

ADME NTP Study S0205 o-Nitrotoluene

The contract laboratory abbreviation for the test article is ONT.

Species: adult male and female F-344 rats and male B6C3F1 mice.

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

CASRN 88-72-0

Radiolabeled with carbon-14 in the phenyl ringl o-Nitrotoluene, [Ring-U-¹⁴C]-

o-Nitrotoluene Studies Performed:

1. Single 2 mg/kg oral gavage dose in male and female rats with sacrifice 72 hours postdose (N=3).
2. Single 200 mg/kg oral gavage dose in male and female rats with sacrifice 72 hours postdose (N=4).
3. Repeat 200 mg/kg/day dose 14-day oral gavage study in male rat with sacrifice on day 15 (N=3).
4. Single 2 mg/kg oral gavage dose in male mice with sacrifice 72 hours postdose (N=3).
5. Single 200 mg/kg oral gavage dose in male mice with sacrifice 72 hours postdose (N=4).
6. Single 200 mg/kg oral gavage dose in male rats for serial blood collection with sacrifice at 24 hours postdose (N=4).

In Study 3, male rats received 14 daily oral doses of 200 mg ONT per kg body weight. Non-radiolabeled ONT was administered on days 1-11 and 13-14. On Day 12, radiolabeled ONT was added to the nonradiolabeled ONT dose solution for the same 3 rats. Excreta was collected for time intervals up to 72 hours following radiolabeled dosing on Day 12.

No toxicokinetic analysis was performed.

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Table 1

**Cumulative Excretion of Radioactivity following Oral Administration of
[¹⁴C]ONT (2 mg/kg) to Rats and Mice**

Collection period (h)	Percent of dose excreted in:						
	Urine		Feces		Total		
Male rats							
0-24	98.2	± 5.21	4.93	± 1.37	103	± 4.06	
24-48	104	± 4.24	5.31	± 1.39	110	± 2.97	
48-72 ^a	106	± 2.94	5.54	± 1.46	112	± 1.53	
Female rats							
0-24	97.1	± 13.5	2.73	± 0.92	99.9	± 13.3	
24-48	104	± 17.6	3.16	± 0.78	107	± 17.3	
48-72 ^a	108	± 20.0	3.39	± 0.84	113	± 19.8	
Male mice							
0-24	60.4	± 18.9	15.8	± 2.42	76.2	± 19.6	
24-48	69.0	± 17.6	22.5	± 2.03	91.5	± 15.8	
48-72 ^a	84.9	± 8.16	23.2	± 2.23	108	± 6.70	

^a Includes cage rinse

Table 2**Cumulative Excretion of Radioactivity 72 h after Oral Administration of [14C]ONT (200 mg/kg) to Male F-344 Rats^a**

End of Period (h)	Percent of Dose Recovered in		
	Urine	Feces	Total
4	7.3 ± 5.2	ND ^b	7.3 ± 5.2
8	34.6 ± 8.9	0.1 ± 0.0	34.7 ± 8.9
24	85.9 ± 7.5	1.9 ± 1.0	87.8 ± 7.9
48	99.4 ± 4.2	3.3 ± 0.6	103 ± 4
72	102 ± 3	3.5 ± 0.6	106 ± 2

a N=4

b ND=None detected

Cumulative Urinary Excretion of Radioactivity after Oral Administration of [14C]ONT (200 mg/kg) to Male F-344 Rats^c

Collection period (h)	Percent of dose Recovered
0-24	82.5 ± 5.5
24-48	89.0 ± 3.5
48-72	89.6 ± 3.4

c N=3

Table 3**Cumulative Excretion of Radioactivity 72 h after Oral Administration of [¹⁴C]ONT (200 mg/kg) to Female F-344 Rats^a**

End of Period (h)	Percent of Dose Recovered in		
	Urine	Feces	Total
4	9.4 ± 7.2	ND ^b	9.4 ± 7.2
8	33.4 ± 9.3	0.0 ± 0.1	33.4 ± 9.3
24	91.9 ± 7.4	2.0 ± 0.9	93.9 ± 6.6
48	101 ± 5	3.0 ± 1.3	104 ± 4
72	103 ± 4	3.2 ± 1.4	106 ± 3

a N=4
b ND=None detected

Cumulative Urinary Excretion of Radioactivity after Oral Administration of [¹⁴C]ONT (200 mg/kg) to Female F-344 Rats^c

Collection period (h)	Percent of Dose Recovered
0-24	83.9 ± 6.9
24-48	90.8 ± 2.3
48-72	91.5 ± 2.0

c N=3

Table 4

**Cumulative Excretion of Radioactivity following Administration of [¹⁴C]ONT
during a 14-day Repeat Oral Dosing (200 mg/kg/day^a) of Male Rats**

Collection Period (h)	Percent of dose excreted in:					
	Urine		Feces		Total	
0-24	77.7	± 12.5	10.2	± 13.7	87.9	± 1.27
24-48	84.7	± 16.0	10.7	± 13.6	95.5	± 2.16
48-72 ^b	87.4	± 15.9	10.9	± 13.6	98.4	± 2.75

^a Radiolabeled dose on day 12.

^b Includes cage rinse.

Table 5

**Cumulative Excretion of Radioactivity 72 h after Oral Administration
of [¹⁴C]ONT at 200 mg/kg to Male B6C3F1 Mice^a**

End of Period (h)	Percent of Dose Recovered in:		
	Urine	Feces	Total
4 h	12.1 ± 17.4	ND ^b	12.1 ± 17.4
8 h	38.8 ± 6.1	0.5 ± 0.6	39.3 ± 5.7
24 h	66.3 ± 12.6	1.1 ± 0.8	67.4 ± 12.2
48 h	74.1 ± 13.7	6.6 ± 4.6	80.7 ± 12.8
72 h	78.0 ± 13.4	8.6 ± 5.1	86.6 ± 14.6

a N=4

b ND = none detected

Table 6**Concentration of ONT in Plasma after Oral Administration (200 mg/kg) to Male Rats**

Time (h)	Rat 1^a	Rat 2	Rat 3	Rat 4	Mean ± SD
0.25	8239	10928	8738	7811	8929 ± 1385
0.5	9647	9600	8931	8943	9280 ± 397
1	9091	6942	9183	10249	8866 ± 1386
2	8126	5227	4179	7970	5200 ± 3610
4	2807	2431	1257	2765	2315 ± 725
8	429	365	347	267	352 ± 67
24	<LD ^b	<LD	<LD	<LD	<LD

^a Values are the average of two determinations

^b LD (limit of detection) was ~ 50 ng/g plasma