ADME NTP Study S0091 1,1,1-Trichloroethane

The contract laboratory used the abbreviation TCEN for the test article.
Sex/Species: adult male F344 rats and adult female B6C3F1 mice.
Vehicles: intravenous, Emulphor EL-620; oral, Emulphor EL-620.

CASRN 71-55-6

Radiolabeled with carbon-14 in the 2-position; 1,1,1-Trichloroethane, [2-^{14}C]-

Studies Performed:

1. Single oral gavage administration of 100, 300, or 1000 mg/kg TCEN to male rats with sacrifice 1 hour postdose (1000 mg/kg dose only) and 24 hours postdose.

2. Single intravenous administration of 100 mg/kg TCEN to male rats with sacrifice 24 hours postdose.

3. Single intravenous administration of 100 mg/kg TCEN to female mice with sacrifice 24 hours postdose.

4. Single oral gavage administration of 1000 mg/kg TCEN to female mice with sacrifice 2 hours postdose.

5. Single oral gavage administration of 300 or 3000 mg/kg TCEN to female mice with sacrifice 24 hours postdose.

Serial blood samples were taken from male rats for 24 hours following an oral dose of 1000 mg/kg. The data is displayed in a figure and not shown here. The highest concentration of TCEN equivalents measured was 30 ug-equivalent TCEN/g blood at 2 hours. For female mice, the blood concentration was 40 ug-equivalent TCEN/g blood at 2 hours following an oral dose of 1000 mg/kg.

Mice were housed 3 animals to a metabolism cage and given one dose per cage divided amongst the 3 mice in that cage. The excretion and tissue distribution results are displayed as mouse units. Each mouse unit is the combined result from the 3 mice housed in a single metabolism chamber. For each concentration, there were 3 sets of 3 mice (oral administrations) or 4 sets of 3 mice (100 mg/kg intravenous adminstration) averaged to obtain the mean and standard deviation for 3 or 4 mouse units, respectively.

For intravenous injections in both rats and mice, the infusions were made over a 1.0-1.5 minute period to help prevent fatalities. Some breath may not have been captured during the intravenous dosing period.

TCEN was predominately excreted as volatiles present in the breath (> 90%) whereas excretion in urine and feces was low, approximately 1% and 0.5% of the dose, respectively. Less than 0.2% was recovered in the sodium hydroxide breath traps.

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Table 1

Excretion of Radioactivity in Breath After Oral Administration of [^{14}C]TCEN to Rats (% Dose)[a]

Time (h)	100 mg/kg (N=3)	300 mg/kg (N=4)	1000 mg/kg (N=4)
0-1	11.2 ± 1.3	8.0 ± 1.4	7.8 ± 2.5
1-2	15.9 ± 3.9	13.8 ± 3.0	10.8 ± 3.3
2-4	28.5 ± 4.5	21.5 ± 1.4	22.7 ± 5.7
4-8	30.4 ± 1.5	24.6 ± 5.9	33.5 ± 3.9
8-12	9.2 ± 2.2	14.6 ± 4.8	15.6 ± 6.0
12-24	2.5 ± 0.5	9.4 ± 2.5	6.5 ± 2.0
Total	96.7 ± 1.6	92.0 ± 3.1	98.9 ± 0.5

[a] Values are means ± standard deviations.

Table 2

Tissue Distribution of Carbon-14 Residues One Hour After Oral Administration of [^{14}C]TCEN (1000 mg/kg) to Rats[a]

Tissue	% Dose	Tissue/Blood Ratio
Adipose	5.09 ± 2.83	67.28 ± 56.85
Blood	0.056 ± 0.012	Unity
Kidney	0.047 ± 0.015	6.67 ± 3.14
Liver	0.953 ± 0.429	22.66 ± 8.80
Lung	0.039 ± 0.024	5.58 ± 1.37
Muscle	1.39 ± 0.43	3.23 ± 0.90
Skin	0.593 ± 0.120	4.63 ± 1.11
Thyroid	0.001 ± 0.001	23.48 ± 22.87
Total	8.16 ± 2.79	

[a] Values are means ± standard deviations for 4 animals.

Table 3

Tissue Distribution of Carbon-14 Residues 24 Hours After Oral Administration of ^{14}C-TCEN to Rats[a]

Tissue	100 mg/kg (N=3)		300 mg/kg (N=4)		1000 mg/kg (N=4)	
	% Dose	Tissue/Blood Ratio	% Dose	Tissue/Blood Ratio	% Dose	Tissue/Blood Ratio
Adipose	0.120 ± 0.050	6.87 ± 6.86	0.307 ± 0.381	19.90 ± 20.02	0.168 ± 0.069	16.45 ± 10.07
Blood	0.010 ± 0.000	unity	0.009 ± 0.004	unity	0.007 ± 0.002	unity
Kidney	0.003 ± 0.001	2.14 ± 0.58	0.003 ± 0.002	2.42 ± 1.74	0.003 ± 0.000	3.25 ± 0.41
Liver	0.021 ± 0.009	2.64 ± 0.41	NA[b]	NA	0.015 ± 0.001	2.73 ± 0.46
Lung	0.001 ± 0.001	0.93 ± 0.24	0.001 ± 0.001	0.87 ± 0.61	0.001 ± 0.000	1.39 ± 0.37
Muscle	0.076 ± 0.013	1.14 ± 0.56	0.080 ± 0.069	1.04 ± 0.78	0.053 ± 0.012	0.95 ± 0.13
Skin	0.027 ± 0.003	1.30 ± 0.47	0.045 ± 0.042	1.93 ± 1.49	0.032 ± 0.008	1.91 ± 0.27
Thyroid	ND[c]	ND	NA	NA	ND	ND
Total	0.259 ± 0.053		0.443 ± 0.496		0.248 ± 0.059	

[a] Values are means ± standard deviations.
[b] NA = not assayed
[c] ND = none detected

Table 4

Excretion of Radioactivity in the Breath After Intravenous Administration of [^{14}C]TCEN (100 mg/kg) to Rats and Mice (% Dose)[a]

Time (h)	Rats	Mice
0-1	40.6 ± 21.9	39.1 ± 13.2
1-2	17.5 ± 1.0	21.9 ± 3.2
2-4	10.9 ± 2.0	13.2 ± 7.3
4-8	11.3 ± 8.2	4.3 ± 2.8
8-12	5.7 ± 5.0	1.0 ± 0.7
12-24	4.6 ± 4.3	0.5 ± 0.3
Total	90.6 ± 1.8	80.0 ± 2.6

[a] Values are means ± standard deviations for 3 rats or 4 mouse units. A mouse unit is the combined results from three mice housed in a single metabolism chamber.

Table 5

Tissue Distribution of Carbon-14 Residues 24 Hours After Intravenous Administration of [^{14}C]TCEN (100 mg/kg) to Rats and Mice[a]

Tissue	Rats		Mice	
	% Dose	Tissue/Blood Ratio	% Dose	Tissue/Blood Ratio
Adipose	0.316 ± 0.342	28.40 ± 21.87	0.007 ± 0.003	2.32 ± 1.98
Blood	0.006 ± 0.0003	unity	0.003 ± 0.002	unity
Kidney	0.003 ± 0.001	3.22 ± 0.47	0.002 ± 0.000	2.84 ± 1.78
Liver	0.018 ± 0.009	4.67 ± 2.70	0.007 ± 0.002	3.64 ± 2.70
Lung	0.001 ± 0.001	1.08 ± 0.47	0.001 ± 0.000	3.76 ± 1.77
Muscle	0.068 ± 0.054	1.44 ± 1.11	0.009 ± 0.002	0.52 ± 0.31
Skin	0.041 ± 0.028	3.04 ± 2.29	0.010 ± 0.006	1.64 ± 0.82
Thyroid	ND[b]	ND	NA[c]	NA
Total	0.453 ± 0.422		0.038 ± 0.014	

[a] Values are means ± standard deviations for 3 rats or 4 mouse units. See text or Table 5 for definition of a mouse unit.
[b] ND = none detected
[c] NA = not assayed

Table 6

Excretion of Radioactivity in Breath After Oral Administration of [^{14}C]TCEN to Mice (% Dose)[a]

Time (h)	300 mg/kg	3000 mg/kg	1000 mg/kg
0-1	18.5 ± 1.7	10.6 ± 3.5	15.8 ± 3.0
1-2	17.9 ± 2.5	18.1 ± 7.7	28.4 ± 9.3
2-4	20.0 ± 2.7	23.8 ± 3.1	
4-8	19.2 ± 2.4	20.4 ± 3.7	
8-12	15.1 ± 0.9	11.9 ± 1.7	
12-24	4.4 ± 4.7	6.0 ± 4.8	
Total	95.4 ± 1.0	90.7 ± 2.7	44.2 ± 11.2

[a] Values are averages ± standard deviations for 3 mouse units. See test or Table 5 for definition of a mouse unit.

Table 7

Tissue Distribution of Carbon-14 Residues 24 Hours After Oral Administration of [^{14}C]TCEN to Mice[a]

Tissue	300 mg/kg		3000 mg/kg	
	% Dose	Tissue/Blood Ratio	% Dose	Tissue/Blood Ratio
Adipose	0.025 ± 0.012	3.91 ± 3.98	0.058 ± 0.085	3.94 ± 1.51
Blood	0.007 ± 0.008	unity	0.008 ± 0.011	unity
Kidney	0.002 ± 0.001	2.20 ± 1.54	0.002 ± 0.002	1.76 ± 0.65
Liver	0.005 ± 0.001	3.92 ± 2.43	0.017 ± 0.020	2.82 ± 0.98
Lung	0.001 ± 0.001	2.08 ± 1.32	0.002 ± 0.002	1.52 ± 0.35
Muscle	0.048 ± 0.036	1.06 ± 0.47	0.166 ± 0.247	2.15 ± 1.31
Skin	0.012 ± 0.003	1.15 ± 0.88	0.015 ± 0.021	0.73 ± 0.18
Total	0.114 ± 0.065		0.267 ± 0.389	

[a] Values are averages ± standard deviations for 3 mouse units. See text or Table 5 for definition of a mouse unit.

Table 8

Tissue Distribution of Carbon-14 Residues 2 Hours After Oral Administration of [^{14}C]TCEN (1000 mg/kg) to Mice (N=3)

Tissue	% Dose	Tissue/Blood Ratio
Adipose	9.29 ± 1.66	28.15 ± 6.04
Blood	0.220 ± 0.083	unity
Kidney	0.137 ± 0.007	2.93 ± 1.11
Liver	1.14 ± 0.36	9.09 ± 1.03
Lung	0.053 ± 0.028	1.56 ± 0.29
Muscle	3.14 ± 1.48	1.75 ± 0.20
Skin	1.06 ± 0.16	2.22 ± 0.78
Stomach	2.46 ± 0.96	85.06 ± 42.25
Total	17.54 ± 3.67	