ADME NTP Study S0670 1,2,3-Trichloropropane Toxicokinetics

Sex/Species: male F344 rats.
Vehicle: intravenous, not specified.

CASRN 96-18-4

Radiolabeled with carbon-14 (labeled in the 1, 3 positions); [1,3-^{14}C]1,2,3-Trichloropropane

Studies Performed:

Single 3.6 mg/kg intravenous dose to rats with sacrifice at 0.25, 0.5, 1, 2, 4, 8, 24, 48, 96, and 144 hours postdose. (n = 3 per time point)

Toxicokinetics:

Equations describing data sets were fit by the nonlinear regression program NONLIN or by the method of residuals. The percent dose as parent trichloropropane in major tissues and the percent dose as radioactivity in adipose tissue, skin and muscle was described by the biphasic elimination equation (1) $x = Ae^{-\alpha t} + Be^{-\beta t}$.

Percent dose as ^{14}C in liver, kidney, blood, small intestine, and large intestine were described by the triphasic equation (2) $x = Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-\gamma t}$. In these equations, x represents percent dose in a tissue; A, B, and C are constants; α, β, and γ are first-order rate constants; and t is time.

For parent trichloropropane in blood, the curve has the characteristic shape indicating a two-compartment system. Several tissues exhibited a phase 0, or absorption phase (negative term in equation 2).

Note on Accessibility: Persons with disabilities or using assistive technology may find some documents are not fully accessible. For assistance, contact Central Data Management or use our contact form and identify the documents/pages for which access is required. We will assist you in accessing the content of the files. NIEHS has helpful information on accessibility.

Table 1. Percent dose as unchanged parent compound (P) and metabolites (M) in selected tissues after 3.6 mg/kg intravenous 1,2,3-trichloropropane ($\bar{x}$ ± SD, n=3).

		15 min	30 min	1 hr	2 hr	4 hr	8 hr	1 da	2 da	4 da	6 da
Liver	P	2.76 ±0.30	1.33 ±0.08	0.64 ±0.05	0.40 ±0.12	0.16 ±0.03	0.094 ±0.012	0.081 ±0.007	0.048 ±0.003	0.033 ±0.006	0.009 ±0.003
	M	1.72 ±0.77	1.91 ±1.11	6.61 ±1.30	6.42 ±0.96	5.43 ±0.19	4.26 ±0.52	1.73 ±0.46	1.26 ±0.19	1.047 ±0.203	0.764 ±0.014
Kidneys	P	0.65 ±0.06	0.26 ±0.04	0.14 ±0.04	0.085 ±0.033	0.052 ±0.022	0.047 ±0.008	0.029 ±0.006	0.016 ±0.003	0.009 ±0.001	0.002 ±0.000
	M	0.43 ±0.081	0.70 ±0.21	2.43 ±0.64	2.67 ±0.24	2.24 ±0.19	1.70 ±0.063	0.588 ±0.130	0.391 ±0.057	0.264 ±0.060	0.191 ±0.029
Adipose Tissue	P	16.41 ±10.81	16.30 ±1.74	19.86 ±4.29	10.26 ±2.21	3.78 ±0.14	1.21 ±0.24	0.121 ±0.025	0.101 ±0.057	0.053 ±0.007	0.018 ±0.001
	M	20.91 ±8.46	8.74 ±3.53	7.28 ±8.99	6.62 ±5.72	1.73 ±1.52	2.08 ±0.58	0.209 ±0.049	0.194 ±0.235	0.137 ±0.035	0.132 ±0.020
Skin	P	11.13 ±0.69	8.28 ±3.96	2.61 ±0.66	2.29 ±0.74	0.73 ±0.31	0.32 ±0.19	0.133 ±0.005	0.130 ±0.004	ND	ND
	M	4.93 ±6.59	0.95 ±1.64	5.00 ±2.66	2.57 ±0.65	2.56 ±0.84	3.31 ±0.89	0.997 ±0.104	0.58 ±0.072	ND	ND
Muscle	P	11.08 ±5.04	6.76 ±1.59	4.76 ±2.23	1.92 ±0.70	0.79 ±0.35	0.050 ±0.12	0.039 ±0.03	ND	ND	ND
	M	6.90 ±5.23	0.39 ±1.22	5.72 ±3.39	4.96 ±1.13	6.02 ±1.40	3.70 ±0.42	1.70 ±0.10	ND	ND	ND
Blood	P	2.41 ±0.35	1.46 ±0.27	0.99 ±0.19	0.73 ±0.21	0.69 ±0.23	0.62 ±0.16	0.32 ±0.030	0.19 ±0.075	ND	ND
	M	1.32 ±0.13	1.83 ±0.28	3.55 ±0.24	2.30 ±0.22	1.62 ±0.21	0.93 ±0.08	0.56 ±0.02	0.45 ±0.02	ND	ND

ND = not detected.

Table 2. Disposition of Radioactivity 6 Days Following Intravenous Administration of 3.6 mg/kg [^{14}C]1,2,3-Trichloropropane to Male Fischer 344 Rats – Group 4

Distribution in Tissues (15 minutes to 6 days)[a]
Percent Dose Recovered Versus Time

Tissue	15 minutes	30 minutes	1 hour	2 hours	4 hours	8 hours	1 day	2 days	4 days	6 days
Brain	0.47 ± 0.06	0.21 ± 0.03	0.27 ± 0.04	0.17 ± 0.03	0.21 ± 0.08	0.14 ± 0.01	0.067± 0.008	0.041± 0.015	0.046± 0.010	0.033± 0.003
Lungs	0.21 ± 0.06	0.13 ± 0.03	0.30 ± 0.10	0.18 ± 0.02	0.16 ± 0.03	0.11 ± 0.02	0.079± 0.018	0.048± 0.009	0.043± 0.002	0.028± 0.004
Liver	4.49 ± 1.02	3.23 ± 1.03	7.25 ± 1.31	6.82 ± 0.92	5.60 ± 0.22	4.36 ± 0.52	1.81 ± 0.46	1.31 ± 0.19	1.08 ± 0.21	0.77 ± 0.02
Kidneys	1.09 ± 0.12	0.96 ± 0.18	2.57 ± 0.65	2.76 ± 0.21	2.29 ± 0.21	1.75 ± 0.07	0.62 ± 0.13	0.41 ± 0.06	0.27 ± 0.06	0.19 ± 0.03
Spleen	0.052± 0.002	0.042± 0.002	0.092± 0.012	0.066± 0.008	0.061± 0.009	0.051± 0.009	0.024± 0.003	0.014± 0.004	0.016± 0.002	0.012± 0.002
Small Intestine	1.25 ± 0.62	2.47 ± 1.87	9.29 ± 4.32	8.01 ± 4.78	3.81 ± 0.56	1.27 ± 0.23	0.32 ± 0.15	0.14 ± 0.03	0.073± 0.006	0.046± 0.002
Large Intestine	0.37 ± 0.43	0.19 ± 0.06	0.25 ± 0.08	0.32 ± 0.11	0.88 ± 0.72	2.01 ± 1.52	0.12 ± 0.04	0.041± 0.004	0.021± 0.003	0.016± 0.002
Testes	0.31 ± 0.03	0.15 ± 0.08	0.41 ± 0.08	0.25 ± 0.04	0.24 ± 0.03	0.17 ± 0.01	0.054± 0.005	0.034± 0.020	0.037± 0.011	0.023± 0.006
Epididymides	NC[b]	0.13 ± 0.10	0.29 ± 0.19	0.14 ± 0.14	NC	NC	NC	0.014± 0.001	0.013± 0.003	0.011± 0.001
Adipose Tissue	37.32 ± 5.62	25.04 ± 2.09	23.81 ± 9.38	16.88 ± 6.30	5.02 ± 2.49	3.29 ± 0.55	0.33 ± 0.02	0.29 ± 0.25	0.19 ± 0.04	0.15 ± 0.02
Skin	16.06 ± 6.63	8.21 ± 4.80	7.60 ± 3.13	4.86 ± 0.09	3.98 ± 1.48	3.63 ± 0.69	1.13 ± 0.11	0.71 ± 0.07	0.51 ± 0.15	0.43 ± 0.04
Muscle	17.98 ± 1.17	7.15 ± 0.25	10.48 ± 2.39	6.88 ± 0.46	6.81 ± 1.28	3.75 ± 0.38	1.74 ± 0.10	0.97 ± 0.44	1.04 ± 0.12	0.94 ± 0.17
Blood	3.73 ± 0.24	3.31 ± 1.21	4.64 ± 0.12	3.09 ± 0.22	2.32 ± 0.24	1.55 ± 0.08	0.88 ± 0.02	0.64 ± 0.09	0.64 ± 0.08	0.48 ± 0.04
Total in tissues	83.33 ± 2.56	51.22 ± 1.57	67.25 ± 3.09	50.43 ± 2.21	31.38 ± 0.96	22.01 ± 0.55	7.17 ± 0.15	4.65 ± 0.16	3.98 ± 0.08	3.13 ± 0.05

[a]All values expressed as mean ± standard deviation. The target dose was 3.6 mg/kg body weight (~ 14 μCi/mg). The actual dose delivered was 3.6 ± 0.4 mg (24.4 μmol)/kg (2.08 ± 0.24 μCi/μmol) for the n = 30 rats used for urine, feces and tissue collection (Group 4). N = 3 per time point for Group 4.
[b]NC = not collected

Disposition Summary[a]
Percent Dose Recovered in Excreta and Tissues (15 minutes to 6 days)

Sample	15 minutes	30 minutes	1 hour	2 hours	4 hours	8 hours	1day	2 days	4 days	6 days
Excreta[b]	3.1	5.0	22.1	44.1	52.2	77.8	88.6	95.9	96.8	99.3
Tissues	83.3	51.2	67.3	50.4	31.4	22.0	7.1	4.7	3.98	3.1
Total	**86.4**	**56.2**	**89.4**	**94.5**	**83.6**	**99.8**	**95.7**	**100.6**	**102.6 [sic]**	**102.4**

[a]All values expressed as means. The dose was 3.6 mg/kg body weight.
[b]Excreta includes cumulative percent dose recovered for urine, feces, and expired air. However, the expired air was not collected at 15 minutes or after 1 day. The 15 minute value was an estimate obtained by halving the 30-minute measurement. The 1-day measurement was used for estimating excreta totals at subsequent times.

Table 3. Pharmacokinetic parameters for unchanged trichloropropane and for radioactivity after 3.6 mg/kg intravenous 1,2,3-trichloropropane.

	Phase 0			Phase 1			Phase 2		
	C (%)	γ (hr^{-1})	$t_{1/2}$ (hr)	A (%)	α (hr^{-1})	$t_{1/2}$ (hr)	B (%)	β (hr^{-1})	$t_{1/2}$ (hr)
Unchanged trichloropropane									
Liver				2.6	1.2	0.57	0.13	0.017	40
Kidneys				0.83	2.2	0.31	0.058	0.023	30
Adipose Tissue				21	0.39	1.8	0.20	0.016	44
Skin				9.7	0.79	0.87	0.30	0.019	36
Muscle				10	0.69	1.0	0.057	0.016	45
Blood				2.8	2.4	0.29	0.75	0.030	23
Radioactivity									
Liver			a	6.7	0.13	5.3	1.8	0.0055	125
Kidneys	11	5.2	0.13	3.0	0.13	5.3	0.60	0.0080	87
Adipose Tissue				31	0.33	2.1	0.39	0.0068	101
Skin				7.8	0.13	5.2	0.89	0.0052	133
Muscle				12	0.22	3.2	1.5	0.0038	182
Blood			a	4.0	0.23	3.0	0.89	0.0043	163
Small Intestine	14	0.83	0.83	13	0.33	2.1	0.36	0.015	45
Large Intestine	10	0.26	2.7	10	0.21	3.4	0.061	0.0098	71

[a] No phase 0 parameters could be calculated because of low recovery of radioactivity at 30 min.