

ADME NTP Study S0208 2,4-Tolulene diisocyanate

The contract laboratory used the abbreviation 2,4-TDI for the test article.

Sex/Species: adult male F344 rats.

Vehicle: oral, corn oil (dried by heating and stored under nitrogen).

CASRN 584-84-9

Radiolabeled with carbon-14 in the ring; 2,4-Toluene diisocyanate, [Ring-¹⁴C]-

Studies Performed:

- Single oral gavage administration of 7, 70, or 700 mg/kg 2,4-TDI to rats with sacrifice 72 hours postdose.

Like the 2,6-toluene diisocyanate isomer, 2,4-TDI given orally in corn oil was converted mostly to polymers in the gastrointestinal (GI) tract. These polymeric 2,4-TDI derived materials were excreted in feces or were found in the GI tract 72 hours postdose in the 700 mg/kg dosed animals. The polymer appeared to have prevented passage of some of the stomach contents into the intestine. The stomachs of animals given the lower two doses appeared normal and did not contain visible polymer.

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Table 1

Excretion of Total ^{14}C After Oral Administration of
 $[^{14}\text{C}]2,4\text{-TDI}$ to Fischer 344 Male Rats (% Dose)

Dose (mg/kg)	Excreta Time (h)	Urine	Feces	Total
7	0-6	5.2 ± 2.3	a	
	6-12	12.1 ± 1.1		
	12-24	14.6 ± .8	54.6 ± 5.0	69.2 ± 4.4
	24-48	15.7 ± 1.0	71.4 ± 4.2	87.1 ± 3.4
	48-72	16.3 ± 1.1	74.1 ± 4.9	90.5 ± 4.0

Dose (mg/kg)	Excreta Time (h)	Urine	Feces	Breath	Total
70	0-6	1.7 ± 1.2	a	.0 ± .0	1.7 ± 1.2
	6-12	4.2 ± 1.9		.0 ± .0	4.2 ± 1.9
	12-24	5.6 ± 1.9	54.2 ± 15.2	.0 ± .0	59.8 ± 16.3
	24-48	6.1 ± 1.8	77.2 ± 4.6	.0 ± .0	83.3 ± 5.8
	48-72	6.3 ± 1.8	83.4 ± 3.1	.0 ± .0	89.7 ± 4.6

Dose (mg/kg)	Excreta Time (h)	Urine	Feces	Total
700	0-6	1.0 ± .3	a	
	6-12	2.3 ± .5		
	12-24	3.0 ± .5	33.4 ± 2.1	36.4 ± 1.9
	24-48	3.3 ± .5	65.2 ± 2.5	68.4 ± 3.0
	48-72	3.5 ± .4	72.8 ± 2.9	76.3 ± 3.2

Table 2

Total Recovery of ^{14}C 72 Hours After Oral Administration
of 2,4-TDI to F344 Male Rats

Dose (mg/kg)	Urine	Feces	Tissues	Intestinal Contents	Total
7	16.3 ± 1.1 ^a	74.1 ± 4.9 ^a	1.7 ^{b,d}	0.3 ^b	92.4
70	6.3 ± 1.8 ^a	83.4 ± 3.1 ^a	0.7 ^b	1.1 ^b	91.5
700	3.5 ± 0.4 ^a	72.8 ± 2.9 ^a	0.7 ^c	10.6 ^c	87.6

^a Average % dose for 4 rats.

^b Average % dose for 3 rats.

^c Average % dose for 2 rats.

^d Not all tissues taken.

Table 3

Amount of ^{14}C Contained in Tissues 72 Hours After
Oral Administration of [^{14}C]2,4-TDI to F344 Male Rats^a

Tissue Name	% Dose in Total Tissue Ratio		
	7 mg/kg	70 mg/kg	700 mg/kg
Adipose	.07616 ± .02020	.02782 ± .00542	.03351
Adrenal gland		.00025 ± .00006	.00051
Bladder	.01111 ± .00804	.00097 ± .00112	.01013
Blood	.18906 ± .03532	.08680 ± .01864	.03700
Brain		.00074 ± .00011	.00103
Cecum	.00517 ± .00108	.01079 ± .00821	.02369
Esophagus		.00041 ± .00011	.00127
Eye		.00106 ± .00008	.00171
Heart		.00198 ± .00065	.00148
Intestine, large	.00857 ± .00144	.01246 ± .01342	.01358
Intestine, small	.01664 ± .00126	.00917 ± .00332	.00967
Kidney	.03860 ± .00291	.01763 ± .00178	.00910
Liver	.19493 ± .02878	.08030 ± .01407	.05978
Lung		.00320 ± .00145	.00180
Muscle	.81189 ± .14207	.27679 ± .06623	.27390
Plasma	.09642 ± .00949	.03617 ± .00603	.00967
Prostate		.00058 ± .00012	.00201
Seminal vesicle		.00076 ± .00012	.00177
Skin	.34769 ± .01423	.12889 ± .00519	.12776
Spleen		.00136 ± .00047	.00101
Stomach	.00629 ± .00039	.04625 ± .05311	.08221
Testis		.00221 ± .00042	.00117
Trachea		.00039 ± .00016	.00049
Stomach Contents	.00813 ± .00213	.00610 ± .00330	8.47877
Small Intest Cont	.1676 ± .00173	.01908 ± .01041	.11278
Large Intest Cont	.11880 ± .05270	.59935 ± .67588	.66648
Cecum Contents	.10818 ± .02540	.50651 ± .43530	1.34741
Total,			
excluding plasma	1.95777	1.84183	11.30003
excluding plasma			
and contents	1.555	0.711	0.695

^a Values are mean ± SD for 3 animals; other values for 20 animals only.

Table 4

Concentration of ^{14}C -Labeled Compounds in Tissues 72 Hours After Oral Administration of [^{14}C]2,4-TDI to F344 Male Rats^a

Tissue Name	ng-eq Compound per g Tissue		
	7 mg/kg	70 mg/kg	700 mg/kg
Adipose	54. ± 14.	197. ± 38.	2418.
Adrenal gland		1082. ± 171.	19232.
Bladder	2489. ± 2011.	2048. ± 2182.	414490.
Blood	211. ± 38.	974. ± 192.	4216.
Brain		84. ± 16.	1224.
Cecum	155. ± 54.	4322. ± 3410.	74275.
Esophagus		512. ± 177.	14733.
Eye		779. ± 26.	15455.
Heart		504. ± 188.	3586.
Intestine, large	143. ± 48.	2405. ± 2609.	23799.
Intestine, small	107. ± 13.	855. ± 258.	8638.
Kidney	362. ± 40.	1764. ± 250.	8614.
Liver	358. ± 40.	1593. ± 271.	10770.
Lung		629. ± 318.	3758.
Muscle	114. ± 20.	391. ± 87.	3942.
Plasma	207. ± 19.	781. ± 117.	2132.
Prostate		386. ± 24.	11656.
Seminal vesicle		178. ± 31.	4445.
Skin	163. ± 5.	609. ± 13.	6126.
Spleen		555. ± 136.	3532.
Stomach	120. ± 8.	10456. ± 12101.	94818.
Testis		169. ± 26.	907.
Trachea		748. ± 90.	12560.
Stomach Contents	10. ± 1.	111. ± 67.	2216005.
Small Intest Cont	39. ± 6.	315. ± 129.	25184.
Large Intest Cont	293. ± 158.	16219. ± 13171.	200819.
Cecum Contents	151. ± 75.	5600. ± 4782.	194771.

^a Values are mean ± SD for 3 animals; other values for 2 animals only

Table 5

Concentration of ^{14}C -Labeled Compounds in Tissues 72 Hours
After Oral Administration of [^{14}C]2,4-TDI to F344 Male Rats^a

Tissue Name	Tissue-Blood Ratio		
	7 mg/kg	70 mg/kg	700 mg/kg
Adipose	.264 ± .100	.208 ± .057	.601
Adrenal gland		1.131 ± .237	4.763
Bladder	10.906 ± 8.038	2.397 ± 2.864	87.694
Blood	1.000 ± 0.000	1.000 ± 0.000	1.000
Brain		.091 ± .034	.303
Cecum	.717 ± .151	4.995 ± 4.244	18.002
Esophagus		.527 ± .152	3.245
Eye		.819 ± .146	3.875
Heart		.514 ± .138	.886
Intestine, large	.663 ± .118	2.585 ± 2.768	5.512
Intestine, small	.513 ± .040	.933 ± .420	2.176
Kidney	1.744 ± .302	1.831 ± .223	2.150
Liver	1.739 ± .421	1.681 ± .481	2.630
Lung		.625 ± .197	.908
Muscle	.553 ± .128	.401 ± .024	.957
Plasma	.993 ± .103	.808 ± .055	.535
Prostate		.405 ± .075	2.666
Seminal vesicle		.186 ± .042	.998
Skin	.789 ± .129	.639 ± .110	1.480
Spleen		.570 ± .075	.859
Stomach	.583 ± .132	12.552 ± 15.456	21.514
Testis		.175 ± .024	.220
Trachea		.782 ± .134	3.241
Stomach Contents	.049 ± .005	.125 ± .095	631.392
Small Intest Cont	.183 ± .005	.349 ± .201	6.790
Large Intest Cont	1.328 ± .553	18.316 ± 14.792	43.984
Cecum Contents	.711 ± .293	6.537 ± 6.059	46.964

^a Values are mean ± SD for 3 animals; other values for 2 animals only