0.00	17 ± 4	0.3 ± 0.1	0.00 ± 0.00	5 ± 1	0.4 ± 0.1	0.00 ± 0.00
Cecum	NA[b]	NA[b]	-	139 ± 43	2.3 ± 0.5	0.01 ± 0.00	74 ± 39	5.9 ± 2.2	0.02 ± 0.01
Heart	12 ± 1	1.0 ± 0.3	0.00 ± 0.00	28 ± 6	0.5 ± 0.0	0.00 ± 0.00	6 ± 1	0.5 ± 0.1	0.00 ± 0.00
Intestine, large	NA[b]	NA[b]	-	91 ± 31	1.5 ± 0.5	0.01 ± 0.00	33 ± 14	2.6 ± 0.8	0.01 ± 0.00
Intestine, small	NA[b]	NA[b]	-	90 ± 51	1.5 ± 0.6	0.02 ± 0.01	20 ± 3	1.6 ± 0.1	0.02 ± 0.00
Kidney	78 ± 223	6.8 ± 1.3	0.06 ± 0.01	224 ± 26	3.9 ± 0.7	0.06 ± 0.01	60 ± 12	5.1 ± 1.1	0.07 ± 0.02
Liver	151 ± 17	13.5 ± 2.2	0.56 ± 0.03	232 ± 40	4.2 ± 1.9	0.29 ± 0.05	48 ± 3	4.0 ± 0.5	0.24 ± 0.04
Lung	31 ± 9	2.7 ± 0.0	0.01 ± 0.00	77 ± 4	1.3 ± 0.3	0.01 ± 0.01	23 ± 2	2.0 ± 0.5	0.01 ± 0.00
Muscle	10 ± 1	0.9 ± 0.3	0.41 ± 0.05	20 ± 4	0.3 ± 0.0	0.30 ± 0.06	3 ± 1	0.3 ± 0.0	0.18 ± 0.02
Nasopharynx	16 ± 2	1.4 ± 0.0	0.01 ± 0.00	102 ± 46	1.7 ± 0.5	0.02 ± 0.01	36 ± 2	3.0 ± 0.6	0.04 ± 0.00
Plasma	5 ± 1	0.4 ± 0.0	0.01 ± 0.00	45 ± 59	0.7 ± 0.8	0.01 ± 0.01	2 ± 0	0.1 ± 0.0	0.01 ± 0.00
Skin	17 ± 3	1.5 ± 0.4	0.26 ± 0.04	32 ± 10	0.5 ± 0.1	0.17 ± 0.06	7 ± 1	0.6 ± 0.1	0.14 ± 0.00
Spleen	37 ± 5	3.3 ± 0.5	0.01 ± 0.00	40 ± 17	0.7 ± 0.1	0.00 ± 0.00	9 ± 0	0.8 ± 0.1	0.00 ± 0.00
Testis	5 ± 0	0.5 ± 0.1	0.01 ± 0.00	17 ± 5	0.3 ± 0.0	0.01 ± 0.00	5 ± 2	0.4 ± 0.1	0.01 ± 0.00
Trachea	31 ± 8	2.9 ± 1.0	0.00 ± 0.00	57 ± 5	1.0 ± 0.3	0.00 ± 0.00	26 ± 8	2.3 ± 1.1	0.00 ± 0.00

a Values are mean ± SD for three rats.
b NA = Not Analyzed.

Table 6

Concentration of ^{55}Fe in Tissues of F-344 Male Rats 72 h after Administration of [^{55}Fe]FCN by Intravenous or Inhalation Exposure[a]

Route	Iv		Inhalation			
Dose	1 mg FCN/kg body weight[b]		25 ng FCN/mL Air[c]		5 ng FCN/mL Air	
Tissue Name	µg-eq cmpd per g Tissue	Percent of Administered ^{55}Fe in Total Tissue[b]	µg-eq cmpd per g Tissue	Percent of Recovered ^{55}Fe in Total Tissue[d]	µg-eq cmpd per g Tissue	Percent of Recovered ^{55}Fe in Total Tissue[d]
Adipose	0.12 ± 0.01	0.6 ± 0.1	0.27 ± 0.04	0.7 ± 0.1	0.12 ± 0.02	0.75 ± 0.11
Bladder	0.05 ± 0.01	e ± e	0.09 ± 0.02	e ± e	0.07 ± 0.02	e ± e
Blood	1.77 ± 0.31	7.4 ± 1.5	4.38 ± 0.47	8.1 ± 1.6	-	-
Brain	0.03 ± e	f ± e	0.06 ± e	f ± e	0.06 ± 0.01	0.04 ± 0.01
Heart	0.39 ± 0.05	0.1 ± e	1.87 ± 1.17	0.3 ± 0.2	0.79 ± 0.46	0.28 ± 0.18
Kidney	1.12 ± 0.17	0.9 ± 0.1	7.27 ± 0.41	2.0 ± 1.1	2.41 ± 0.20	2.13 ± 0.08
Liver	5.23 ± 0.34	22.2 ± 2.3	12.81 ± 2.29	15.5 ± 2.4	4.14 ± 0.32	19.04 ± 0.68
Lung	1.11 ± 0.14	1.1 ± 0.1	3.97 ± 0.74	1.1 ± 0.1	2.61 ± 0.35	2.20 ± 0.17
Muscle	0.02 ± e	0.6 ± 0.1	0.05 ± 0.02	0.8 ± 0.4	0.03 ± 0.01	1.46 ± 0.21
Nasopharyngeal	1.52 ± 0.49	0.5 ± 0.1	9.33 ± 1.03	1.62 ± 0.5	5.07 ± 0.79	3.12 ± 0.49
Skin	0.05 ± 0.01	0.7 ± 0.1	0.17 ± 0.04	1.0 ± 0.1	0.07 ± 0.02	1.13 ± 0.28
Spleen	0.84 ± 0.20	0.3 ± 0.1	3.18 ± 0.97	0.3 ± 0.1	0.99 ± 0.29	0.28 ± 0.08
Testis	0.05 ± e	0.1 ± e	0.14 ± 0.02	0.1 ± f	0.08 ± 0.02	0.09 ± 0.02
Trachea	1.29 ± 0.27	0.1 ± f	7.98 ± 1.42	0.2 ± f	4.64 ± 1.06	0.35 ± 0.06
Carcass	0.03 ± e	7.6 ± 0.8	0.10 ± 0.01	10.18 ± 1.9	0.04 ± 0.01	10.78 ± 1.53

a Values are mean ± SD for three rats. Rats in the low dose inhalation study died between 51 and 66 h after end of exposure. No blood samples were available for these animals. Therefore, calculation of Tissue to blood Ratios was not possible.

b Tissue to Blood Ratio for liver was 3.0. Tissue to Blood Ratios for all other tissues were <1.

c Tissue to Blood Ratios that were <1.0 are as follows: liver, 3.0; nasopharyngeal region, 2.1; trachea, 1.8; kidney, 1.7.

d Percent of recovered ^{55}Fe was based on the total radioactivity in the urine and feces plus the radioactivity present in tissues. Adipose assumed to be 7.0% of body weight; blood = 5.2%; muscle = 48%; skin = 17%; plasma = 52% of blood.

e Value is less than 0.005.

f Value is less than 0.05.

Table 7

Concentration of ^{14}C in Blood of F-344 Male Rats During and following Administration of Ferrocene (ng-eq/g Blood)[a]

Route	Intravenous		Inhalation (nose-only)							
Dose	1 mg FCN/kg body wt.		25 ng FCN/mL air				5 ng FCN/mL air			
			Group A[c]		Group B[d]		Group A[c]		Group B[d]	
Time (h)[b]	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
-5.75					72.4	9.9			18.5	2.6
-5.5					120.5	27.3			27.3	3.7
-5					153.1	31.2			35.9	3.4
-4					189.3	40.6			41.3	1.9
-2					285.6	41.4			60.3	6.1
0					366.7	34.9			84.4	7.2
0.5	239.2	1.6	278.9	30.2			72.5	13.4		
1	150.4	24.9	238.9	17.6			68.8	14.1		
2	140.7	9.3	237.6	8.7			51.4	7.7		
3	101.5	7.3	205.7	10.0			48.1	5.9		
6	96.7	7.3	166.2	17.8			36.5	1.5		
12	61.3	5.7	118.0	3.3			27.5	5.2		
24	32.7	3.7	93.1	18.0			22.9	3.9		
48	18.3	8.8	69.5	22.3			18.2	4.5		
72	11.5	3.1	51.1	10.9			12.0	2.2		

[a] Mean ± SD for three rats.
[b] All time points referenced to time of administered iv dose or end of 6 h exposure.
[c] These animals were sacrificed 72 h after end of exposure.
[d] These animals were sacrificed at end of exposure.

Table 8

Concentration of ^{55}Fe in Blood of F-344 Male Rats During and Following Administration of Ferrocene (ng eq/g Blood)[a]

Route	iv		Inhalation							
Dose	1 mg FCN/kg Body Weight		25 ng FCN/mL Air				5 ng FCN/mL Air			
			Group A[d]		Group B[e]		Group A[f]		Group B[e]	
Time (h)[b]	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
-5.75					20.9	8.5			5.4	2.5
-5.5					32.4	6.4			11.4	4.3
-5					49.0	18.8			22.7	11.6
-4					85.4	22.8			56.2	34.1
-3			243.9	78.2			79.8	29.2	125.2	51.1
-2					157.5	55.4				
0			408.0	77.7	262.1	91.4	160.9	57.2	196.9	75.6
0.5	101.6	63.5	233.6	82.6			124.0	74.2		
1	71.3	46.0	250.2	66.5			126.2	52.9		
2	64.7	34.4	216.8	63.7			141.9	58.8		
3	60.3	28.6	202.2	53.2			160.0	55.1		
6	64.1	13.7	331.3	117.7			214.5	46.1		
12	118.9	5.1	588.4	182.3			339.2	119.1		
24	314.3	2.8	1164.6	215.2			754.9	232.4		
48	739.1	120.1	1674.4	910.7			1410.5	439.3		
72	2132.7	c	4380.6	468.8						

a Mean ± SD for three rats.
b All time points referenced to time of administered iv dose or end of 6 h exposure.
c These animals were sacrificed 72 h after dosing, but terminal blood sample was collected from only one animal in the group for analysis.
d These animals were sacrified 72 h after end of exposure.
e These animals were sacrificed at end of exposure.
f These animals were found dead 66 h after exposure. No 72 h blood was collected.

Table 9

Concentration of ^{55}Fe in Plasma and Erythrocytes of F-344 Male Rats Following iv Administration of 1 mg FCN/kg Body Weight (ng eq/g Plasma or Erythrocytes)[a]

	Plasma		Erythrocytes	
Time (h)[b]	Mean	SD	Mean	SD
0.0	0.1	0.1	1.3	0.7
0.5	169.4	84.0	83.1	0.6
1.0	120.1	77.8	35.8	20.6
2.0	135.4	66.7	42.1	22.6
3.0	148.9	60.0	51.6	35.7
6.0	138.5	30.4	85.7	35.0
12.0	144.1	68.3	140.1	68.3
24.0	75.6	10.5	887.1	289.6
48.0	49.0	10.5	3734.1	1145.9
72.0	49.3	21.7	5576.4	1078.9
145.0	39.9	10.5	9792.2	1059.6

[a] Mean ± SD for three rats.

[b] Time points referenced to time of iv dosing.

Table 10

Concentration of Ferrocene in Blood of F-344 Male Rats During and Following Administration of Ferrocene (ng/g Blood)[a]

Route	iv		Inhalation							
Dose	1 mg FCN/kg Body Weight[c]		25 ng FCN/mL Air				5 ng FCN/mL Air			
			Group A[c]		Group B[d]		Group A[e]		Group B[d]	
Time (h)[b]	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
-5.75					20.4	2.8			4.9	1.0
-5.5					35.3	2.6			10.1	4.6
-5					51.4	28.9			14.8	4.5
-4					68.7	16.9			18.9	4.5
-3			176.0	104.3			25.6	6.8		
-2					141.9	45.2			33.0	14.7
0			412.0[f]	435.3	185.9	34.5	28.5	6.5	34.5	19.2
0.5	98.8	2.69[g]	389.0[h]	498.9			23.3	6.8		
1	52.2	34.1	85.2	51.2[i]			18.5	8.1		
2	40.3	14.8	59.4	19.8			10.9	2.3		
3	30.0	17.5	63.0	17.8			6.9	0.7		
6	22.6	7.9	36.5	14.0			3.6	0.7		
12	10.5	2.4	7.6	5.1			1.5	1.0		
24	4.6	7.5[i]	4.5	1.1[i]			0.8	0.4		
48	<1	-[j]	<2	-[j]			0.6	0.2		
72			<0.7	-[j]						

a Values are Mean ± SD for three rats, unless stated otherwise.
b All time points referenced to time of administered iv dose or end of 6 h exposure.
c These animals were sacrificed 72 h following iv dosing or end of exposure.
d These animals were sacrificed at end of exposure.
e These animals were found dead 66 h after exposure. No 72 h blood was collected.
f Individual animal data were 914.2 ng/g, 179.6 ng/g and 142.2 ng/g.
g Value is from a single rat.
h Individual animal data were 961.9 ng/g, 49.5 ng/g and 155.7 ng/g.
i Values are Mean ± SD for two rats.
j FCN concentrations for 1 or more animals was below the limit of quantitation of ca. 0.5 ng/g blood.

Table 11

Pharmacokinetic Parameter Estimates Derived to Describe the Disposition of Intravenously Administered Ferrocene (1 mg/kg) in the Rat

Parameter	Estimate	±	SE	
K12	2.203	±	0.735	h^{-1}
K21	0.645	±	0.103	h^{-1}
K13	0.322	±	0.179	h^{-1}
K31	0.041	±	0.041	h^{-1}
CL_{Fe}	0.465	±	0.577	µg/kg/h
Cl_D	0.009	±	0.033	µg/kg/h
Cl_{feces}	0.025	±	0.029	µg/kg/h
Cl_{out}	0.404	±	0.235	µg/kg/h
V	2.778	±	1.259	l/kg
V_P	3.306	±	3.470	l/kg
V_B	0.011	±	0.037	l/kg

Table 12

Pharmacokinetic Parameter Estimates Derived Using the Basic 3-Compartment Model to Describe Concentrations of Ferrocene in Blood following iv, Low Dose Inhalation, and High Dose Inhalation Exposures in the Rat

Parameter	Estimate ± SE	Estimate ± SE
	iv Data Only	iv, Low Dose Inhalation and High Dose Inhalation Data
Cl total	1.59 ± 0.27 l/kg/h	2.42 ± 0.44 l/kg/h
K01 (low dose inhalation)	-	128.9 ± 47.1 µg/kg/h
K02 (high dose inhalation)	-	733.5 ± 105.0 µg/kg/h

NOTE: The parameter V was estimated from the iv data (Table 15) and held constant.