ADME NTP Study S0183 tris(2-Chloroethyl) phosphate

The contract laboratory used the abbreviation TRCP for the test article.
Sex/Species: adult male F344 rats.
Vehicle: oral, corn oil.

CASRN 115-96-8

Radiolabeled with carbon-14 in the 1-position; tris(2-Chloroethyl) phosphate, [1-^{14}C]-

Studies Performed:

- Single 88 mg/kg oral dose of TRCP to male rats with sacrifice 72 hours postdose.
- Single 88 mg/kg oral dose of TRCP to male rats with sacrifice 96 hours postdose (serial blood collection).

Toxicokinetics:

Elimination of equivalents from both blood and blood cell compartments was biphasic. The rates of elimination of the compound equivalents were calculated by fitting simple exponential functions to the plasma and blood cell concentration-time curves following iterative polyexponential curve stripping with JANA (Dunne, A . JANA : A New Iterative Polyexponetial Curve Stripping Program. Comput. Meth. Prog. Biomed. 20:269-275, 1985). The apparent volume of distribution at equilibrium (V) of compound equivalents was determined from the y-intercept (C_0) of the slope of the initial phase of elimination from plasma (V = Dose Absorbed/C_0). The areas under the concentration-time curves (AUC) were calculated by trapezoidal integration of the data points, with extrapolation (based on the slope of the terminal elimination phase) to infinity.

TRCP was at least 90% absorbed and TRCP equivalents distributed into an apparent volume of distribution equal to that of total body water (0.6 1/kg). Up to 24 hours after dosing, the ratio of TRCP equivalent concentrations in blood cells to those in plasma was circa 0.6.

TABLE 1

Excretion of ^{14}C-radioactivity by male Fischer-344 rats after administration of ^{14}C-TRCP at 88 mg/kg p.o.

Time (hr)	Urine	Feces	Expired Air
	Mean ± SD Dose Excreted (%)[a]		
0-4	9.6 ± 5.6	0.0 ± 0.1	0.2 ± 0.1
4-7	27.3 ± 6.8	#[b]	0.1 ± 0.1
7-24	52.1 ± 13.7	4.9 ± 0.9	0.3 ± 0.2
24-31	2.3 ± 0.7	0.8 ± 0.3	0.1 ± 0.1
31-48	4.3 ± 0.5	1.3 ± 0.3	0.1 ± 0.1
48-72	1.7 ± 0.6	0.4 ± 0.2	
	Mean ± SD Dose Excreted (Cumulative %)[a]		
0-4	9.6 ± 5.6	0.0 ± 0.1	0.2 ± 0.1
0-7	30.1 ± 11.0		0.3 ± 0.2
0-24	82.2 ± 5.2	4.9 ± 0.9	0.7 ± 0.3
0-31	84.4 ± 5.8	5.6 ± 1.0	0.8 ± 0.4
0-48	88.7 ± 5.7	6.9 ± 1.3	0.9 ± 0.4
0-72	90.4 ± 5.2	7.3 ± 1.4	

[a] Mean of data from 3-4 rats.

[b] Either no sample at this time interval or no sample collected.

TABLE 2

Recovery of ^{14}C-radioactivity in 72 hr after administration of ^{14}C-TRCP to male Fischer-344 rats at 88 mg/kg p.o.

	Mean ± SD Dose Recovered (%)[a]	
	Study 1[b]	Study 2[c]
Urine	105.1 ± 16.0[d]	90.4 ± 5.2
Feces		7.3 ± 1.4
CO_2	0.9 ± 0.4	
Total	106.1 ± 16.1	97.7 ± 5.1

[a] Mean of data from 3-4 rats.

[b] Excretion in exhaled air, urine and feces determined.

[c] Excretion in urine and feces determined.

[d] Data represents radioactivity in urine and feces because separation of excreta in Roth cages was poor.

TABLE 3

Concentration of ^{14}C-TRCP equivalents in plasma of male Fischer-344 rats after administration of ^{14}C-TRCP at 88 mg/kg p.o.

	Concentration (nmol/g)				
	Rat				
Time	981	982	983	984	Mean ± SD
5 (min)	51.1	20.9	38.5	33.9	36.1 ± 12.5
15	133.2	125.3	118.7	116.0	123.3 ± 7.7
30	172.6	144.2	135.0	142.0	148.5 ± 16.6
1 (hr)	145.9	119.1	113.1	118.7	124.2 ± 14.7
2	130.6	79.1	89.6	83.5	95.7 ± 23.7
5	76.9	64.9	59.7	55.4	64.2 ± 9.3
7	47.9	55.6	38.0	39.9	45.4 ± 8.1
8	43.4	48.2	32.3	34.2	39.5 ± 7.5
12	19.8	18.9	18.5	17.3	18.6 ± 1.0
24	10.9	10.5	9.5	9.0	10.0 ± 0.9
28	5.8	8.3	8.5	8.8	7.9 ± 1.4
31	9.2	8.3	8.5	7.1	8.3 ± 0.9
48	6.5	5.5	5.4	5.2	5.7 ± 0.6
55	5.4	4.7	4.8	4.3	4.8 ± 0.5
72	3.8	3.6	3.4	3.5	3.6 ± 0.2
96	3.6	2.3	2.4	2.3	2.7 ± 0.6

TABLE 4

Concentration of ^{14}C-TRCP equivalents in blood cells of male Fischer-344 rats after administration of ^{14}C-TRCP at 88 mg/kg p.o.

	Concentration (nmol/g)				
	Rat				
Time	981	982	983	984	Mean ± SD
5 (min)	34.3	11.7	23.0	20.7	22.4 ± 9.3
15	81.1	78.5	70.4	71.0	75.3 ± 5.4
30	105.4	89.7	79.9	86.3	90.3 ± 10.8
1 (hr)	89.7	71.0	66.5	66.7	73.5 ± 11.0
2	81.1	53.2	53.0	48.5	59.0 ± 14.9
5	46.9	38.1	36.1	31.6	38.2 ± 6.4
7	27.5	31.8	21.6	20.8	25.4 ± 5.2
8	23.0	27.4	18.1	18.5	21.8 ± 4.4
12	11.8	10.2	9.8	8.5	10.1 ± 1.4
24	8.8	7.1	6.0	6.8	7.2 ± 1.2
28	12.5	5.8	5.7	6.1	7.5 ± 3.3
31	9.8	8.5	5.9	8.2	8.1 ± 1.6
48	8.5	7.8	6.2	6.3	7.2 ± 1.1
55	8.5	9.2	**[a]	6.4	8.0 ± 1.5
72	10.7	9.2	13.0	5.8	8.6 ± 2.5
96	7.4	6.8	5.5	5.6	6.3 ± 0.9

[a] Sample not collected.

TABLE 5

Pharmacokinetic parameters of ^{14}C-TRCP equivalents in plasma and blood cells of male Fischer-344 rats after administration of ^{14}C-TRCP at 88 mg/kg p.o.

The kinetic parameters were calculated from the data listed in Tables 3 and 4, as described in the text.

Tissue	Peak Concentration		Elimination Rate (half-time)			AUC[a]		
	(nmol/g)	(hr)	1 (hr)	2 (hr)	(days)	0-24 hr (nmol-hr/g)	0-96 hr (nmol-hr/g)	0-∞ (nmol-hr/g)
Plasma	148.5	0.5	3.4	43	1.8	907	1269	1361
Blood Cells	90.3	0.5	3.0	259	10.8	538	1094	3389

[a] Area under the concentration-time curve.