ADME NTP Study S0897 Tetrabromobisphenol A Toxicokinetics

The contractor used the abbreviation of TBBPA for the test article.
Sex/Species: male F344 rats.
Vehicle: intravenous, ethanol:cremophore EL:saline mixture 1:2:7 (v/v/v); oral, ethanol:cremophore EL:saline mixture 1:2:7 (v/v/v);

CASRN 79-94-7

Radiolabeled with carbon-14 in the ring; [Ring-^{14}C] Tetrabromobisphenol A

Studies Performed:

- Single 20 mg/kg intravenous dose to rats with sampling at 0.17, 0.5, 2, 8, and 24 hours postdose (Group A, n = 3) and at 0.083, 0.33, 1, 4, 12, and 36 hours postdose (Group B, n = 3). Another group (Group C, n = 3) was dosed a week later providing additional data at 0.5, 1, 1.5, 2, 4 and 6 hours postdose.

- Single 20 mg/kg (50 μCi) gavage dose to rats with sampling at 0.125, 0.25, 0.5, 1, 2, 4, and 6 hours postdose and sacrifice 6 hour postdose. (n = 3)

- Single 20 mg/kg (200 μCi) gavage dose to rats with sampling at 0.125, 0.25, 0.5, 1, 2, 4, 6, and 8 hours postdose and sacrifice 6 hour postdose. (n = 4)

Toxicokinetics:

The oral and intravenous dose concentration-time curves for TBBPA were analyzed by compartmental analysis. A computer modeling program (WinNonlin, Scientific Consulting Inc., 1995) was utilized to fit the data to a suitable multi-compartment model using non-linear regression analysis and assuming first-order kinetics for all processes. Average parameter values (± standard deviation) were obtained from the arithmetic average with the exception of $t_{1/2}$, which is expressed as the harmonic mean and "psuedo" standard deviation (Lam et. al., 1985).

The terminal rate constant was calculated from a log-linear regression of the data in the terminal phase. From this value, the terminal half-life ($t_{1/2}$) was determined (0.693/k). The AUC was calculated with the linear trapezoidal rule using the last measure concentration to extrapolate to infinity.

The concentrations-time profile following intravenous administration of [^{14}C]TBBPA could be described by a biexponential equation that is consistent with a two compartment model. The terminal rate constant was k = 0.0084 min^{-1}. The half-life for distribution ($t_{1/2\alpha}$) was 5 minutes. The concentrations for the concentration-time curve for intravenous administration were displayed in a figure and are not shown here. Blood concentrations at times greater than 4 hours could not be determined accurately (at or below the limit of quantitation (LOQ). Following intravenous administration the

predominant route of elimination of TBBPA 14C-equivalents was fecal with 73 ± 8% eliminated in the feces within the first 24 hours.

The amount of total [^{14}C] equivalents found in whole blood following oral gavage administration of 20 mg/kg 50 μCi is shown in Table 2. Toxicokinetic parameters for the parent (UV/Vis-radio HPLC, 210 nm) and for total [^{14}C]equivalents (LSC) are shown in Table 3. The concentration of parent TBBPA was displayed in a figure and is not shown here. About 50% of an oral dose (20 mg/kg 50 μCi) was found in the bile within 2 hours. Systemic bioavailability (F) of orally administered TBBPA was low (< 5%).

For the 20 mg/kg 200 μCi oral dose toxicokinetic parameters, the parent (UV/Vis-radio HPLC) and total radioactivity (LSC) values are shown in Table 5. The amount of total [^{14}C] equivalents found in whole blood following oral gavage administration of 20 mg/kg 200 μCi is shown in Table 4. The concentration of parent TBBPA was displayed in a figure and is not shown here but represented less than 0.1% of the dose. The concentration of parent TBBPA in whole blood did not exceed 0.3 ug/ml at any time (C_{max} at 30 minutes) and could not be detected after 6 hours.

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.

Kinetic parameters for TBBPA following intravenous administration of [^{14}C] TBBPA (20 mg/kg, 50 μCi/kg) to male F-344 rats. $t_{1/2}$: terminal half-life. AUC: area under the blood concentration-time curve from time 0 to infinity. Cl: systemic blood clearance. V_{ss}: volume of distribution at steady-state. MRT: mean residence time.

$t_{1/2}$ (min)	AUC (ug·min/ml)	CL (ml/min)	Vss (ml)	MRT (min)
82.1	1440	2.44	126	51.6

*Multiple animals (N=9) were staggered in order to obtain enough data points early after administration of TBBPA. These concentrations were combined in order to generate a single blood concentration-time profile for calculation of each kinetic parameter.

Table 2.

Percent of dose recovered from blood at different timepoint following oral administration of [^{14}C] TBBPA (20 mg/kg, 50 μCi/kg) to male F-344 rats (N=3).

	Percent of dose recovered (%)				
	51005-01	**51005-02**	**51005-03**	**Mean**	**SD**
Time (h)					
0.125	0.12	0.14	0.19	**0.15**	**0.04**
0.25	0.22	0.18	0.28	**0.23**	**0.05**
0.5	0.28	0.32	0.51	**0.37**	**0.12**
1	0.35	0.22	0.26	**0.28**	**0.07**
2	0.07	0.05	0.04	**0.05**	**0.02**
4	0.07	0.05	0.06	**0.06**	**0.01**
6	0.03	0.03	0.04	**0.03**	**0.01**

Table 3.

Pharmacokinetic parameters calculated from whole blood for TBBPA (20 mg/kg), following oral administration of [^{14}C] TBBPA (20 mg/kg, 50 µCi/kg) to male F-344 rats (N=3).

Detection Method	AUC (µg*min/ml)	C_{max} (µg/ml)	T_{max} (h)	F
LSC	126 ± 19	0.71 ± 0.13	0.58 ± 0.19	9%
UV/Vis-radio HPLC	62 ± 13	0.76 ± 0.07	0.50 ± 0.21	4%

Two detection methods were utilized: LSC, for detection of total [^{14}C] equivalents in whole blood and UV/Vis-radio HPLC, for detection of [^{14}C] TBBPA in extracts of whole blood.

Table 4.

Percent of dose recovered from blood at different time points following oral administration of [^{14}C] TBBPA (20 mg/kg, 200 μCi/kg) to male F-344 rats (N=4).

	Percent of dose recovered (%)					
	60315-01	**60315-02**	**60315-03**	**60315-04**	**Mean**	**SD**
Time (h)						
0.125	0.28	0.29	0.17	0.26	**0.25**	**0.05**
0.25	0.63	0.66	0.45	0.51	**0.56**	**0.10**
0.5	0.63	0.74	0.43	0.63	**0.61**	**0.13**
1	0.34	0.24	0.35	0.31	**0.31**	**0.05**
2	0.07	0.07	0.06	0.07	**0.07**	**0.01**
4	0.18	0.16	0.11	0.18	**0.16**	**0.03**
6	0.08	0.06	0.06	0.07	**0.07**	**0.01**
8	0.04	0.03	0.03	0.03	**0.03**	**0.01**

Table 5.

Pharmacokinetic parameters of [^{14}C] TBBPA (20 mg/kg, 200 µCi/kg) following oral administration of [^{14}C] TBBPA (20 mg/kg, 200 µCi/kg) to male F-344 rats (N=3).

Detection Method	AUC (µg*min/ml)	C_{max} (µg/ml)	T_{max} (h)	F
LSC	185 ± 25	1.1 ± 0.4	0.46 ± 0.045	13%
UV/Vis-radio HPLC	24 ± 10	0.19 ± 0.08	0.53 ± 0.31	2%

Two detection methods were utilized: LSC, for detection of total [^{14}C] equivalents in whole blood and UV/Vis-radio HPLC, for detection of [^{14}C] TBBPA in extracts of whole blood.