

TK NTP Study S0654, S0811 Hexachlorobenzene

Sex/Species: female Sprague Dawley rats

Vehicles: intravenous, corn oil:cholic acid:lecithin:Ringers Solution (5:15:0,15:95) (v:w:w:v); oral, corn oil.

CASRN 118-74-1

Studies Performed:

- Single intravenous dose of 100 or 1000 ug/kg. Whole blood and tissues (liver, lung, and mesenteric fat) were collected ($n \geq 4$ per time point) at 19 time points postdose (0.25, 0.5, 1, 2, 3, 8, 12 hours and 1, 2, 3, 5, 7, 10, 14, 28, 42, 56, 70, and 84 days).
- Single oral gavage dose of 30, 300, or 30000 ug/kg. Whole blood and tissues (liver, lung, and mesenteric fat) were collected ($n \geq 4$ per time point) at 19 time points postdose as above for 300 ug/kg dosed animals. Whole blood and tissues were collected ($n \geq 4$ per time point) at 17 time points postdose for 30 and 30000 ug/kg (0.5, 1, 3, 8, 12, 24, 48 hours, 3, 5, 7, 10, 14, 28, 42, 56, 70 and 84 days).

The parameters were estimated using compartmental models for the blood and the non-compartmental analysis (NCA) for the tissues using Phoenix WinNonlin, Version 8.0 software. The number of animals for time points were 5 animals except for 0.5, 1, 12 hours; 5 and 10 days which had 10 animals for the blood collections. The data shown here are from remodeling of data presented in hexachlorobenzene study reports S0654 and S0811.

Table 1.**Hexachlorobenzene Blood TK Parameters for Female Sprague Dawley Rats following a Single IV Administration of Hexachlorobenzene^{a,b}**

Parameter	100 µg/kg^c	1. 1000 µg/kg^c
Cmax_obs (ng/mL) ^d	126	1540
Cmax_pred (ng/mL) ^e	127 ± 11	1490 ± 120
Alpha_Half-life (hr)	0.783 ± 0.065	0.724 ± 0.058
Beta_Half-life (hr)	1240 ± 110	1630 ± 170
K10 (hr ⁻¹)	0.00983 ± 0.00112	0.00857 ± 0.00103
K10_Half-life (hr)	70.5 ± 8.0	80.9 ± 9.7
K12 (hr ⁻¹)	0.876 ± 0.081	0.902 ± 0.075
K21 (hr ⁻¹)	0.0535 ± 0.0039	0.0476 ± 0.0031
AUC_0-T (ng/mL·hr) ^c	8350	99600
AUCinf_pred (ng/mL·hr)	13000 ± 900	174000 ± 15000
Cl (mL/hr/kg)	7.71 ± 0.54	5.74 ± 0.50
CID2 (mL/hr/kg)	687 ± 39	604 ± 31
MRT (hr)	1770 ± 160	2330 ± 250
V1 (mL/kg)	784 ± 69	669 ± 54
V2 (mL/kg)	12900 ± 500	12700 ± 500

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat² weighting.
- b. Parameter estimates are reported to three significant figures.
- c. Estimate ± SEM
- d. Observed values do not have a reported SEM.
- e. Cmax_pred based on the model prediction at 0 minutes.

Table 2.**Hexachlorobenzene Blood TK Parameters for Female Sprague Dawley Rats following a Single Gavage Administration of Hexachlorobenzene^{a,b}**

Parameter	30 µg/kg ^c	300 µg/kg ^c	30000 µg/kg ^c
Cmax_obs (ng/mL) ^d	11.0	87.2	7410
Cmax_pred (ng/mL)	10.6 ± 1.1	67.5 ± 7.8	6630 ± 750
Tmax_obs (hr) ^c	3.00	3.00	3.00
Tmax_pred (hr)	4.23 ± 0.38	4.11 ± 0.37	3.18 ± 0.34
Alpha_Half-life (hr)	3.30 ± 3.21	2.86 ± 4.34	2.46 ± 1.93
Beta_Half-life (hr)	3340 ± 1060	1560 ± 210	1190 ± 120
K01 (hr ⁻¹)	0.346 ± 0.320	0.324 ± 0.499	0.507 ± 0.398
K01_Half-life (hr)	2.00 ± 1.85	2.03 ± 2.96	1.37 ± 1.07
K10 (hr ⁻¹)	0.00124 ± 0.00117	0.00235 ± 0.00332	0.00244 ± 0.00174
K10_Half-life (hr)	559 ± 526	295 ± 414	284 ± 202
K12 (hr ⁻¹)	0.174 ± 0.198	0.194 ± 0.357	0.212 ± 0.212
K21 (hr ⁻¹)	0.0351 ± 0.0068	0.0459 ± 0.0095	0.0670 ± 0.0132
AUC_0-T (ng/mL·hr) ^c	5310	34300	3190000
AUCinf_pred (ng/mL·hr)	16800 ± 4700	58800 ± 6300	4950000 ± 360000
Cl_F (mL/hr/kg)	1.78 ± 0.50	5.10 ± 0.55	6.06 ± 0.44
CID2_F (mL/hr/kg)	250 ± 75	421 ± 195	527 ± 170
V1_F (mL/kg)	1440 ± 1240	2170 ± 3020	2480 ± 1750
V2_F (mL/kg)	7110 ± 1230	9180 ± 2930	7860 ± 1710

- a. Based on a two-compartment model with first order input, first order output, and 1/Yhat² weighting.
- b. Parameter estimates are reported to three significant figures.
- c. Estimate ± SEM
- d. Observed values do not have a reported SEM.

Table 3.**Hexachlorobenzene Tissue TK Parameters for Female Sprague Dawley Rats following a Single IV Administration of Hexachlorobenzene^{a,b,c}**

Parameter	Fat 100 µg/kg	Fat 1000 µg/kg	Liver 100 µg/kg	Liver 1000 µg/kg	Lung 100 µg/kg	Lung 1000 µg/kg
Cmax (ng/mL)	334	3180	82.4	630	101	2180
Tmax (hr)	336	72.0	2.00	2.00	2.00	2.00
HL_Lambda_z (hr)	1230	1740	1350	1950	860	1280
AUClast (ng/mL·hr)	409000	4590000	29400	212000	11000	198000
AUCinf_pred (ng/mL·hr)	608000	8270000	45800	404000	19700	287000

- a. Based on non-compartmental analysis.
- b. Parameter estimates are reported to three significant figures.
- c. Estimate

Table 4.**Hexachlorobenzene Tissue TK Parameters for Female Sprague Dawley Rats following a Single Gavage Administration of Hexachlorobenzene^{a,b,c}**

Parameter	Fat 30 µg/kg	Fat 300 µg/kg	Liver 30000 µg/kg	Liver 30 µg/kg	Liver 300 µg/kg	Liver 30000 µg/kg	Lung 30 µg/kg	Lung 300 µg/kg	Lung 30000 µg/kg
Cmax (ng/mL)	226	1320	168000	39.6	202	16100	11.0	127	4420
Tmax (hr)	72.0	72.0	24.0	3.00	3.00	3.00	3.00	3.00	8.00
HL_Lambda_z (hr)	3770	1140	1120	2050	981	1470	1480	763	2930
AUClast (ng/mL·hr)	281000	1730000	201000000	13500	87200	5940000	7890	64100	4190000
AUCinf_pred (ng/mL·hr)	903000	2480000	281000000	28800	122000	9550000	13300	82200	11300000

- a. Based on non-compartmental analysis.
- b. Parameter estimates are reported to three significant figures.
- c. Estimate