

ADME NTP Study S0615 Toluene

The contract laboratory abbreviation for the test article is TOL.

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

Vehicles: oral, corn oil.

CASRN 108-88-3

Radiolabeled with carbon-14 randomly in the phenyl ring; Toluene, [Ring (UL)-¹⁴C]-

Toluene Studies Performed:

1. Single 0.05 mg/kg oral gavage dose in rats acclimated to metabolism cage for 2 days, sacrifice 48 hours postdose. (Table 1)
2. Single 1.5 mg/kg oral gavage dose in rats acclimated to metabolism cage for 2 days, sacrifice 48 hours postdose. (Table 1)
3. Single 0.005 mg/kg oral gavage dose in rats acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.
4. Single 0.05 mg/kg oral gavage dose in rats acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose. (Table 2)
5. Single 1.9 mg/kg oral gavage dose in rats acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.
6. Single 45 mg/kg oral gavage dose in rats acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.
7. Repeat 0.05 mg/kg/day 8-day oral gavage administration in rats, radiolabel dosed on day 7 and sacrifice 48 hours post radiolabel dosing. (Table 3)
8. Single 0.05 mg/kg oral gavage dose in rats acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose. (Table 4)
9. Single 0.05 mg/kg oral gavage dose in rats acclimated to metabolism cage for 2 days with restricted feed 24 hours prior to dose administration, sacrifice 48 hours postdose. (Table 4)
10. Single 0.005 mg/kg oral gavage dose in mice acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.
11. Single 0.05 mg/kg oral gavage dose in mice acclimated to metabolism cage for 2 days, sacrifice 48 hours postdose. (Table 5)

12. Single 0.5 mg/kg oral gavage dose in mice acclimated to metabolism cage for 2 days, sacrifice 48 hours postdose.
13. Single 5 mg/kg oral gavage dose in mice acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.
14. Single 50 mg/kg oral gavage dose in mice acclimated to metabolism cage for 1 day, sacrifice 48 hours postdose.

It was observed that differences in the metabolism cage acclimation period (prior to dosing) affected the metabolite profile so comparison studies were conducted having one versus two day acclimation days at identical doses.

For both of the 0.05 and 1.5 mg/kg single dose studies with 2 day cage acclimation periods (Table 1), the rats had restricted feed (2 pellets of Certified Purina Rodent Chow (5002)) during the second day of the cage acclimation period). Otherwise the animals were given food and tap water *ad libitum*.

For the 8 day repeat dose study, the rats received a daily oral dose of nonradiolabeled toluene for 6 days, followed by a radiolabeled dose on day 7. On day 8, an additional dose of nonradiolabeled toluene was administered. Excreta was collected for 48 hours following the radiolabeled dose.

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Table 1

**Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male F-344 Rats
Acclimated in Metabolism Cages for Two Days^a**

1.5 mg/kg

End of Collection Period	Percent of Dose Measured in:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.0121 ± 0.0152	0.318 ± 0.420	0.330 ± 0.434
4 h	8.35 ± 16.7	0.0193 ± 0.0386	NC	NC	8.70 ± 16.7
6 h	NC	NC	0.0157 ± 0.0166	0.364 ± 0.455	8.75 ± 16.8
8 h	56.9 ± 11.2	NC	NC	NC	57.3 ± 11.1
11 h	NC	NC	0.0260 ± 0.0194	0.449 ± 0.411	57.4 ± 11.1
24 h	93.2 ± 3.83	0.967 ± 0.447	0.0696 ± 0.0564	0.532 ± 0.426	94.8 ± 4.64
48 h ^b	95.5 ± 3.58	1.51 ± 1.11	0.119 ± 0.0893	0.556 ± 0.430	97.8 ± 4.99

0.05 mg/kg

End of Collection Period	Percent of Dose Measured in:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.319 ± 0.0142	5.05 ± 6.07	5.08 ± 6.06
4 h	12.6 ± 10.0	0.51 ± 2.65	NC	NC	19.2 ± 12.1
6 h	NC	NC	0.0328 ± 0.0012	5.84 ± 7.11	20.0 ± 12.9
8 h	52.8 ± 10.5	NC	NC	NC	60.1 ± 5.52
11 h	NC	NC	0.371 ± 0.545	6.25 ± 7.56	60.9 ± 6.00
24 h	82.4 ± 11.1	4.33 ± 4.31	1.14 ± 1.75	6.67 ± 8.05	94.6 ± 5.79
48 h ^b	90.1 ± 7.9	4.77 ± 3.91	2.12 ± 3.03	6.78 ± 8.20	104 ± 4.58

^a N=4

^b Urine value includes cage rinse

NC Not Collected

Table 2
Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male F-344 Rats
Acclimated in Metabolism Cages for One Day^a

45 mg/kg

End of Collection Time	Percent of Dose Measured in:				
	Urine	Feces	CO ₂	Volatile Breath	Total
3 h	NC	NC	0.00884 ± 0.0067	4.01 ± 1.40	4.02 ± 1.40
4 h	0.757 ± 1.45	0.00165 ± 0.0016	NC	NC	4.77 ± 1.52
6 h	NC	NC	0.0133 ± 0.0064	6.37 ± 1.09	7.14 ± 0.484
8 h	61.3 ± 8.60	NC	NC	NC	67.7 ± 9.44
11 h	NC	NC	0.0201 ± 0.0054	6.90 ± 1.15	68.2 ± 9.43
24 h	95.8 ± 2.71	0.634 ± 0.544	0.0242 ± 0.0040	7.06 ± 1.16	103 ± 1.81
48 h ^b	98.7 ± 2.24	0.684 ± 0.556	0.0332 ± 0.0062	7.08 ± 1.16	106 ± 1.19

1.9 mg/kg

End of Collection Period	Percent of Dose Measured in:				
	Urine	Feces	CO ₂	Volatile Breath	Total
3 h	NC	NC	0.00600 ± 0.0026	0.153 ± 0.174	0.160 ± 0.17
4 h	13.6 ± 17.1	0.0483 ± 0.055	NC	NC	13.8 ± 17.0
6 h	NC	NC	0.0118 ± 0.0043	0.199 ± 0.184	13.9 ± 16.9
8 h	56.0 ± 9.09	NC	NC	NC	56.3 ± 8.95
11 h	NC	NC	0.0205 ± 0.0038	0.235 ± 0.187	56.3 ± 8.95
24 h	88.3 ± 3.54	0.695 ± 0.705	0.0234 ± 0.0038	0.251 ± 0.190	90.9 ± 4.97
48 h ^b	92.4 ± 1.65	0.762 ± 0.772	0.0273 ± 0.0045	0.258 ± 0.188	94.9 ± 3.57

0.050 mg/kg

End of Collection Period	Percent of Dose Measured in:				
	Urine	Feces	CO ₂	Volatile Breath	Total
3 h	NC	NC	0.0267 ± 0.0007	0.0454 ± 0.0154	0.0721 ± 0.0148
4 h	15.3 ± 30.7	0.0010 ± 0.0003	NC	NC	15.4 ± 30.7
6 h	NC	NC	0.0485 ± 0.0034	0.0795 ± 0.0253	15.5 ± 30.7
8 h	75.3 ± 11.3	NC	NC	NC	75.5 ± 11.3
11 h	NC	NC	0.700 ± 0.0104	0.0935 ± 0.0260	75.5 ± 11.3
24 h	99.5 ± 0.886	0.437 ± 0.594	0.0851 ± 0.0130	0.102 ± 0.0253	100 ± 1.29
48 h ^b	101. ± 0.424	0.474 ± 0.594	0.154 ± 0.0318	0.107 ± 0.0227	102 ± 0.864

0.005 mg/kg

End of Collection Period	Percent of Dose Measured in:				
	Urine	Feces	CO ₂	Volatile Breath	Total
3 h	NC	NC	0.0973 ± 0.0315	0.414 ± 0.491	0.489 ± 0.475
4 h	20.3 ± 24.3	0.00289 ± 0.00195	NC	NC	20.8 ± 24.1
6 h	NC	NC	0.159 ± 0.0453	0.459 ± 0.521	20.9 ± 24.1
8 h	71.1 ± 14.0	NC	NC	NC	71.6 ± 13.8
11 h	NC	NC	0.239 ± 0.0389	0.472 ± 0.533	71.7 ± 13.8
24 h	94.8 ± 2.53	0.298 ± 0.206	0.309 ± 0.0485	0.474 ± 0.531	95.8 ± 2.23
48 h ^b	96.4 ± 1.90	0.379 ± 0.243	0.551 ± 0.173	0.479 ± 0.536	97.7 ± 1.55

^a N=4 except N=3 for 1.9 mg/kg study
^b Urine value includes cage rinse
 NC Not Collected

Table 3

**Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male F-344 Rats pretreated with TOL for 6 days^{ac}
0.05 mg/kg**

Period of Collection Period	Percent of Dose Measured in:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.01 ± 0.01	0.09 ± 0.1	0.1 ± 0.1
4 h	31.3 ± 6.0	0.01 ± 0.01	NC	NC	31.4 ± 6.0
6 h	NC	NC	0.02 ± 0.01	0.11 ± 0.1	31.5 ± 6.0
8 h	59.1 ± 12.2	NC	NC	NC	59.3 ± 12.2
11 h	NC	NC	0.03 ± 0.01	0.13 ± 0.10	59.3 ± 12.2
24 h	95.6 ± 2.8	0.3 ± 0.1	0.04 ± 0.01	0.15 ± 0.10	96.0 ± 2.9
48 h ^b	98.5 ± 1.8	0.3 ± 0.1	0.05 ± 0.01	0.16 ± 0.10	99.0 ± 1.8

- a N=3
- b Urine value includes cage rinse
- c Dosed with nonradiolabeled TOL on days 1-6 and day 8
- NC Not Collected

Table 4

Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male F-344 Rats^a

0.05 mg/kg (1 Day Acclimation)

End of Collection	Percent of Dose Measured in:				Total
Period	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.008 ± 0.010	0.05 ± 0.04	0.05 ± 0.03
4 h	22.3 ± 29.4	0.6 ± 1.0	NC	NC	22.9 ± 28.8
6 h	NC	NC	0.02 ± 0.01	0.07 ± 0.04	23.0 ± 28.8
8 h	50.3 ± 30.1	NC	NC	NC	50.9 ± 29.1
11 h	NC	NC	0.02 ± 0.01	0.09 ± 0.05	50.9 ± 29.1
24 h	84.9 ± 10.6	1.2 ± 1.1	0.02 ± 0.02	0.1 ± 0.04	86.2 ± 9.5
48 h ^b	91.3 ± 6.77	1.3 ± 1.2	0.03 ± 0.02	0.1 ± 0.05	92.7 ± 5.5

0.05 mg/kg (2 Day Acclimation)

End of Collection	Percent of Dose Measured in:				Total
Period	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.02 ± 0.004	2.4 ± 4.0	2.4 ± 4.0
4 h	0.003 ± 0.004	0.04 ± 0.07	NC	NC	2.4 ± 4.1
6 h	NC	NC	0.03 ± 0.001	2.7 ± 4.5	2.8 ± 4.5
8 h	32.9 ± 8.9	NC	NC	NC	35.6 ± 12.8
11 h	NC	NC	0.03 ± 0.004	3.0 ± 4.8	35.9 ± 13.1
24 h	76.9 ± 6.8	2.5 ± 1.0	0.04 ± 0.02	3.1 ± 5.0	82.6 ± 6.8
48 h ^b	91.1 ± 4.6	2.7 ± 1.0	0.05 ± 0.02	3.2 ± 5.0	97.1 ± 1.3

^a N=3
^b Urine value includes cage rinse
NC Not Collected

Table 5
Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male B6C3F₁ Mice

50 mg/kg^{ab}

End of Collection Period	Percent of Dose Measured In:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.06 ± 0.01	0.21 ± 0.05	0.27 ± 0.06
4 h	6.1 ± 11.8	0.003 ± 0.007	NC	NC	6.41 ± 11.8
6 h	NC	NC	0.11 ± 0.01	0.24 ± 0.06	6.49 ± 11.8
8 h	13.3 ± 16.4	NC	NC	NC	13.6 ± 16.4
11 h	NC	NC	0.14 ± 0.01	0.27 ± 0.07	13.7 ± 16.4
24 h	37.0 ± 22.9	10.1 ± 6.4	0.16 ± 0.01	0.33 ± 0.09	47.6 ± 25.6
48 h	59.4 ± 16.7	15.1 ± 5.2	0.17 ± 0.01	0.40 ± 0.08	90.0 ± 3.2 ^c

5 mg/kg^{bd}

End of Collection Period	Percent of Dose Measured In:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.2 ± 0.0	0.03 ± 0.003	0.2 ± 0.0
4 h	0.02 ± 0.03	0.2 ± 0.3	NC	NC	0.4 ± 0.4
6 h	NC	NC	0.2 ± 0.0	0.04 ± 0.01	0.5 ± 0.4
8 h	2.0 ± 1.7	NC	NC	NC	2.4 ± 1.9
11 h	NC	NC	0.3 ± 0.0	0.1 ± 0.1	2.6 ± 1.9
24 h	57.7 ± 23.1	4.9 ± 3.1	0.3 ± 0.0	0.3 ± 0.2	63.3 ± 25.0
48 h ^e	82.4 ± 7.1	6.3 ± 3.1	0.3 ± 0.0	0.4 ± 0.4	89.5 ± 8.1

0.5 mg/kg^{fg}

End of Collection Period	Percent of Dose Measured In:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.193 ± 0.0350	0.460 ± 0.866	0.653 ± 0.832
4 h	10.5 ± 14.1	NE	NC	NC	11.2 ± 14.1
6 h	NC	NC	0.276 ± 0.0267	0.544 ± 0.921	11.3 ± 14.2
8 h	12.0 ± 15.0	NC	NC	NC	12.8 ± 15.3
11 h	NC	NC	0.341 ± 0.0918	0.804 ± 0.879	13.1 ± 15.4
24 h	20.1 ± 15.6	22.0 ± 25.0	0.384 ± 0.107	1.22 ± 0.805	43.8 ± 26.8
48 h ^e	47.9 ± 19.6	35.7 ± 24.9	0.417 ± 0.116	1.62 ± 0.865	85.6 ± 7.40

- a N=5
- b Mice acclimated in metabolism cages for one day prior to dosing
- c Total includes percent dose in cage rinse of 14.92 ± 16.55
- d N=3
- e Urine value includes cage rinse
- f Mice acclimated in metabolism cages for two days prior to dosing
- g N=4
- NC Not Collected
- NE None Excreted

Table 5 (continued)

Cumulative Excretion of Radioactivity following Oral Administration
of [¹⁴C]TOL to Male B6C3F₁ Mice

0.05 mg/kg^f_g

End of Collection Period	Percent of Dose Measured In:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	0.151 ± 0.0801	0.0317 ± 0.0262	0.182 ± 0.077
4 h	1.48 ± 2.94	NE	NC	NC	1.66 ± 2.96
6 h	NC	NC	0.180 ± 0.111	0.138 ± 0.215	1.79 ± 3.13
8 h	3.05 ± 4.83	NC	NC	NC	3.37 ± 5.04
11 h	NC	NC	0.206 ± 0.0936	0.360 ± 0.528	3.62 ± 5.33
24 h	18.9 ± 24.2	10.5 ± 11.3	0.298 ± 0.102	0.872 ± 1.06	30.6 ± 20.3
48 h ^e	53.2 ± 35.3	32.6 ± 29.5	0.408 ± 0.171	1.63 ± 1.47	87.8 ± 16.4

0.005 mg/kg^b_d

End of Collection Period	Percent of Dose Measured In:				Total
	Urine	Feces	CO ₂	Volatile Breath	
3 h	NC	NC	1.0 ± 0.4	0.2 ± 0.0	1.2 ± 0.4
4 h	10.5 ± 18.1	0.8 ± 1.2	NC	NC	12.4 ± 19.5
6 h	NC	NC	1.4 ± 0.8	0.2 ± 0.0	12.9 ± 19.4
8 h	30.2 ± 26.2	NC	NC	NC	32.6 ± 26.1
11 h	NC	NC	2.0 ± 1.0	0.9 ± 0.0	33.8 ± 25.9
24 h	69.1 ± 3.3	8.5 ± 3.9	2.6 ± 1.2	1.5 ± 0.3	81.7 ± 2.3
48 h ^e	81.1 ± 5.6	10.0 ± 4.9	3.5 ± 1.3	2.2 ± 0.4	96.8 ± 3.1

- a N=5
- b Mice acclimated in metabolism cages for one day prior to dosing
- c Total includes percent dose in cage rinse of 14.92 ± 16.55
- d N=3
- e Urine value includes cage rinse
- f Mice acclimated in metabolism cages for two days prior to dosing
- g N=4
- NC Not Collected
- NE None Excreted