

## ADME NTP Study S0633 *p*-Nitrotoluene

The contract laboratory abbreviation for the test article is PNT.

Sex/Species: adult male and female F344 rats and B6C3F1 mice.

Vehicles: oral, corn oil.

CASRN 99-99-0

Radiolabeled with carbon-14 uniformly labeled in the phenyl ring; 4-Nitrotoluene, [Ring-<sup>14</sup>C(U)]-

### *p*-Nitrotoluene Studies Performed:

1. Single 2 mg/kg oral gavage dose in male and female rats with sacrifice 72 hours postdose.
2. Single 200 mg/kg oral gavage dose in male and female rats with sacrifice 72 hours postdose.
3. Single 200 mg/kg oral gavage dose in male rats with sacrifice 6 hours postdose (bile excretion study).
4. Single 200 mg/kg oral gavage dose in male and female rats with sacrifice 8 hours postdose (toxicokinetic).
5. Repeat 200 mg/kg/day dose 12-day oral gavage study in male rat with sacrifice on day 13.
6. Single 2 mg/kg oral gavage dose in male and female mice with sacrifice 72 hours postdose.
7. Single 200 mg/kg oral gavage study in male and female mice with sacrifice 72 hours postdose.
8. Single 200 mg/kg oral gavage study in male and female mice with sacrifice 24 hours postdose (toxicokinetic).

In Study 5, male rats received 12 daily oral doses of 200 mg PNT per kg body weight (N = 5). Non-radiolabeled PNT was administered on days 2-4, 6-8, 10-12. On days 1, 5, and 9, radiolabeled PNT was added to the non-radiolabeled PNT dose solution for the same 5 rats. Excreta was collected for time intervals following radiolabeled dosing on days 1, 5, or 9. The collection time was 96 hours following radiolabel administration for Day 1 and Day 5 dosing and 24 hours (2 animals) and 96 hours (3 animals) following Day 9 dosing.

Blood was collected in the 200 mg/kg dose studies 1, 2, 4, and 8 for toxicokinetics. No curve fitting analyses were performed.

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**Table 1**  
**Cumulative Excretion of Radioactivity following Oral Single-Doses**  
**of [<sup>14</sup>C]PNT to Male and Female F-344 Rats<sup>a</sup>**

**Males 2 mg/kg**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	21.5 ± 26.1	NC	21.5 ± 26.1
8h	59.2 ± 5.5	NC	59.2 ± 5.5
24h	90.3 ± 6.6	2.5 ± 1.1	92.9 ± 6.4
48h	93.7 ± 6.3	3.3 ± 1.0	97.0 ± 6.2
72h <sup>b</sup>	95.3 ± 6.2	3.5 ± 1.0	98.8 ± 6.0

**Males 200 mg/kg**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	7.4 ± 8.5	NC	7.4 ± 8.5
8h	34.0 ± 11.3	NC	34.0 ± 11.3
24h	81.1 ± 5.1	2.9 ± 3.2	84.0 ± 3.7
48h	84.9 ± 4.2	3.6 ± 3.2	88.5 ± 1.5
72h <sup>b</sup>	87.2 ± 3.9	4.7 ± 2.9	92.0 ± 1.1

**Females 2 mg/kg**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	0.0 ± 0.0	NC	0.0 ± 0.0
8h	17.1 ± 23.4	NC	17.1 ± 23.4
24h	73.8 ± 10.7	3.3 ± 3.4	77.1 ± 11.4
48h	80.1 ± 9.7	4.7 ± 3.7	84.8 ± 11.4
72h <sup>b</sup>	82.6 ± 9.7	5.0 ± 3.6	87.6 ± 11.1

**Females 200 mg/kg**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	7.8 ± 6.2	NC	7.8 ± 6.2
8h	27.1 ± 10.1	NC	27.1 ± 10.1
24h	79.7 ± 11.2	1.1 ± 1.4	80.7 ± 9.7
48h	83.7 ± 10.0	2.2 ± 1.4	85.9 ± 8.7
72h <sup>b</sup>	85.2 ± 9.9	2.5 ± 1.5	87.7 ± 8.4

- <sup>a</sup> Values are mean ± SD for four rats.
- <sup>b</sup> Urine value includes cage rinse.
- NC Feces were collected over a 0-24 h interval.

**Table 2**  
**Cumulative Excretion of Radioactivity following Oral Repeated-Doses (200 mg/kg/day) of**  
**[<sup>14</sup>C]PNT to Male F-344 Rats<sup>a</sup>**

**Day 1**

End of Collection Period	Percent of Dose Measured in:		Total
	Urine	Feces	
4 h	10.4 ± 5.7	NC	10.4 ± 5.7
8 h	25.9 ± 9.0	NC	25.9 ± 9.0
24 h	84.0 ± 3.7	3.6 ± 1.0	87.6 ± 2.7
48 h	90.0 ± 2.4	4.4 ± 1.0	94.4 ± 1.5
72 h	90.1 ± 2.4	4.5 ± 1.0	94.5 ± 1.4
96 h	90.1 ± 2.4	4.5 ± 1.0	94.6 ± 1.4

**Day 5**

End of Collection Period	Percent of Dose Measured in:		Total
	Urine	Feces	
4 h	11.0 ± 9.5	NC	11.0 ± 9.5
8 h	34.3 ± 6.0	NC	34.3 ± 6.0
24 h	85.6 ± 3.2	3.1 ± 0.9	88.7 ± 2.4
48 h	91.4 ± 1.7	3.6 ± 0.8	95.0 ± 1.3
72 h	91.5 ± 1.7	3.6 ± 0.8	95.1 ± 1.3
96 h	91.6 ± 1.7	3.6 ± 0.8	95.2 ± 1.3

**Day 9**

End of Collection Period	Percent of Dose Measured in:		Total
	Urine	Feces	
4 h	11.9 ± 7.0	NC	11.9 ± 7.0
8 h	24.5 ± 8.6	NC	24.5 ± 8.6
24 h <sup>b</sup>	82.6 ± 2.8	4.5 ± 2.1	87.2 ± 3.0
48 h	87.9 ± 1.4	6.2 ± 2.3	94.1 ± 1.1
72 h	88.0 ± 1.4	6.2 ± 2.4	94.3 ± 1.1
96 h <sup>c</sup>	88.1 ± 1.4	6.2 ± 2.4	94.3 ± 1.2

- a N=5 except N=3 for 48, 72 and 96 h timepoints for dose day 9.
- b Urine value includes urine taken directly from the bladder for rats sacrificed 24 h following the Day 9 dosing.
- c Urine value includes urine taken directly from the bladder.
- NC Feces were collected over a 0-24 h interval.

**Table 3**

**Cumulative Percentage of Radiolabeled Dose Excreted in Bile of Male F-344 Rats following Oral Administration of PNT (200 mg/kg)**

<b>Sample Time (h)</b>	<b>Rat 1</b>	<b>Rat 2</b>	<b>Rat 4</b>	<b>Rat 5</b>	<b>Mean ± SD</b>
0.5	0.4	0.5	0.5	0.1	0.4 ± 0.2
1	1.1	1.3	1.0	0.3	0.9 ± 0.4
1.5	1.8	1.9	1.8	0.5	1.5 ± 0.7
2	2.5	2.7	2.8	0.7	2.2 ± 1.0
3	3.8	4.9	4.5	1.4	3.6 ± 1.6
4	4.9	6.5	5.9	2.8	5.0 ± 1.6
5	5.8	8.3	7.0	3.8	6.2 ± 1.9
6	6.5	8.7	7.9	4.8	7.0 ± 1.7

**Table 4**  
**Cumulative Excretion of Radioactivity following Oral Single-Doses**  
**of [<sup>14</sup>C]PNT to Male and Female B6C3F<sub>1</sub> Mice<sup>a</sup>**

<b>Males 2 mg/kg</b>			
<b>End of Collection Period</b>	<b>Cumulative Percent of Dose Recovered in:</b>		<b>Total</b>
	<b>Urine</b>	<b>Feces</b>	
8 h	0.0 ± 0.0	NC	0.0 ± 0.0
24 h <sup>b</sup>	85.1 ± 2.4	5.7 ± 0.7	90.8 ± 1.7
48 h <sup>b</sup>	88.2 ± 3.1	6.7 ± 0.8	94.9 ± 2.4
72 h <sup>b</sup>	89.1 ± 2.4	6.8 ± 0.9	95.9 ± 1.6

<b>Males 200 mg/kg</b>			
<b>End of Collection Period</b>	<b>Cumulative Percent of Dose Recovered in:</b>		<b>Total</b>
	<b>Urine</b>	<b>Feces</b>	
8 h	15.3 ± 26.4	NC	15.3 ± 26.4
24 h <sup>b</sup>	87.9 ± 3.4	5.1 ± 0.5	93.0 ± 3.1
48 h <sup>b</sup>	90.7 ± 1.7	5.9 ± 0.5	96.7 ± 1.3
72 h <sup>b</sup>	91.1 ± 1.8	6.1 ± 0.5	97.2 ± 1.2

<b>Females 2 mg/kg</b>			
<b>End of Collection Period</b>	<b>Cumulative Percent of Dose Recovered in:</b>		<b>Total</b>
	<b>Urine</b>	<b>Feces</b>	
8 h	25.2 ± 24.4	NC	25.2 ± 24.4
24 h <sup>b</sup>	70.5 ± 15.8	14.2 ± 11.0	84.7 ± 9.5
48 h <sup>b</sup>	76.1 ± 14.6	16.2 ± 11.4	92.3 ± 4.6
72 h <sup>b</sup>	76.9 ± 14.6	16.8 ± 11.7	93.7 ± 3.8

<b>Females 200 mg/kg</b>			
<b>End of Collection Period</b>	<b>Cumulative Percent of Dose Recovered in:</b>		<b>Total</b>
	<b>Urine</b>	<b>Feces</b>	
8 h	8.2 ± 11.4	NC	8.2 ± 11.4
24 h <sup>b</sup>	76.9 ± 5.7	9.0 ± 6.1	85.9 ± 0.8
48 h <sup>b</sup>	82.2 ± 5.6	10.7 ± 6.3	92.9 ± 1.0
72 h <sup>b</sup>	83.3 ± 5.7	11.2 ± 6.5	94.5 ± 1.0

<sup>a</sup> Values are mean ± SD for three mice.  
<sup>b</sup> Urine value includes cage rinse.  
 NC Feces were collected over a 0-24 h interval.

**Table 5**  
**Concentration of Radiolabel ( $\mu\text{g-eq/g}$ ) in Blood and Plasma after Oral Administration**  
**of [ $^{14}\text{C}$ ]PNT to F-344 Rats<sup>a</sup>**

<b>Sample<sup>b</sup></b>	<b>Males 2 mg/kg</b>	<b>Females 2 mg/kg</b>	<b>Males 200 mg/kg</b>	<b>Females 200 mg/kg</b>
Blood 2 h	0.406 $\pm$ 0.113	0.715 $\pm$ 0.238	60.7 $\pm$ 8.96	87.0 $\pm$ 11.3
Blood 4 h	0.250 $\pm$ 0.032	0.173 $\pm$ 0.032	87.0 $\pm$ 22.1	102 $\pm$ 11.2
Blood 6 h	0.102 <sup>c</sup> $\pm$ 0.047 <sup>c</sup>	0.119 $\pm$ 0.023	99.9 $\pm$ 16.8	114 $\pm$ 28.0
Blood 8 h	0.054 $\pm$ 0.025	0.081 $\pm$ 0.010	97.4 $\pm$ 29.4	115 $\pm$ 23.9
Blood 24 h	0.007 $\pm$ 0.001	0.007 $\pm$ 0.001	0.754 $\pm$ 0.130	1.26 $\pm$ 0.46
Blood 72 h	0.004 $\pm$ 0.001	0.003 $\pm$ 0.000	0.277 $\pm$ 0.065	0.254 $\pm$ 0.027
Plasma 2 h	0.745 $\pm$ 0.235	1.28 $\pm$ 0.483	89.1 $\pm$ 14.4	120 $\pm$ 13.9
Plasma 4 h	0.449 $\pm$ 0.073	0.26 $\pm$ 0.061	131 $\pm$ 28.2	145 $\pm$ 12.8
Plasma 6 h	0.146 $\pm$ 0.091	0.177 $\pm$ 0.022	145 $\pm$ 23	160 $\pm$ 33.1
Plasma 8 h	0.082 $\pm$ 0.049	0.12 $\pm$ 0.017	137 $\pm$ 37.4	149 $\pm$ 22.2
Plasma 24 h	0.010 $\pm$ 0.002	0.009 $\pm$ 0.002	0.71 $\pm$ 0.127	1.55 $\pm$ 0.998
Plasma 72 h	0.006 $\pm$ 0.001	0.006 $\pm$ 0.002	0.116 $\pm$ 0.079	0.178 $\pm$ 0.117

<sup>a</sup> Mean  $\pm$  SD for four rats, except where indicated otherwise.

<sup>b</sup> All time points referenced to sampling time after administered oral dose.

<sup>c</sup> Sample lost during processing; mean  $\pm$  SD for three rats.

**Table 6**

**Concentration of Radiolabel ( $\mu\text{g-eq/g}$ ) in Blood and Plasma after Oral Administration of [ $^{14}\text{C}$ ]PNT to B6C3F<sub>1</sub> Mice<sup>a</sup>**

Sample <sup>b</sup>	Males 200 mg/kg			Females 200 mg/kg		
	Mean	±	SD	Mean	±	SD
Blood 5 min	17.9	±	14.5	8.2	±	1.9
Blood 10 min	59.9	±	11.2	82.8	±	13.8
Blood 20 min	65.0	±	48.8	131.0	±	31.0
Blood 40 min	125.0	±	53.1	88.1	±	28.5
Blood 1 h	67.2	±	23.2	121.0	±	31.2
Blood 1.5 h	74.7	±	5.0	80.9	±	35.8
Blood 2 h	39.6	±	16.0	62.8	±	17.2
Blood 4 h	15.5	±	6.5	50.3	±	30.3
Blood 8 h	2.2	±	0.5	8.0	±	5.9
Blood 24 h	0.4	±	0.0	0.5	±	0.1
Plasma 5 min	26.8	±	21.3	13.3	±	2.3
Plasma 10 min	91.0	±	9.6	123.0	±	19.2
Plasma 20 min	104.0	±	68.1	202.0	±	46.2
Plasma 40 min	183.0	±	75.8	132.0	±	42.3
Plasma 1 h	97.0	±	39.0	162.0	±	52.1
Plasma 1.5 h	93.8	±	35.1	125.0	±	50.6
Plasma 2 h	83.7	±	42.2	98.4	±	29.2
Plasma 4 h	25.1	±	11.3	77.4	±	43.2
Plasma 8 h	2.8	±	1.0	11.8	±	8.4
Plasma 24 h	0.2	±	0.0	0.5	±	0.2

<sup>a</sup> Mean  $\pm$  SD for three mice.

<sup>b</sup> All time points referenced to sampling time after administered oral dose.



**Table 7**  
**Concentration of PNT in Plasma following an Oral Single-Dose of**  
**[<sup>14</sup>C]PNT at 200 mg/kg to F-344 Rats**  
**(ng/g Plasma)**

**Males**

Sample Time (h) <sup>a</sup>	5-M1	5-M2	5-M3	Mean ± SD
0.08	5091	7446	8596	7044 ± 1787
0.25	6370	12393	7149	8637 ± 3276
0.5	5877	7679	3579	5712 ± 2055
1	3162	3872	1598	2877 ± 1163
2	1058	2822	4345	2742 ± 1645
4	647	577	NQ	
8	313	NQ	NA	

<sup>a</sup> All timepoints referenced to time after administered oral dose.  
 NQ Not Quantited; below limit of quantitation (305 ng/g).  
 NA Not Analyzed by GC; sample <sup>14</sup>C content indicated PNT level below limit of quantitation.

**Females**

Sample Time (h) <sup>a</sup>	5-F1	5-F2	5-F3	Mean ± SD
0.08	8517	8899	8554	8657 ± 211
0.25	9192	7953	8677	8607 ± 622
0.5	4365	6383	4570	5106 ± 1111
1	3264	7321	3276	4620 ± 2339
2	1415	2669	2088	2057 ± 628
4	1879	689	899	1156 ± 635
8	NQ	NA	NA	

<sup>a</sup> All timepoints referenced to time after administered oral dose.  
 NQ Not Quantited; below limit of quantitation (305 ng/g).  
 NA Not Analyzed by GC; sample <sup>14</sup>C content indicated PNT level below limit of quantitation.

**Table 8**  
**Concentration of PNT in Plasma following an Oral Single-Dose of**  
**[<sup>14</sup>C]PNT at 200 mg/kg to B6C3F<sub>1</sub> Mice**  
**(ng/g Plasma)**

**Males**

Sample Time (h) <sup>a</sup>	3-M1 <sup>b</sup>	3-M2 <sup>b</sup>	3-M3 <sup>b</sup>	Mean ± SD
0.08	6018	2421	985	3141 ± 2593
0.17	6042	2996	7315	
0.33	2676	593	NQ	5451 ± 2219
0.67	1204	ND	222	
1	NQ	NQ	152	
1.5	1513	1331	NQ	
2	1000	290	ND	
4	ND	72.5	ND	

<sup>a</sup> All timepoints referenced to time after administered oral dose.

<sup>b</sup> Each data point is from a separate animal.

NQ Not Quantited; concentration of PNT <145 ng/g.

ND Not detected.

**Females**

Sample Time (h) <sup>a</sup>	3-F1 <sup>b</sup>	3-F2 <sup>b</sup>	3-F3 <sup>b</sup>	Mean ± SD
0.08	734	1344	638	905 ± 383
0.17	10669	9207	18462	12779 ± 4975
0.33	2060	6169	243	2824 ± 3036
0.67	278	681	ND	
1	NQ	2293	333	
1.5	347	NQ	453	
2	NQ	382	NQ	
4	ND	NQ	NQ	

<sup>a</sup> All timepoints referenced to time after administered oral dose.

<sup>b</sup> Each data point is from a separate animal.

NQ Not Quantited; concentration of PNT <145 ng/g.

ND Not detected.