

## ADME NTP Study S0231 2,4,7-Trinitro-fluoren-9-one

The contract laboratory abbreviation is TNF.

Sex/Species: adult female F344 rats.

Vehicles: intravenous, dimethyl sulfoxide (DMSO):serum (1:3), oral, corn oil; dermal, acetone; intrainestinal, DMSO:serum (1:3).

CASRN 129-79-3

Radiolabeled with carbon-14 at the carbonyl carbon; 2,4,7-Trinitro[9-<sup>14</sup>C]fluorenone

Studies performed:

1. Single 47 µg/2 cm<sup>2</sup> dermal dose in rats with covered dose site and sacrifice 24 hours postdose. (Mean body weight and standard deviation is 135 ± 5 g; n=4, 2 cm<sup>2</sup> dose area).
2. Single 400 µg/2 cm<sup>2</sup> dermal dose in rats with covered dose site and sacrifice 72 hours postdose. (Mean body weight and standard deviation is 128 ± 4 g; n=4, 2 cm<sup>2</sup> dose area).
3. Single 1, 10, or 100 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose.
4. Single 1 mg/kg intravenous dose in rats with sacrifice 72 hours postdose.
5. Single 1 mg/kg intravenous dose in rats with bile collected to 6 hours postdose.
6. Single 1 mg/kg intrainestinal dose with bile collected to 6 hours postdose.
7. Single 10 mg/kg oral gavage dose to control animals and those pretreated with lincomycin/neomycin designed to determine the contribution of gut flora to the disposition of TNF. Rats were sacrificed at 6 hours.

The intrainestinal dose for the bile cannulation study was administered into the proximal end of the small intestine, approximately 1-2 cm south of the pylorus.

For Table 4, the original heading had a concentration value of 400 mg/2 cm<sup>2</sup> which was contradicted in multiple places in the report text. This value has been corrected to 400 µg/2 cm<sup>2</sup>.

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Table 1

Distribution of Radioactivity in Urine and Feces after  
Dermal Administration of [<sup>14</sup>C]TNF (47 μg/2 cm<sup>2</sup>) to Rats

Time	% Dose <sup>a</sup>		Total
	Urine	Feces	
6 h	0.34 ± 0.36	-	-
12 h	1.46 ± 0.19	0.02 ± 0.01	1.48 ± 0.20
24 h	3.54 ± 0.57	4.04 ± 0.43	7.59 ± 0.15

<sup>a</sup> Values are means ± standard deviations for N=3 rats.

Table 2

Tissue Distribution of Carbon-14 Residues 24 h after  
 Dermal Administration of [<sup>14</sup>C]TNF (47 μg/2 cm<sup>2</sup>) to Rats<sup>a</sup>

Tissue Name	ng-eq compd per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	1	0.25 ± 0.13	0.035 ± 0.015
Adrenal gland	4	0.87 ± 0.37	<sup>b</sup>
Blood	5	Unity	0.088 ± 0.010
Brain	<sup>c</sup>	0.04 ± 0.03	0.001 ± 0.000
Heart	3	0.56 ± 0.02	0.003 ± 0.000
Intestine, large	22	4.60 ± 0.67	0.028 ± 0.010
Intest0.03line, small	23	4.79 ± 1.32	0.093 ± 0.031
Kidney	24	5.06 ± 0.31	0.053 ± 0.002
Liver	20	4.16 ± 0.11	0.242 ± 0.030
Lung	4	0.75 ± 0.14	0.010 ± 0.003
Muscle	1	0.24 ± 0.06	0.164 ± 0.029
Ovary	2	0.39 ± 0.16	<sup>b</sup>
Plasma	9	1.88 ± 0.07	0.122 ± 0.069
Skin	3	0.61 ± 0.05	0.127 ± 0.005
Stomach	4	0.91 ± 0.68	0.006 ± 0.005
Total (excluding plasma)			0.828 ± 0.010

<sup>a</sup> Values are means ± standard deviation for 3 animals.

<sup>b</sup> Less than .0005% of dose.

<sup>c</sup> Less than 1 ng-eq per g tissue.

Table 3  
 Distribution of Radioactivity after Dermal Administration of [<sup>14</sup>C]TNF (400 μg/2 cm<sup>2</sup>)  
 to the Skin of Female Fischer F-344 Rats

Time (h)	% Dose <sup>a</sup>			Dose Site	% Absorbed	% Dose <sup>a</sup> (Skin Wash/Gauze)	Total Recovery
	Urine	Feces	Tissues <sup>b</sup>			% Unabsorbed	
0-6	0.06 ± 0.05						
6-12	0.16 ± 0.11	0.02 ± 0.01					
12-24	0.34 ± 0.17	0.40 ± 0.11					
24-48	0.57 ± 0.24	0.87 ± 0.40					
48-72	0.76 ± 0.28	1.36 ± 0.51	0.30 ± 0.11	0.14 ± 0.05	2.57 ± 0.90	85.7 ± 2.8	88.2 ± 2.2

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> Sum of % dose recovered from the following tissues: adipose, adrenals, blood, brain, heart, large intestine, small intestine, kidney, liver, lung, muscle, ovaries, plasma, skin and stomach.

Table 4  
 Tissue Distribution of Carbon-14 Residues 72 h after  
 Administration of [<sup>14</sup>C]TNF (400 ug/2 cm<sup>2</sup>) to  
 Female Fischer F-344 Rats<sup>a</sup>

Tissue Name	ng-eq compd per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	8	0.59 ± 0.68	0.025 ± 0.015
Adrenal gland	25	1.11 ± 1.28	b
Blood	22	Unity	0.044 ± 0.024
Brain	4	0.38 ± 0.42	0.002 ± 0.001
Heart	8	0.54 ± 0.36	0.001 ± 0.001
Intestine, large	23	1.54 ± 1.12	0.007 ± 0.001
Intestine, small	18	1.21 ± 0.81	0.010 ± 0.003
Kidney	30	2.02 ± 1.51	0.009 ± 0.001
Liver	16	1.37 ± 1.63	0.020 ± 0.009
Lung	6	0.33 ± 0.10	0.002 ± 0.001
Muscle	6	0.41 ± 0.29	0.112 ± 0.075
Ovary	11	0.65 ± 1.13	b
Plasma	7	0.44 ± 0.34	0.007 ± 0.002
Skin	12	1.14 ± 1.46	0.061 ± 0.041
Stomach	14	0.95 ± 0.73	0.002 ± 0.001
Total (excluding plasma)			0.297 ± 0.112

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> Less than .0005% of dose.

Table 5  
 Distribution of Radioactivity 72 h after Oral Administration of  
<sup>14</sup>C]TNF (10 mg/kg) to Female Fischer F-344 Rats

Time (h)	Cumulative % Dose <sup>a</sup>				% Recovery
	Urine	Feces	Contents <sup>c</sup>	Tissues <sup>d</sup>	
6	5.69 ± 1.76				
6-12	11.00 ± 2.44	0.07 ± 0.01			
12-24	19.14 ± 3.74 <sup>b</sup>	2.77 ± 2.62			
24-48	21.68 ± 4.48 <sup>b</sup>	57.56 ± 9.26			
48-72	21.87 ± 4.55 <sup>b</sup>	67.02 ± 5.22	0.18 ± 0.13	0.50 ± 0.37	89.88 ± 1.02

<sup>a</sup> Values are means ± standard deviations for four animals.

<sup>b</sup> Values include cage rinses.

<sup>c</sup> Sum of % dose recovered from contents of the following tissues: stomach, small intestine, cecum, large intestine.

<sup>d</sup> Sum of % dose recovered from the following tissues: adipose, blood, cecum, large intestine, small intestine, kidney, liver, muscle, plasma, skin, stomach.

Table 6

Distribution of Radioactivity 72 h after Oral Administration of  
 $[^{14}\text{C}]$ TNF (1 mg/kg) to Female Fischer F-344 Rats

Time (h)	Cumulative % Dose <sup>a</sup>				% Recovery
	Urine	Feces	Contents <sup>e</sup>	Tissues <sup>d</sup>	
6	8.50 ± 2.77 <sup>b</sup>				
6-12	13.57 ± 0.37	0.02 ± 0.00			
12-24	17.20 ± 0.53 <sup>c</sup>	55.27 ± 4.33			
24-48	17.78 ± 0.50 <sup>c</sup>	67.75 ± 3.56			
48-72	17.92 ± 0.46 <sup>c</sup>	68.59 ± 3.36	0.04 ± 0.03	0.53 ± 0.11	87.08 ± 3.56

<sup>a</sup> Values are means ± standard deviations for four animals.

<sup>b</sup> n = 3

<sup>c</sup> Values include cage rinses.

<sup>d</sup> Sum of % dose recovered from the following tissues: adipose, blood, cecum, large intestine, small intestine, kidney, liver, muscle, plasma, skin, stomach.

<sup>e</sup> Sum of % dose recovered from contents of the stomach, small intestines, cecum and large intestines.

Table 7  
 Distribution of Radioactivity 72 h after Oral Administration of  
<sup>14</sup>C]TNF (100 mg/kg) to Female Fischer F-344 Rats

Time (h)	Cumulative % Dose <sup>a</sup>				% Recovery
	Urine	Feces	Contents <sup>c</sup>	Tissues <sup>d</sup>	
6	1.46 ± 0.67				
6-12	4.39 ± 1.36	0.65 ± 0.77			
12-24	10.48 ± 1.20 <sup>b</sup>	12.09 ± 8.16			
24-48	16.90 ± 2.36 <sup>b</sup>	62.8 ± 4.99			
48-72	17.06 ± 2.40 <sup>b</sup>	67.94 ± 2.62	0.12 ± 0.07	0.46 ± 0.04	85.57 ± 1.79

<sup>a</sup> Values are means ± standard deviations for four animals.

<sup>b</sup> Values include cage rinses.

<sup>c</sup> Sum of % dose recovered from contents of the following tissues: stomach, small intestine, cecum, large intestine.

<sup>d</sup> Sum of % dose recovered from the following tissues: adipose, blood, cecum, large intestine, small intestine, kidney, liver, muscle, plasma, skin, stomach.



Table 8

Tissue Distribution of Carbon-14 Residues 72 h after  
Oral Administration of [<sup>14</sup>C]TNF (1.0 mg/kg) to  
Female Fischer F-344 Rats

Tissue Name	ng-eq Compound per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	2	0.18 ± 0.11	0.022 ± 0.015
Blood	11	unity	0.073 ± 0.023
Cecum	7	0.66 ± 0.25	0.003 ± 0.000
Intestines, lg	5	0.43 ± 0.09	0.002 ± 0.000
Intestines, sm	7	0.67 ± 0.16	0.011 ± 0.002
Kidney	61	5.86 ± 1.25	0.058 ± 0.007
Liver	41	3.90 ± 0.83	0.189 ± 0.017
Muscle	1	0.13 ± 0.05	0.074 ± 0.031
Plasma	15	1.41 ± 0.16	0.052 ± 0.012
Skin	6	0.57 ± 0.12	0.099 ± 0.037
Stomach	16	1.32 ± 0.56	0.008 ± 0.006
Total (excluding plasma)			0.532 ± 0.113

Table 9

Tissue Distribution of Carbon-14 Residues 72 h after  
Oral Administration of [<sup>14</sup>C]TNF (10 mg/kg) to  
Female Fischer F-344 Rats

Tissue Name	ng-eq Compound per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	32	0.23 ± 0.05	0.029 ± 0.010
Blood	140	Unity	0.078 ± 0.018
Cecum	154	1.14 ± 0.48	0.005 ± 0.003
Intestines, lg	100	0.73 ± 0.22	0.005 ± 0.001
Intestines, sm	117	0.83 ± 0.15	0.012 ± 0.004
Kidney	847	6.09 ± 0.51	0.062 ± 0.013
Liver	578	4.11 ± 0.40	0.222 ± 0.060
Muscle	32	0.23 ± 0.04	0.140 ± 0.012
Plasma	160	1.12 ± 0.55	0.046 ± 0.026
Skin	157	1.13 ± 0.14	0.208 ± 0.045
Stomach	1132	7.59 ± 3.40	0.050 ± 0.033
Total (excluding plasma)			0.811 ± 0.184

Table 10

Tissue Distribution of Carbon-14 Residues 72 h after  
Oral Administration of [<sup>14</sup>C]TNF (100 mg/kg) to  
Female Fischer F-344 Rats

Tissue Name	ng-eq Compound per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	74	0.14 ± 0.07	0.010 ± 0.004
Blood	503	1.00 ± 0.00	0.044 ± 0.005
Cecum	776	1.41 ± 0.39	0.003 ± 0.001
Intestines, lg	406	0.80 ± 0.12	0.003 ± 0.001
Intestines, sm	482	0.92 ± 0.23	0.008 ± 0.001
Kidney	2705	5.27 ± 0.51	0.028 ± 0.001
Liver	1846	3.45 ± 0.68	0.099 ± 0.006
Muscle	97	0.18 ± 0.05	0.063 ± 0.010
Plasma	301	0.65 ± 0.30	0.015 ± 0.008
Skin	886	1.71 ± 0.18	0.180 ± 0.032
Stomach	2481	4.60 ± 0.81	0.017 ± 0.005
Total (excluding plasma)			0.461 ± 0.044

Table 11

Tissue Distribution of Carbon-14 Residues 6 h after Oral Administration of [<sup>14</sup>C]TNF (10 mg/kg) to Female Fischer F-344 Rats<sup>a</sup>

Tissue Name	ng-eq compd per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Blood	18116	Unity	0.99 ± 0.29 <sup>b</sup>
Intestines, lg.	21670	12.96 ± 6.30 <sup>b</sup>	1.85 ± 0.84
Intestines, sm.	42710	27.64 ± 10.72 <sup>b</sup>	5.74 ± 1.17
Stomach	56740	30.68 ± 12.27 <sup>b</sup>	3.04 ± 0.55
Plasma <sup>c</sup>	3097	1.67 ± 0.02	0.88 ± 0.36
Total (excluding plasma)			11.4 ± 1.4

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> n = 3

<sup>c</sup> n = 2

Table 12  
 Distribution of Radioactivity 6 h after  
 Oral Administration of [<sup>14</sup>C]TNF (10 mg/kg) to  
 Female Fischer F-344 Rats

	% Dose <sup>a</sup>
Urine	8.45 ± 3.13
Feces	1.07 ± 2.02
Tissues <sup>b</sup>	11.4 ± 1.4
Contents	
Sm Int.	24.6 ± 12.7
Lg Int.	17.9 ± 5.7
<u>Stomach</u>	16.4 ± 2.2
Total in contents	58.9 ± 8.1
 Total Recovery	 79.7 ± 5.8

<sup>a</sup> Values are means ± standard deviation for 4 animals.  
<sup>b</sup> Sum of % dose recovered from the following tissues:  
 small intestines, large intestines, and stomach.

Table 13

Tissue Distribution of Carbon-14 Residues 6 h after Oral  
Administration of [<sup>14</sup>C]TNF (10 mg/kg) to Female Fischer F-344 Rats  
Treated with Antibiotics (lincomycin/neomycin)  
to Eliminate Gut Flora<sup>a</sup>

Tissue Name	ng-eq compd per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Blood	1430	Unity	0.78 ± 0.19
Intestines, lg.	9289	6.86 ± 3.48	1.04 ± 0.38
Intestines, sm.	50830	36.33 ± 7.00	7.45 ± 1.78
Stomach	73680	56.04 ± 27.12	3.84 ± 0.96
Plasma <sup>b</sup>	2930	1.76 ± 0.03	0.83 ± 0.09 <sup>b</sup>
Total (excluding plasma)			12.9 ± 1.1

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> n = 2

Table 14

Distribution of Radioactivity 6 h after  
Oral Administration of [ $^{14}\text{C}$ ]TNF (10 mg/kg)  
to Female Fischer F-344 Rats Treated with  
Antibiotics to Eliminate Gut Microflora

	% Dose <sup>a</sup>
Urine	3.78 ± 2.15
Feces	0.19 ± 0.16
Tissues <sup>b</sup>	13.1 ± 1.5
Contents	
Sm Int.	26.3 ± 16.2
Lg Int.	12.9 ± 6.5
<u>Stomach</u>	19.7 ± 3.6
Total in contents	58.9 ± 13.4
 Total Recovery	 76.0 ± 12.9

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> Sum of % dose recovered from the following tissues:  
small intestines, large intestines, stomach and blood.

Table 15

Distribution of Radioactivity after Intravenous Administration  
of [<sup>14</sup>C]TNF (1 mg/kg) to Female Fischer F-344 Rats

Time (h)	% Dose <sup>a</sup>			% Recovery
	Urine	Feces	Tissues <sup>b</sup>	
6	15.28 ± 2.32			
6-12	19.73 ± 2.34	3.28 ± 2.20		
12-24	23.25 ± 1.84	46.07 ± 8.18		
24-48	24.32 ± 1.76	53.11 ± 9.41		
48-72	24.71 ± 1.77	61.69 ± 2.68	4.40 ± 0.26	90.8 ± 3.5

<sup>a</sup> Values are means ± standard deviation for 4 animals.

<sup>b</sup> Sum of % dose recovered from the following tissues: adipose, adrenals, blood, brain, heart, small intestines, large intestines, kidney, liver, lung, muscle, ovaries, plasma, skin, and stomach.



Table 16

Tissue Distribution of Carbon-14 Residues 72 h after Intravenous Administration of [<sup>14</sup>C]TNF (1 mg/kg) to Female Fischer F-344 Rats<sup>a</sup>

Tissue Name	ng-eq compd per g/tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	18.	0.19 ± 0.03	0.18 ± 0.02
Adrenal	106.	1.10 ± 0.09	0.00 ± 0.00
Blood	97.	Unity	0.60 ± 0.04
Brain	25.	0.26 ± 0.01	0.03 ± 0.00
Cecum	48.	0.49 ± 0.12	0.02 ± 0.01
Heart	223.	2.30 ± 0.08	0.07 ± 0.00
Intestine, large	49.	0.51 ± 0.03	0.02 ± 0.00
Intestine, small	42.	0.43 ± 0.02	0.06 ± 0.02
Kidney	252.	2.59 ± 0.28	0.19 ± 0.04
Liver	102.	1.06 ± 0.05	0.43 ± 0.03
Lung	165.	1.71 ± 0.19	0.10 ± 0.02
Muscle	37.	0.38 ± 0.03	1.78 ± 0.07
Ovary	58.	0.60 ± 0.05	0.00 ± 0.00
Plasma	92.	0.95 ± 0.41	0.21 ± 0.24
Skin	60.	0.62 ± 0.11	0.89 ± 0.17
Stomach	46.	0.47 ± 0.02	0.02 ± 0.00
Total (excluding plasma)			4.40 ± 0.26

<sup>a</sup> Values are means ± standard deviation for 4 animals.

Table 17  
Rate of Biliary Excretion of Carbon-14 after  
Intravenous Administration of [<sup>14</sup>C]TNF (1 mg/kg) to Rats

<b>Time Interval in hours</b>	<b>% Dose</b>
0 – 0.25	8.2 ± 2.5
0.25 – 0.50	9.7 ± 3.5
0.50 – 0.75	6.0 ± 3.4
0.75 – 1.0	3.7 ± 1.4
1.0 – 1.5	6.9 ± 1.5
1.5 – 2.0	3.5 ± 2.0
2.0 – 3.0	6.9 ± 1.4
3.0 – 4.0	4.0 ± 0.8
4.0 – 5.0	2.8 ± 0.4
5.0 – 6.0	1.8 ± 0.3
Total	53.5 ± 13.4

Table 18  
 Biliary Excretion of Carbon-14 after Intraintestinal  
 Administration of [<sup>14</sup>C]TNF (1 mg/kg) to Rats

n	Time at End of Interval (h)	Cum Avg. % Dose Excreted	Avg. % Dose Excreted
5	.25	0.53 ± 0.12	0.53 ± 0.12
5	.50	3.06 ± 1.19	2.53 ± 1.09
5	.75	5.49 ± 2.73	2.39 ± 1.77
4	1.00	8.27 ± 4.69	2.48 ± 1.73
4	1.50	12.08 ± 7.20	4.83 ± 1.88
4	2.00	14.83 ± 8.71	2.76 ± 1.53
4	3.00	17.72 ± 9.12	2.89 ± 1.53
3	4.00	19.42 ± 11.18	2.06 ± 0.19
3	5.00	20.65 ± 10.39	1.22 ± 0.89
2	6.00	17.24 ± 9.49	1.05 ± 0.36