ADME NTP Study S0057 2,4- & 2,6-Toluene diisocyanate

The contractor abbreviated the test article as 2,6-TDI.
Sex/Species: male F344 rats.
Vehicle: oral, corn oil.

CASRN 26471-62-5

Radiolabeled with carbon-14 in the ring; 2,6-Toluene diisocyanate, [Ring-^{14}C]

Studies Performed:

- Single 59 mg/kg oral gavage dose to rats allowed food *ad libitum* prior to dosing with sacrifice 72 hours postdose (n=4).

- Single 900 mg/kg oral gavage dose to rats fasted 18 hours prior to dosing with sacrifice 72 hours postdose (n=3).

- Single 900 mg/kg oral gavage dose to rats allowed food *ad libitum* prior to dosing with sacrifice 72 hours postdose (rats n=4).

The toxicity and carcinogenicity gavage studies were performed with a mixture of toluene diisocyanate isomers; the test article was commerical grade 2,4-(80%) and 2,6-(20%)-toluene diisocyanate and the CASRN 26471-62-5. The ADME studies were performed with different isomers: 2,4-toluene diisocyanate for NTP Study S0208 (CASRN 584-84-9) and 2,6-toluene diisocyanate for NTP Study S0057. The CASRN 91-08-7 which corresponds to the isomer 2,6-toluene diisocyanate was not used. The CASRN 26471-62-5 allows matching of the 2,6-toluene diisocyanate ADME study with the toxicity and carcinogenicity studies.

Note that 2,6-TDI polymerizes and at the higher dose, 900 mg/kg, formed polymers in the gastrointestinal tract. The polymerized TDI usually lined the stomach, slowing or preventing the migration of food into the intestines with stomachs becoming greatly distended but at 60 mg/kg these results were not observed. In addition, the half life of 2,6-TDI in serum was less than 30 seconds; thus, intravenous administration of 2,6-TDI was not possible.

Table 1

Concentration of ^{14}C-Labeled Compounds in Selected Tissues 72 hours after Oral Administration of [^{14}C]2,6-TDI to F344 Male Rats[a]

	µg-eq/g (TBR)[a]		
Dose (mg/kg)	900[b,c]	900[d]	59[d]
Blood	7.4 ± 2.1 (1.0)	4.0 ± 2.3 (1.0)	1.1 ± 0.1 (1.0)
Adipose (Epididymis)	2.4 ± 1.4 (0.31 ± 0.13)	0.80 ± 0.30 (0.13 ± 0.04)	0.076 ± 0.013 (0.070 ± 0.009)
Liver	4.4 ± 1.2 (0.60 ± 0.08)	4.6 ± 2.2 (0.72 ± 0.05)	0.44 ± 0.030 (0.40 ± 0.01)
Muscle (Hind leg)	1.4 ± 0.7 (0.18 ± 0.05)	1.6 ± 0.3 (0.26 ± 0.07)	0.20 ± 0.08 (0.18 ± 0.06)
Skin (Ears)	1.9 ± 1.0 (0.27 ± 0.12)	2.7 ± 0.7 (0.46 ± 0.14)	0.60 ± 0.20 (0.55 ± 0.15)
Lungs	3.1 ± 0.8 (0.43 ± 0.05)	2.6 ± 0.9 (0.42 ± 0.03)	0.52 ± 0.10 (0.48 ± 0.07)
Heart	2.9 ± 1.0 (0.39 ± 0.03)	2.0 ± 0.7 (0.33 ± 0.04)	0.34 ± 0.02 (0.32 ± 0.02)
Kidneys	13.0 ± 4.2 (1.7 ± 0.1)	14.0 ± 5.9 (2.4 ± 0.3)	1.7 ± 0.2 (1.6 ± 0.2)
Esophagus	9.1 ± 4.2 (1.4 ± 1.1)	23 ± 37 (2.6 ± 3.6)	0.39 ± 0.05 (0.36 ± 0.04)
Stomach	120 ± 76 (18 ± 12)		
Small Intestines	9.8 ± 4.0 (1.4 ± 0.6)		
Large Intestines	9.6 ± 5.5 (1.3 ± 0.6)		

[a] Cf. Tables A2-A4 in Appendix for data from individual animals.

[b] (Tissue:Blood Ratio)

[c] Rats fasted for 18 hours prior to dosing. Values are average ± SD for 3 animals.

[d] Rats allowed food ad libitum prior to dosing. Values are average ± SD for 4 animals.

Table 2

Amount of ^{14}C Contained in Selected Tissues 72 hours after Oral Administration of [^{14}C]2,6-TDI to Male F344 Rats

	% Dose in Tissues[a]		
Dose (mg/kg)	900[b]	900[c]	59[c]
Blood[d]	0.052 ± 0.018	0.046 ± 0.013	0.12 ± 0.010
Adipose[d]	0.027 ± 0.018	0.008 ± 0.002	0.012 ± 0.003
Liver	0.017 ± 0.007	0.015 ± 0.004	0.024 ± 0.003
Muscle[d]	0.077 ± 0.04	0.082 ± 0.021	0.16 ± 0.07
Skin[d]	0.032 ± 0.02	0.041 ± 0.005	0.14 ± 0.04
Lungs	0.001 ± 0.0006	0.001 ± 0.00005	0.004 ± 0.001
Heart	0.0008 ± 0.0003	0.0008 ± 0.0001	0.002 ± 0
Kidneys	0.010 ± 0.004	0.012 ± 0.0003	0.020 ± 0.003
Esophagus	0.0006 ± 0.0004	0.002 ± 0.003	0.0004 ± 0.0001
Stomach	0.16 ± 0.07		
Small Intestines	0.031 ± 0.015		
Large Intestines	0.007 ± 0.004		

[a]Values are mean ± SD for 3 animals in the first column; mean ± SD for 4 animals in second and third columns (cf. Tables A5-A7 in Appendix for data from individual animals).

[b]Animals were fasted 18 hours before dosing.

[c]Animals were allowed food ad libitum before dosing.

[d]Skin assumed to be 15% of body weight; muscle - 50% of body weight; adipose - 10% of body weight; blood - 6.3% of body weight.

Table 3
Recovery of Radioactivity after Oral administration of [^{14}C]2,6-TDI to F344 Male Rats

		% Dose Recovered										
Rat I.D.	Dose (mg/kg)	Urine	Feces	Breath	Selected Tissues[a]	Stomach	Stomach Contents	Intestines	Intestine Contents	Carcass	Cage Rinse	Total
1	863	6.58	44.4	0.04	0.26	0.19	19.7	0.03	8.5			79.7
2	885	6.08	29.9	0.04	0.27	0.02	43.2	0.05	2.5			82.1
3	1015	4.09	26.1	0.04	0.08	0.21	49.4	0.02	9.6			89.5
4	1010	5.37	19.3	0.06	0.17		44.4[b]		3.7[c]		0.29	73.2
5	836	3.58	20.9	0.09	0.12		43.8[b]		4.9[c]		0.08	73.5
6	867	6.00	38.0	0.09	0.18		22.1[b]		8.7[c]		0.06	75.1
7	837	5.05	52.6	0.09	0.17		0.09[d]		16.1[c]		0.13	74.2
8	60.2	10.4	63.3	0.09	0.29		0.02[b]		0.04[c]		0.10	74.2
9	58.9	12.9	54.4	0.11	0.50		0.03[b]		0.02[c]		1.1	69.1
10	57.7	11.9	64.9	0.09	0.33		0.01[b]		0.20[c]		0.22	77.6
11	59.4	9.30	64.8	0.08	0.34		0.07[b]		0.21[c]	0.30	0.30	75.4

[a]Tissues included: heart, lungs, kidneys, esophagus, liver, skin, adipose, muscle. Skin assumed to be 15% of body weight; adipose - 10% of body weight; muscle - 50% of body weight.

[b]Values are for stomach contents and stomach tissue

[c]Values are for intestine contents and intestine tissue

[d]This stomach was empty. Value represents percent dose in stomach tissue.

Table 4

Excretion of Total ^{14}C after Oral Administration of 900 mg/kg of [^{14}C]-2,6-TDI to F344 Male Rats (% Dose)

Rat I.D.	Time after Dosing (hr)	Urine	Feces	Breath	Total	Cumulative Total
Rat 1	24	4.59	1.94	0.02	6.55	6.55
	48	1.27	10.5	0.01	11.8	18.4
	72	0.72	32.0	0.01	32.7	51.0
Rat 2	24	4.41	5.25	0.03	9.69	9.69
	48	1.33	20.8	0.01	22.1	31.8
	72	0.34	3.93	0.01	4.28	36.1
Rat 3	24	2.32	5.09	0.02	7.43	7.43
	48	0.90	9.14	0.01	10.0	17.4
	72	0.87	11.9	0.01	12.8	30.2
Rat 4	24	3.67	3.10	0.04	6.81	6.81
	48	1.43	6.43	0.01	7.87	14.7
	72	0.27	9.80	0.01	10.1	24.8
Rat 5	24	2.54	2.33	0.05	4.92	4.92
	48	0.84	11.4	0.02	12.3	17.2
	72	0.20	7.15	0.02	7.37	24.6
Rat 6	24	4.74	0.20	0.05	4.99	4.99
	48	1.06	20.4	0.02	21.5	26.5
	72	0.20	17.4	0.02	17.6	44.1
Rat 7	24	3.94	2.43	0.05	6.42	6.42
	48	0.92	19.5	0.02	20.4	26.8
	72	0.19	30.7	0.02	30.9	57.7

Table 5

Excretion of Total ^{14}C after Oral Administration of 59 mg/kg of [^{14}C]-2,6-TDI to F344 Male Rats (% Dose)

Rat I.D.	Time after Dosing (hr)	Urine	Feces	Breath	Total	Cumulative Total
Rat 8	24	10.3	21.8	0.06	32.2	32.2
	48	1.01	36.3	0.02	37.3	69.5
	72	0.10	5.27	0.01	5.38	73.9
Rat 9	24	11.8	21.8	0.08	33.7	33.7
	48	0.28	17.4	0.02	17.7	51.4
	72	0.81	15.2	0.01	16.0	67.4
Rat 10	24	11.5	25.4	0.07	37.0	37.0
	48	0.20	24.7	0.01	24.9	61.9
	72	0.19	15.6	0.01	15.8	77.7
Rat 11	24	9.08	24.6	0.06	33.7	33.7
	48	0.12	37.2	0.01	37.3	71.0
	72	0.10	3.03	0.01	3.14	74.1
Rat 12	24	12.4	[a]	[a]	-	-
	48	1.4				
Rat 13	24	11.4	[a]	[a]	-	-
	48	1.3				
Rat 14	24	10.7	[a]	[a]	-	-
	48	0.9				

[a]Not collected for these animals.