ADME NTP Study K08036 Tris(4-chlorophenyl)methane Toxicokinetics

The contractor used the abbreviation of TCPME for the test article.
Tris(4-chlorophenyl)methanol (TCPMOH) data was included in the same report.
Sex/Species: male Harlan Sprague Dawley rats and B6C3F1/N mice.
Vehicle: intravenous, Cremophor:saline:ethanol (20:70:80); oral, Cremophor:water 40:60)

CASRN 27575-78-6

Radiolabeled with carbon-14, uniformly; Tris(4-chlorophenyl)methane, [^{14}C(U)]-

Studies Performed:

- Single 10 mg/kg intravenous dose to rats with blood sampling at 0.25, 0.5, 1, 2, 4, 8, 18, 24, 32, 48, and 72 hours postdose. (n = 4)

- Single 10 mg/kg oral gavage dose to rats with blood sampling at 0.5, 2, 6, 8, 12, 18, 24, 32, 48, and 72 hours postdose. (n = 4)

- Single 10 mg/kg intravenous dose to mice with sacrifice at 0.25, 1, 8, 24, 48, 72, 96, and 168 hours postdose. (n = 3 per time point)

- Single 10 mg/kg oral gavage dose to mice with sacrifice at 2, 4, 6, 8, 18, 32, 72, 96, and 168 hours postdose. (n = 3 per time point)

Toxicokinetics:

Concentration versus time data was analyzed using Phoenix software (WinNonlin, Version 6.3, Pharsight Corporation, Cary, NC). Various models and weighting options were explored. Average plasma concentration (total radioactivity [ng-eq/mL] for rat and mouse as well as TCPME [ng/mL] for mice) versus time data were analyzed. Intravenous data was fit to a two compartment model (PK Model 7) with bolus input and 1/y*y weighting. Gavage data were fit to a two compartment model (PK Model 11 or 12) with extravascular input. Initial parameters and bounds were supplied by WinNonlin®.

Table 1

Percent of Plasma Extract as TCPME and TCPMOH Following Intravenous or Gavage Administration of 10 mg/kg [^{14}C]TCPME to Male HSD Rats

- Time Point (h)	iv % TCPMOH	iv % TCPME	gavage % TCPMOH	gavage % TCPME
0.5	4.7	86.7	NA	NA
4	1.6	95.3	NS	NS
12	NA	NS	0.7	96.6
24	0.3	92.4	0.7	95.8
48	4	80.3	11.9	67.0
72	5.1	65.9	2.9	72.8

NA = not analyzed.
NS = no sample.

Table 2

Concentration of Total TCPME (ng-eq/g) Equivalents in Plasma Following Intravenous or Gavage Administration of 10 mg/kg [^{14}C]TCPME to Male HSD Rats

Route	Time Point (h)	Rat 1	Rat 2	Rat 3	Rat 4	Average	SD
iv	0.25	15449	18065	19838	19220	18143	1940
iv	0.5	9986	12467	13820	13691	12491	1778
iv	1	9549	9834	11879	10875	10534	1062
iv	2	7810	7467	8863	8136	8069	596
iv	4	6124	6447	7425	6758	6689	555
iv	8	5112	4851	5138	4979	5020	132
iv	18	2419	2328	2798	2830	2594	257
iv	24	1777	2091	2208	2251	2082	214
iv	32	1404	1529	1651	1792	1594	166
iv	48	929	960	954	1052	974	54
iv	72	645	689	723	763	705	50
gavage	0.5	328	301	487	401	379	83
gavage	2	1350	1266	1941	1256	1453	328
gavage	6	2607	2514	2479	1815	2354	363
gavage	8	2463	2521	2533	1636	2288	436
gavage	12	1900	1774	2199	1451	1831	310
gavage	18	1437	1326	1404	1356	1381	49
gavage	24	1207	991	1203	926	1082	145
gavage	32	892	643	927	607	767	166
gavage	48	507	465	479	433	471	31
gavage	72	368	375	437	371	388	33

Table 3

Plasma Toxicokinetic Parameters for TCPME Equivalents (Based on Total Radioactivity) Following Gavage or Intravenous Administration (10 mg/kg) [^{14}C]TCPME to Male HSD Rats

Gavage

Parameter	Units	Estimate	StdError
V1_F	mL/kg	2640	635
V2_F	mL/kg	10458	21655
K01	1/h	0.23	0.07
K10	1/h	0.02	0.05
K12	1/h	0.06	0.03
K21	1/h	0.01	0.02
Alpha	1/h	0.09	0.04
Beta	1/h	0.0036	0.0117
K01_Half-Life	h	2.97	0.83
K10_Half-Life	h	31.1	68.8
Alpha_Half Life	h	7.69	3.47
Beta_Half-Life	h	195	641
A	ng/mL	5457	3416
B	ng/mL	487	418
Cl1_F	mL/h/kg	58.8	118.9
Cl2_F	mL/h/kg	150.43	88.82
Tmax	h	7.19	0.36
Cmax	ng/mL	2223	99

Intravenous

Parameter	Units	Estimate	StdError
V1	mL/kg	763	87
K10	1/h	0.07	0.01
K12	1/h	0.12	0.05
K21	1/h	0.08	0.03
Alpha	1/h	0.25	0.08
Beta	1/h	0.02	0.00
K10_Half-Life	h	9.66	1.33
Alpha_Half Life	h	2.81	0.87
Beta_Half-Life	h	28.4	5.2
A	ng/mL	9874	1534
B	ng/mL	3600	718
AUC	h*ng/mL	187740	12575
AUMC	h*h*ng/mL	6220747	1228083
Cl	mL/h/kg	54.8	3.7
Cl2	mL/h/kg	88.0	29.7
Cmax	ng/mL	13474	1537
MRT	h	33.1	5.0

Models used were iv bolus 2-compartment model #7 and extravascular input 2-compartment model #11.

Table 4

Concentration of Total TCPME equivalents (ng-eq/g) in Plasma Following Intravenous or Gavage Administration of 10 mg/kg [^{14}C]TCPME to Male B6C3F1/N Mice

Route	Time Point (h)	Replicate 1	Replicate 2	Replicate 3	Average	S.D.
iv	0.25	43122	9527	19273	23974	17284
iv	1	20642	9749	15138	15176	5446
iv	8	2924	6264	4076	4421	1697
iv	24	1359	1412	1458	1410	50
iv	48	845	847	728	806	68
iv	72	731	547	556	611	104
iv	96	352	606	477	478	127
iv	168	315	363	379	352	33
gavage	2	1918	2512	2085	2172	306
gavage	4	2516	2194	2349	2353	161
gavage	6	2573	2589	2069	2410	296
gavage	8	2094	1984	1703	1927	202
gavage	18	997	1350	708	1018	322
gavage	32	640	816	602	686	114
gavage	72	426	400	468	431	34
gavage	96	320	312	446	359	75
gavage	168	205	370	306	294	83
gavage	2	1918	2512	2085	2172	306

Table 5

Percent of Plasma Extract as TCPME and TCPMOH Following Intravenous or Gavage Administration of 10 mg/kg [^{14}C]TCPME to Male B6C3F1/N Mice

-	iv	iv	gavage	gavage
Time Point (h)	% TCPMOH	% TCPME	% TCPMOH	% TCPME
0.25	1.1	94	NS	NS
1	1	95	NS	NS
2	NS	NS	0.6	92.2
4	NS	NS	0.9	88.8
6	NS	NS	1.7	90.4
8	2	93	1.7	90.1
18	NS	NS	0.5	90.2
24	9	66	NS	NS
32	NS	NS	1.1	85.3
48	4	74	NS	NS
72	4	73	1.8	70.8
96	5	66	2.2	70.9
168	6	69	1.4	75.9

NS = no sample

Table 6

Concentration of TCPME (ng/mL) in Plasma Following Intravenous or Gavage Administration of 10 mg/kg [^{14}C]TCPME to Male B6C3F1/N Mice

Route	Time Point (h)	Concentration (ng/mL)[a]
iv	0.25	22536
iv	1	14417
iv	8	4112
iv	24	927
iv	48	597
iv	72	446
iv	96	316
iv	168	243
gavage	2	2003
gavage	4	2090
gavage	6	2179
gavage	8	1736
gavage	18	918
gavage	32	585
gavage	72	305
gavage	96	255
gavage	168	223

[a] Calculated based on percent of chromatogram (see Table 5) contained in TCPME peak. Plasma was pooled by time point within each group and extracted prior to HPLC analysis to determine parent content (extraction recovery > 80%). The percent of each plasma extract sample contained in the TCPME and TCPMOH HPLC peaks is presented in Table 5. The concentration of TCPME (ng/mL) in plasma at each time point was calculated from the LSS-determined ng-eq/g plasma (Table 4) times the percentage contained in the TCPME peak (Table 5); these TCPME concentration values are shown here in Table 6.

Table 7

Toxicokinetic Parameters for TCPME Following Intravenous or Gavage Administration (10 mg/kg) [^{14}C]TCPME to Male B6C3F1/N Mice

Intravenous (Total Radioactivity Data [ng-eq/g])[a]

Parameter	Units	Estimate	StdError
V1	mL/kg	488	74
V2	mL/kg	2821	737
Vss	mL/kg	3308	754
K10	1/h	0.09	0.01
K12	1/h	0.11	0.03
K21	1/h	0.02	0.00
Alpha	1/h	0.21	0.04
Beta	1/h	0.01	0.00
K10_Half-Life	h	8.09	1.34
Alpha_Half-Life	h	3.29	0.59
Beta_Half-Life	h	87	23
A	ng/mL	19332	3111
B	ng/mL	1175	238
Cl1	mL/h/kg	41.8	4.1
Cl2	mL/h/kg	55.2	11.4
AUC	h*ng/mL	239291	23387
AUMC	h*h*ng/mL	18942779	6630845
Cmax	ng/mL	20507	3127
MRT	h	79.2	22.1

Intravenous (TCPME data [ng/mL])[a]

Parameter	Units	Estimate	StdError
V1	mL/kg	514.0	71.6
K10	1/h	0.102	0.015
K12	1/h	0.097	0.020
K21	1/h	0.016	0.004
Alpha	1/h	0.207	0.032
Beta	1/h	0.008	0.002
K10_Half-Life	h	6.82	0.99
Alpha_Half-Life	h	3.35	0.51
Beta_Half-Life	h	85.6	21.1
A	ng/mL	18632	2690
B	ng/mL	821	160.4
Cl1	mL/h/kg	52.2	4.6
Cl2	mL/h/kg	49.8	9.7
AUC	h*ng/mL	191482	16676
AUMC	h*h*ng/mL	12958724	4142480
MRT	h	67.7	17.8

Table 7 (continued)

Gavage (Total Radioactivity Data [ng-eq/g])[b]

Parameter	Units	Estimate	StdError
V1_F	mL/kg	3159	531
V2_F	mL/kg	9539	1933
K01	1/h	0.741	0.858
K10	1/h	0.019	0.005
K12	1/h	0.059	0.012
K21	1/h	0.020	0.004
Alpha	1/h	0.094	0.018
Beta	1/h	0.004	0.001
Tlag	h	0.153	2.019
K01_Half-Life	h	0.935	1.081
K10_Half-Life	h	36.83	9.12
Alpha_Half-Life	h	7.4	1.4
Beta_Half-Life	h	176	53
A	ng/mL	2991	1127
B	ng/mL	556	79
AUC	h*ng/mL	168209	26744
CL1_F	mL/h/kg	59.5	9.5
CL2_F	mL/h/kg	187	21
Tmax	h	3.59	0.70
Cmax	ng/mL	2437	212

Gavage (TCPME data [ng/mL])[b]

Parameter	Units	Estimate	StdError
V1_F	mL/kg	3691	687
V2_F	mL/kg	15038	5137
K01	1/h	0.826	1.373
K10	1/h	0.017	0.007
K12	1/h	0.050	0.009
K21	1/h	0.012	0.004
Alpha	1/h	0.076	0.013
Beta	1/h	0.003	0.001
Tlag	h	0.061	3.138
K01_Half-Life	h	0.839	1.393
K10_Half-Life	h	40.1	15.1
Alpha_Half-Life	h	9.1	1.5
Beta_Half-Life	h	252	133
A	ng/mL	2602	992
B	ng/mL	348	63.4
AUC	h*ng/mL	156896	47574
Cl1_F	mL/h/kg	63.7	19.3
Cl2_F	mL/h/kg	183	26
Tmax	h	3.4	0.8
Cmax	ng/mL	2176	234.1

[a] Model 7 used.

[b] Model 12 used.