

## ADME NTP Study S0642 m-Nitrotoluene

The contract laboratory abbreviation for the test article is MNT.

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

Vehicles: oral gavage, corn oil or ethanol:Emulphor:water (1:1:8).

CASRN 99-08-1

Radiolabeled with carbon-14 in the methyl group; 3-Nitrotoluene [methyl-14C]-

### m-Nitrotoluene Studies Performed:

1. Single 2 mg/kg oral gavage dose in male and female rats with sacrifice at 72 hours postdose (vehicle, corn oil).
2. Single 200 mg/kg oral gavage dose in male and female rats with sacrifice at 72 hours postdose (vehicle, corn oil).
3. Single 200 mg/kg oral gavage dose in male and female rats with sacrifice at 24 hours postdose (vehicle, ethanol:Emulphor:water (1:1:8)).
4. Twelve-day repeat oral gavage dose (200 mg/kg/day) in male rats with sacrifice 96 hours following last radiolabel administration on Day 9 (vehicle, corn oil).
5. Single 200 mg/kg oral gavage dose with bile collection for 6 hours (vehicle, corn oil).
6. Single 2 mg/kg oral gavage dose in male and female mice with sacrifice 72 hours postdose (vehicle, corn oil).
7. Single 200 mg/kg oral gavage study in male and female mice with sacrifice 72 hours postdose (vehicle, corn oil).
8. Single 200 mg/kg oral gavage dose in male and female mice with sacrifice at 4 hours (vehicle, ethanol:Emulphor:water (1:1:8)).

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

In the toxicokinetic studies 1-3 and 8, serial blood samples were collected but no toxicokinetic analysis was performed. The oral toxicokinetic studies were repeated (Studies 3 and 8, Tables 6 and 7) using ethanol:Emulphor:water (1:1:8) to enable direct comparison of MNT to o-nitrotoluene which used the same vehicle. A single 2 mg/kg

oral gavage dose in male and female rats with sacrifice at 24 hours postdose and ethanol:Emulphor:water (1:1:8) vehicle was also performed. The results of this study was displayed in a figure and not shown here.

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Table 1

Disposition of Radioactivity 72 h after Oral Administration of [<sup>14</sup>C]MNT (2 and 200 mg/kg) to Male and Female F-344 Rats

Males 2 mg/kg

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	1.7 ± 3.4		1.67 ± 3.35
8h	29.0 ± 33.5		29.0 ± 33.5
24h	85.7 ± 2.4	1.5 ± 0.7	87.3 ± 2.0
48h	91.6 ± 1.9	2.7 ± 0.5	94.4 ± 1.5
72h	92.4 ± 1.9	2.9 ± 0.5	95.2 ± 1.5
Cage Rinse	92.8 ± 1.7		95.6 ± 1.2

Males 200 mg/kg

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	11.8 ± 7.9		11.8 ± 7.95
8h	29.6 ± 11.8		29.6 ± 11.8
24h	81.2 ± 8.9	1.4 ± 0.4	82.6 ± 9.1
48h	85.9 ± 8.6	2.4 ± 0.6	88.3 ± 9.1
72h	87.0 ± 8.5	2.5 ± 0.6	89.5 ± 9.0
Cage Rinse	88.3 ± 8.3		90.8 ± 7.6

Females 2 mg/kg

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	17.3 ± 31.4		17.3 ± 31.4
8h	46.6 ± 35.0		46.6 ± 35.0
24h	85.0 ± 6.4	1.1 ± 0.1	86.1 ± 6.3
48h	89.6 ± 4.9	1.8 ± 0.6	91.4 ± 4.4
72h	91.3 ± 4.4	1.9 ± 0.6	93.2 ± 3.9
Cage Rinse	92.6 ± 3.5		94.5 ± 3.5

Females 200 mg/kg

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	13.2 ± 3.9		13.2 ± 3.9
8h	37.1 ± 9.8		37.1 ± 9.8
24h	87.4 ± 2.1	0.9 ± 0.5	88.2 ± 2.2
48h	90.9 ± 0.8	2.0 ± 0.2	92.9 ± 1.0
72h	92.0 ± 0.7	2.2 ± 0.3	94.2 ± 0.7
Cage Rinse	92.8 ± 0.6		95.0 ± 0.4

**Table 2**

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

<b>Sample</b>	<b>Males 2.00 mg/kg</b>	<b>Females 2.08 mg/kg</b>	<b>Males 206 mg/kg</b>	<b>Females 210 mg/kg</b>
Blood 2 h	0.211 ± 0.077	0.234 ± 0.082	63.7 ± 13.3	86.0 ± 4.53
Blood 4 h	0.093 ± 0.047	0.077 ± 0.032	76.5 ± 7.68	83.1 ± 23.9
Blood 6 h	0.062 ± 0.034	0.046 ± 0.028	83.6 ± 17.1	116.0 ± 21.8
Blood 8 h	0.035 ± 0.011	0.030 ± 0.007	82.1 ± 16.9	126.0 ± 18.9
Blood 24 h	0.006 ± 0.002	0.003 ± 0.003	0.944 ± 0.0927	1.27 ± 0.379
Blood 72 h	0.003 ± 0.001	0.001 ± 0.00	0.532 ± 0.139	0.350 ± 0.136
Plasma 2 h	0.375 ± 0.132	0.400 ± 0.136	96.1 ± 16.2	122.0 ± 7.84
Plasma 4 h	0.167 ± 0.089	0.138 ± 0.052	108.0 ± 10.5	119.0 ± 29.8
Plasma 6 h	0.106 ± 0.053	0.074 ± 0.044	118.0 ± 21.3	157.0 ± 26.1
Plasma 8 h	0.060 ± 0.021	0.051 ± 0.013	113.0 ± 22.2	163.0 ± 21.9
Plasma 24 h	0.003 ± 0.002	0.003 ± 0.002	0.491 ± 0.108	1.12 ± 0.541
Plasma 72 h	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

<sup>a</sup> Values are mean ± SD for four rats.  
Vehicle is corn oil.

**Table 3**

**Disposition of Radioactivity following Repeat Oral Administration of [<sup>14</sup>C]MNT (200 mg/kg) to Male F-344 Rats<sup>a</sup>**

**Cumulative Excretion of Radioactivity after Day 1**

End of Collection Period	Percent of Dose Recovered in:		Total
	Urine	Feces	
4 h	5.44 ± 5.43		5.44 ± 5.43
8 h	22.1 ± 4.4		22.1 ± 4.4
24 h	83.1 ± 10.7	5.06 ± 1.00	88.1 ± 10.9
48 h	90.3 ± 9.1	5.98 ± 1.08	96.3 ± 9.4
72 h	91.7 ± 8.8	6.15 ± 1.10	97.8 ± 9.1
96 h	92.9 ± 7.7	6.30 ± 1.15	99.2 ± 7.1
Cage Rinse	94.3 ± 7.1		101 ± 7

**Cumulative Excretion of Radioactivity after Day 5**

End of Collection Period	Percent of Dose Recovered in:		Total
	Urine	Feces	
4 h	4.46 ± 6.04		4.46 ± 6.04
8 h	22.4 ± 12.8		22.4 ± 12.8
24 h	84.7 ± 3.0	4.81 ± 1.66	89.5 ± 1.9
48 h	89.8 ± 1.9	5.74 ± 1.66	95.5 ± 1.5
72 h	91.0 ± 5.9	5.92 ± 1.67	96.9 ± 1.2
96 h	91.7 ± 1.6	6.06 ± 1.65	97.8 ± 0.9
Cage Rinse	93.1 ± 2.5		99.1 ± 1.5

**Cumulative Excretion of Radioactivity after Day 9**

End of Collection Period	Percent of Dose Recovered in:		Total
	Urine	Feces	
4 h	8.77 ± 7.21		8.77 ± 7.21
8 h	25.3 ± 11.1		25.3 ± 11.1
24 h	82.0 ± 3.4	4.72 ± 1.28	86.7 ± 3.7
48 h	87.7 ± 2.7	5.93 ± 1.48	93.6 ± 2.8
72 h	89.2 ± 2.6	6.24 ± 1.51	95.4 ± 3.0
96 h	89.7 ± 2.5	6.40 ± 1.48	96.1 ± 2.6
Cage Rinse	90.8 ± 2.5		97.2 ± 3.1

<sup>a</sup> Mean ± SD for five rats

**Table 4**

**Cumulative Percentage of Dose Excreted in the Bile  
of Male F-344 Rats following Oral Administration of MNT<sup>a</sup> (200 mg/kg )**

SampleTime (h) <sup>b</sup>	E-Rat1	E-Rat4	E-Rat5	E-Rat6	Mean ± S.D.
0.5	0.2	0.1	0.0	0.0	0.1 ± 0.1
1	0.8	0.3	0.1	0.1	0.3 ± 0.4
1.5	1.7	0.9	0.3	0.2	0.8 ± 0.7
2	2.7	1.7	0.6	0.3	1.3 ± 1.1
3	4.9	3.6	1.8	0.7	2.7 ± 1.9
4	7.2	5.5	3.4	1.3	4.3 ± 2.6
5	9.1	7.7	5.1	2.1	6.0 ± 3.1
6	11.0	9.8	6.7	3.0	7.6 ± 3.5

<sup>a</sup> Mean ± SD for four rats. The bile from Rats 2 and 3 ceased flowing prior to the 6 h timepoint.

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

**Table 5**

**Disposition of Radioactivity 72 h after an Oral Dose of [<sup>14</sup>C]MNT to B6C3F1 Mice<sup>a</sup>**

**Males (200 mg/kg)**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	2.99 ± 5.86		2.99 ± 5.86
8h	4.23 ± 21.7		4.23 ± 21.7
24h	43.8 ± 21.7	10.9 ± 7.7	54.7 ± 15.6
48h	51.1 ± 21.4	16.7 ± 8.4	67.8 ± 13.8
72h	54.2 ± 21.5	19.1 ± 9.3	73.4 ± 13.7
Cage Rinse	64.4 ± 22.5		83.5 ± 16.8

**Males (2 mg/kg)**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	7.34 ± 14.7		7.34 ± 14.7
8h	7.82 ± 15.6		7.82 ± 15.6
24h	70.2 ± 7.06	8.64 ± 5.36	78.8 ± 6.55
48h	82.5 ± 5.21	9.96 ± 5.20	92.5 ± 3.47
72h	85.6 ± 3.89	10.1 ± 5.36	95.7 ± 2.23
Cage Rinse	86.5 ± 3.73		96.7 ± 2.35

**Females (200 mg/kg)**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	8.88 ± 15.1		8.88 ± 15.1
8h	11.7 ± 17.8		11.7 ± 17.8
24h	52.9 ± 38.1	9.06 ± 7.11	62.0 ± 31.2
48h	63.5 ± 37.1	13.5 ± 10.7	77.0 ± 26.6
72h	70.5 ± 30.3	19.3 ± 16.4	89.8 ± 13.9
Cage Rinse	77.2 ± 23.8		96.5 ± 7.5

**Females (2 mg/kg)**

End of Collection Period	Cumulative Percent of Dose Recovered in:		Total
	Urine	Feces	
4h	1.27 ± 1.73		1.27 ± 1.73
8h	2.22 ± 1.63		2.22 ± 1.63
24h	47.4 ± 32.2	11.5 ± 10.2	58.9 ± 23.8
48h	64.0 ± 24.2	14.7 ± 11.8	78.7 ± 14.8
72h	70.9 ± 19.5	16.8 ± 12.9	87.6 ± 11.8
Cage Rinse	77.8 ± 14.7		94.6 ± 6.13

<sup>a</sup> Mean ± SD for four animals per dosing group.

**Table 6****Concentration of MNT in Plasma (ng/g) following Oral Administration (200 mg/kg) to Rats**

Time (h)	Male 1 <sup>a</sup>	Male 2	Male 3	Male 4	Average
0.25	N.C. <sup>b</sup>	7110	10200	10600	10900
0.5	5140	9890	7910	7010	9700
1	7770	7180	N.C.	2500	7950
2	2480	2860	6180	2400	5690
4	594	991	1880	<LD	2110
8	<LD <sup>c</sup>	574	<LD	<LD	
24	<LD	<LD	<LD	<LD	

  

Time (h)	Female 1	Female 2	Female 3	Female 4	Average
0.25	<i>10100</i>	8390	11400	13600	9290
0.5	8510	8930	9530	11800	7490
1	6340	5980	6810	12700	5820
2	4670	4180	4830	9100	3480
4	1010	2520	1280	3640	1150
8	548	<LD	<LD	<LD	
24	<LD	<LD	<LD	<LD	

<sup>a</sup> all are based on two determinations, except: *Italics = based on one determination*

<sup>b</sup> N.C. = no collection

<sup>c</sup> <LD = below limit of detection (limit of detection was 300 ng MNT/g plasma)



**Table 7**

**Concentration of MNT in Plasma (ng/g) following Oral Administration (200 mg/kg) to Mice**

Time (h)	Male 1 <sup>a</sup>	Male 2	Male 3	Average
0.083	7900	20100	20800	16300
0.17	8530	15600	15400	13200
0.33	10300	11800	15800	12700
0.67	2890	8670	20900	10800
1.00	5350	5500	11800	7550
1.50	2870	652	973	1500
2.00	454	4120	646	550
4.00	136	559	242	312

  

Time (h)	Female 1	Female 2	Female 3	Average
0.083	11100	12300	19800	14400
0.17	15000	18000	17600	16900
0.33	9280	5140	12300	8890
0.67	6090	21300	7970	11800
1.00	3700	5210	1320	3410
1.50	3190	788	673	1550
2.00	225	269	398	298
4.00	N.C. <sup>b</sup>	<LD <sup>c</sup>	937	937

<sup>a</sup> all are based on two determinations

<sup>b</sup> N.C. = no collection

<sup>c</sup> <LD = below the limit of detection (limit of detection = 110 ng MNT/g plasma)