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**DATA SUMMARY AND TEST PLAN**

**FOR**

**PHENOL, 4,4'-ISOPROPYLIDENBIS[2,6-DIBROMO-**  
**(TETRABROMOBISPHENOL A, TBBPA)**

**CAS No. 79-94-7**

**Prepared by**

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## 1.0 INTRODUCTION

The Brominated Flame Retardant Industry Panel (BFRIP) was formed in the 1980s to address issues related to the brominated flame retardants that its members manufacture in common, conduct research, and interact with regulatory agencies and other interested parties. Its members, who are global manufacturers of brominated flame retardants, are Albemarle Corporation, Ameribrom Inc. (a subsidiary of Dead Sea Bromine Group), and Great Lakes Chemical Corporation. Akzo-Nobel is an associate member. BFRIP, organized under the American Chemistry Council, volunteered under the U.S. EPA's High Production Volume (HPV) program to prepare the Data Summary/Test Plan and Robust Summaries for phenol, 4,4'-isopropylidenebis(2,6-dibromo. This compound (CAS No. 79-94-7) is also known as tetrabromobisphenol A or TBBPA. As discussed below, TBBPA is a data-rich chemical, including valid guideline studies or other information for all SIDS endpoints. For that reason, no additional tests are proposed for purposes of this program.

## 2.0 TBBPA STRUCTURE AND PROPERTIES

TBBPA, a solid at room temperature, is a brominated phenolic molecule with a molecular weight of 543.87 (Figure 1). The composition of the commercial product is typically 98% TBBPA with the remainder composed of other brominated bisphenol A compounds. Its measured vapor pressure and log octanol/water partition coefficient are  $<1.19 \times 10^{-5}$  Pa (Lezotte, F. and Nixon, W. Project Number 439C-128. 2001. Wildlife International, Ltd, Easton, MD) and 5.903 (MacGregor, J. and Nixon, W. Project Number: 439C-129. 2001. Wildlife International, Ltd. Easton, MD), respectively. TBBPA's melting point is  $181^{\circ}\text{C}$  (Albemarle Corporation, 2001), and its water solubility has been described as 0.001002 mg/L (estimated, EPIWIN V3.04);  $<0.5$  ug/L (Albemarle Corporation 2000);  $\leq 0.8$  ug/L (Brekelman, 2000).

TBBPA has been analyzed for the presence of 15 2,3,7,8-substituted polybrominated-p-dibenzodioxins and dibenzofurans. None of the analytes were present at or above the quantitation limits established by the U.S. Environmental Protection Agency (Ranken et al., *Bul. Soc. Chim. Belg.*, 103/5-6, 1994).

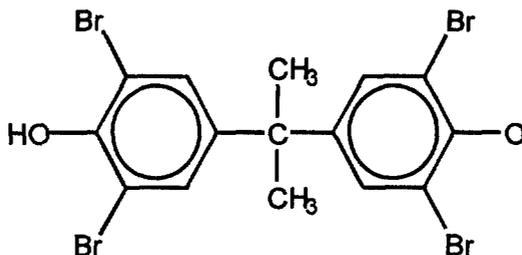


Figure 1. Tetrabromobisphenol A (TBBPA)

## 3.0 TBBPA APPLICATIONS

TBBPA is used as a reactive flame retardant in epoxy resin printed circuit boards and as an additive flame retardant in acrylonitrile-butadiene-styrene (ABS) resins for electronic enclosures. In the epoxy resin circuit boards, TBBPA covalently reacts with the epoxy resin backbone and ceases to exist as a chemical entity. TBBPA is the predominant flame retardant used in printed circuit boards worldwide. The reasons for TBBPA's dominance is that it is highly effective as a flame retardant and needs only low load levels, highly cost effective, compatible with the circuit board's other components, able to maintain the board's physical properties, qualified for use, and has health and safety data supporting its use. TBBPA is also used as the starting material for the production of TBBPA-derived flame retardants.

#### 4.0 TBBPA TOXICOLOGY DATA SUMMARY

##### 4.1 Environmental Fate (BFRIP)

TBBPA's measured and predicted environmental fate parameters are provided in Table 1.

TBBPA is predicted to partition to soil and sediment if released to the environment. Based on a release of 1,000 kg/hr to air, water and soil, the predicted partitioning is: air – 0.0000004%, water - 1.13%, soil - 44.9%, and sediment - 53.9% (*Level III Fugacity Model, EPIWIN V3.04, Syracuse Research Corporation*). The majority would be reacted in sediment and soil (83.9%) with only 16.1% of the total undergoing advection. TBBPA is expected to be essentially immobile in soil, where it can undergo degradation. Actual test data shows TBBPA's half-life in a 64-day aerobic and anaerobic soil studies to be approximately 50 days and in a 56-sediment/water degradation study, 48 to 84 days (*Fackler 1989*).

TBBPA is not expected to volatilize from water based on its air-water partition coefficient and its river and lake volatilization half lives, and is expected to partition to biomass (*EPIWIN V3.04, Syracuse Research Corporation*).

While not expected to undergo biodegradation during sewage treatment, TBBPA is expected to be removed from the effluent during passage through a wastewater treatment plant. Removal is estimated to be via sludge adsorption (93.14%) with only minimal biodegradation (0.78%). A total removal of 93.9% is predicted (*STP Fugacity Model, EPIWIN V3.04, Syracuse Research Corporation*).

##### 4.1.1 Photodegradation

TBBPA may undergo abiotic degradation. TBBPA's calculated half-life in water by UV radiation was 10.2 days in spring, 6.6 days in summer, 25.9 days in autumn, and 80.7 days in winter. The half-life of TBBPA adsorbed onto silica gel and exposed to UV radiation was 0.12 days. (*reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

Photolysis of TBBPA in the presence of UV light and hydroxyl radicals has also been reported; TBBPA was reported to totally degrade within 5-6 days with an estimated 33 hour half-life (*Eriksson and Jakobsson, 1998, Organohalogen Compounds, Vol 23, 419-422*).

**Table 1. Environmental Fate Parameters for TBBPA.**

Parameter	Estimation Program or Test Result	Result
Photodegradation	WHO EHC #172, 1992	Has potential to undergo photodegradation; However, not likely to be a significant route of environmental degradation due to low vapor pressure
Hydrolysis	-	Not likely to be a significant route of environmental degradation due to low water solubility
Distribution	Estimated (EPI win, V.3.04)	Level III Fugacity Model predicts at 1000 kg/Hr emissions to air, water and soil: Air 0.0000004 %, Water 1.3%, Soil 45%, Sediment 54%
Atmospheric Oxidation	Estimated (EPI win, V.3.04)	Overall OH Rate Constant = $2.9 \times 10^{-12}$ cm <sup>3</sup> /molecule-sec Half-Life = 3.6 Days (12-hr day; $1.56 \times 10^{+6}$ OH/cm <sup>3</sup> ) Half-Life = 43.4 Hrs
Henry's Law Constant	Estimated (EPI win, V.3.04)	$2.31 \times 10^{-13}$ atm-m <sup>3</sup> /mole at 25 °C $9.43 \times 10^{-12}$ unitless at 25 °C
Soil Koc	Estimated (EPI win, V.3.04)	$5.6 \times 10^{+6}$
Octanol-Water Partition Coefficient	Estimated (EPI win, V.3.04)	$1.6 \times 10^{+7}$
Air-Water Partition coefficient	Estimated (EPI win, V.3.04)	$9.4 \times 10^{-12}$
Biomass to Water Partition Coefficient	Estimated (EPI win, V.3.04)	$3.1 \times 10^{+6}$
Volatization from Water	Estimated (EPI win, V.3.04)	Half life: $6.7 \times 10^{+5}$ years (River); $7.3 \times 10^{+6}$ years (Lake)
Sewage Treatment Plant Fugacity Model	Estimated (EPI win, V.3.04)	Total Removal: 94%, Total Biodegradation: 0.78%, Primary Sludge: 59.8%, Waste Sludge: 33.3%, Final Water Effluent: 6%
Level III Fugacity Model	Estimated (EPI win, V.3.04)	At Emissions to Air, Water, Soil and Sediment of 1,000, 1,000, 1,000 and 0 kg/hr, respectively:  Fugacity (atm): Air $4.3 \times 10^{-17}$ , Water $4.5 \times 10^{-20}$ , Soil $1.5 \times 10^{-21}$ , Sediment $8 \times 10^{-20}$  Reaction (kg/hr): Air 0.0007, Water 48, Soil $1.9 \times 10^{+3}$ , Sediment 570  Advection (kg/hr): Air 0.0009, Water 247, Soil 0, Sediment 237  Reaction (%): Air $2.5 \times 10^{-5}$ , Water 2, Soil 63, Sediment 19  Advection (%): Air $3 \times 10^{-5}$ , Water 8, Soil 0, Sediment 8
Biodegradation	CITI-Japan, 1992	Not readily biodegradable
	Fackler P., 1989	Aerobic Soil (64 D): Degradable, Half-life ~50 D
	Fackler P., 1989	Anaerobic Soil (64 D): Degradable, Half-life ~50 D
	Fackler P., 1989	Sediment/Water (56 D): Degradable, Half-life 67 D

#### 4.1.2 Water Stability (Hydrolysis)

A hydrolysis study has not been conducted on TBBPA, and the EPIWIN software is unable to make a prediction for this chemical structure. However, if it occurs, hydrolysis is unlikely to be a significant route of environmental degradation for TBBPA due to its low water solubility.

#### 4.1.3 Biodegradation

TBBPA is not "readily" biodegradable by sewage sludge, but can be degraded in soil and sediment. TBBPA's half-life in a 64-day aerobic and anaerobic soil studies was approximately 50 days. TBBPA's half-life in a 56-sediment/water degradation study was 48 to 84 days.

While not expected to be biodegraded in a wastewater treatment plant, 93.92% removal is predicted. Removal is estimated to be mainly by sludge adsorption (93.14%) with only minimal biodegradation (0.78%).

##### 4.1.3.1 64-Day Aerobic Soil Degradation (BFRIP)

The biodegradability of <sup>14</sup>C-TBBPA was tested under aerobic conditions in three soil types, i.e., Massachusetts sandy loam, a California clay loam, and Arkansas silty loam. The three soil types contained: sand (83%)-silt (13%)-clay (4%), sand (16%)-silt (58%)-clay (26%), and sand (43%)-silt (24%)-clay (33%), respectively. Thin layer chromatography (TLC) showed biodegradation of TBBPA in all soil types. Less than or equal to 6% of the applied radioactive TBBPA was recovered in the volatile traps, indicating partial degradation to CO<sub>2</sub>. Results of the TLC analysis indicated variable degradation rates of TBBPA which were dependent on soil type. After 64 days, the amount of TBBPA remaining in the soils ranged from 36 to 82%, with the highest level in sandy loam soil and the lowest in the silty loam soil. Degradation products (2 or 3 depending on soil type) were not specifically identified, but the dimethyl and diethyl derivatives of TBBPA were ruled out based on TLC characteristics of authentic standards. (*Fackler 1989, SLS Report 88-11-2848; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.*)

##### 4.1.3.2 64-Day Anaerobic Soil Degradation (BFRIP)

The biodegradability of TBBPA was tested under anaerobic conditions in three soil types; Massachusetts sandy loam (MSL), Arkansas silty loam (ASL), and California clay loam (CCL). The three soil types contained: sand (83%)-silt (13%)-clay (4%), sand (16%)-silt (58%)-clay (26%), and sand (43%)-silt (24%)-clay (33%), respectively. Thin layer chromatography showed biodegradation of TBBPA in all soil types. Less than 0.5% of the radiolabel was recovered in the volatile traps, indicating little degradation to CO<sub>2</sub>. The recovered radioactivity in all traps was almost exclusively CO<sub>2</sub>. Results of the TLC

analysis indicated variable degradation rates that were dependent on the soil type. After 64 days, the amount of TBBPA remaining in the soils were MSL: 43.7-57.4%, ASL: 53.4-65%, and CCL: 89.5-90.6%. Radioactivity recovered from the water ranged from 0.5 to 2.5%. Degradation products (2 or 3 depending on soil type) were not specifically identified, but the dimethyl and diethyl derivatives of TBBPA were ruled out based on TLC characteristics of authentic standards. (Fackler 1989, SLS Report 88-11-2849; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.*)

#### 4.1.3.3 56-Day Sediment/Water Microbial Degradation (BFRIP)

The biodegradability of <sup>14</sup>C-TBBPA was tested under aerobic conditions in a sediment/water microbial test system using natural river sediment and water. The test conditions were pH 5.5, field moisture capacity 15.9%, temperature 24-26 degrees C, and the composition of the soil (6.8% carbon) was 925 sand, 6% silt, and 2% clay. TBBPA biodegraded at all tested concentrations (0.01, 0.1 and 1 mg/L). Half-lives calculated for TBBPA in the sediment/water microbial test systems ranged between 48 days at 0.01 ug/L concentration and 84 days at the 1 mg/L concentration with apparent correlations between half-life and TBBPA concentration and half-life and microbial population. The half-life in sterile soil was extrapolated to be 1300 days, indicating that the degradation observed in the active test systems was due to microbial degradation rather than physical processes. Less than 8% of the applied radioactive carbon from TBBPA was recovered in the volatile traps indicating partial degradation to CO<sub>2</sub>. Filtered water contained less than 5% of the applied radioactivity. The amount of radioactivity observed to be remaining in the sediment at test termination, 44.7, 64.2, and 60.8% in the 0.01, 0.1 and 1 mg radioactive TBBPA/L treatments, respectively, was comparable to the amounts reported in the aerobic degradation study in soil. Half-lives calculated for TBBPA in the sediment/water microbial test systems ranged between 48 and 84 days, with an apparent correlation between half-life and concentration of TBBPA and half-life and microbial population. (Fackler 1989, SLS Report 89-8-3070; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.*)

#### 4.1.3.4 Sequential Anaerobic Aerobic Microbial Degradation

The degradation of TBBPA was evaluated in a sequential anaerobic-aerobic system. TBBPA was incubated with a slurry of anaerobic sediment from a wet ephemeral desert stream bed contaminated with chemical industry waste. Anaerobic incubation resulted in an 80% decrease in the original TBBPA concentration. One metabolite was produced and identified as bisphenol A (BPA). BPA persisted in the anaerobic slurry but was degraded aerobically by gram negative bacteria present in the contaminated soil. Thus, sequential anaerobic-aerobic degradation of TBBPA was observed (Ronen *et al.*, *Appl. Environ. Microbiol.*, 66(6), 2372-2377, 2000).

#### 4.1.3.5 14-Day Activated Sludge Biodegradation

TBBPA was tested in Japan's activated sludge biodegradation test. No biodegradation was observed over the 14-day study (*Data of Existing Chemicals Based on the CSCL Japan, CITI, 1992, Tokyo*).

#### 4.1.4 Transport (Fugacity) (BFRIP)

If released in equal amounts to air, water and soil, TBBPA was predicted to partition to soil and sediment. Based on a release of 1,000 kg/hr to air, water and soil, the predicted partitioning would be: air - 0.0000004%, water - 1.13%, soil - 44.9%, and sediment - 53.9%. The majority would be reacted in sediment and soil (83.9%) with only 16.1% of the total undergoing advection (*Level III Fugacity Model, EPIWIN modeling software, V3.04, Syracuse Research Corporation*).

### 4.2 Ecotoxicology Data

All LC50 and EC50 values derived from acute tests in fish, daphnia, freshwater alga, and marine alga were greater than TBBPA's estimated and measured water solubility.

TBBPA's water solubility was estimated to be 0.001 mg/L using Syracuse Research Corporation's modeling software (*EPIWIN V3.04*). Its estimated octanol water partition coefficient is 7.20 using the same software. TBBPA's measured water solubility is  $\leq$  0.08 mg/L (*Brekelman, 2000*).

#### 4.2.2 Acute Toxicity to Fish (BFRIP)

The 96-hour LC50 values for bluegill sunfish (*Calmbacher 1978*), rainbow trout (*Calmbacher 1978*) and fathead minnow (*Surprenant 1988; SLS Report #88-10-2834*) were 0.51, 0.40 and 0.54 mg/L, respectively. The LC50 in killifish was determined to be 8.2 mg/L at 48 hours. These acute studies were reported in the Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.

#### 4.2.3 Acute Toxicity to Aquatic Invertebrates (BFRIP, Other)

The 48-hour LC50 for *Daphnia magna* was 0.96 mg/L (*Morrissey 1978*). The 96 hour EC50 for the Eastern oyster was 0.098 mg/L (*Surprenant, 1989, Report #89-1-2898*). The 96 hour EC50 in <1, 5, or 10 day old Mysid shrimp was 0.86, 1.1, and 1.2 mg/L, respectively (*Goodman et al., Bull. Environ. contam. Toxicol. (1988) 41:746-753*). These acute studies were reported in the Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.

#### 4.2.4 Acute Toxicity to Aquatic Plants (BFRIP, Other)

The growth of freshwater green algae, *Selenastum capricornutum*, was not affected by 5.6 mg/L, the highest level tested (*Giddings 1988, Report No 88-10-2828; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

The growth of marine unicellular alga, *Skeletonema costatum*, *Thalassiosira pseudonana*, and *Chlorella* sp. was investigated following TBBPA exposure. The 96 hr EC50 for *Chlorella* was > 1.5 mg/L, the highest dose tested. The 72 hr EC50 for *S. costatum* ranged from 0.09-1.14 mg/L. The 72 hr EC50 for *T. pseudonana* ranged from 0.13-1.0 mg/L. All EC50's were higher than TBBPA's water solubility. (Walsh et al., *Ecotoxicology and Environmental Safety* 14, 215-222 (1987); reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.2.5 Prolonged Exposure Data

Prolonged exposure to TBBPA was not toxic at the limit of its water solubility to fish early life stages, the water flea *D. magna*, or the sediment midge *C. tentans*.

##### 4.2.5.1 Fish Early Life Stage (BFRIP)

In an early life stage test, fathead minnow embryos and larvae were continuously exposed for 35 days to TBBPA concentrations 0, 0.024, 0.04, 0.084, 0.16 or 0.31 mg/L. Survival of embryos to doses less than 0.31 mg/L was unaffected; survival at 0.31 mg/L was less than controls. Growth was not affected at any dose level. The Maximum Acceptable Toxicant Concentration (MATC), the range encompassing the highest test concentration that had no significant effect and the lowest concentration that had a significant effect, was 0.22 mg/L for fathead minnow embryos and larvae exposed continuously for 35 days. The MATC in this fish early life stage test was greater than TBBPA's estimated and measured water solubility (Surprenant, D., 1989, Study No. 89-2-2937; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

##### 4.2.5.2 Daphnia Life Cycle (BFRIP)

In a chronic study on an aquatic invertebrate specie, *Daphnia magna* were continuously exposed (flow-through) for 21 days to mean measured concentrations of 0.056, 0.1, 0.19, 0.30, 0.98 mg <sup>14</sup>C-TBBPA/L. Nominal concentrations were 0.31, 0.25, 0.5, 1.0, 2.0 mg/L. After 21 days, daphnia survival ranged from 95-100% in all treatment groups and was statistically comparable to control survival. Organism growth, e.g. individual body length, in the all treatment groups was also comparable to the control means and was not affected by treatment at any dose level. Reproduction at the highest dose level (0.98 mg/L measured or 2 mg/L nominal) was approximately one-third of that in the control groups and was statistically significantly different from controls. Reproduction at all other dose levels was statistically comparable to controls. The maximum acceptable toxicant concentration (MATC) for reproduction was > 0.3 and < 0.98 mg/L (measured concentration) or > 1 and < 2 mg/L (nominal concentration). The MATC for survival and growth was  $\geq$  0.98 mg/L (measured) or  $\geq$  2 mg/L (nominal). Survival and growth were not affected by chronic exposure of *Daphnia* to TBBPA. Reproduction in *Daphnia* was not affected by doses < 0.98 or 2 mg/L, measured or nominal, respectively. The MATC for chronic exposure of *Daphnia* to TBBPA was > 0.98 or 2 mg/L, measured or

nominal, respectively. All of these doses are greater than TBBPA's estimated or measured water solubility. (*Surprenant, D., 1989, Study No. 89-01-2925; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.2.5.3 Sediment Organism Toxicity (BFRIP)

The subchronic effects of the sediment-bound form of TBBPA to a representative benthic invertebrate species, the midge *Chironomus tentans*, were determined. The study consisted of a series of three 14-day (partial life cycle) tests. Each test was conducted with sediment containing different organic carbon levels: high (6.8% organic carbon), mid (2.7%) or low (0.25%) organic carbon content. The sediments were physically characterized as having a high sand content, 2-8% silt, and were slightly acidic (pH 5.4-5.5). The sediment concentration of TBBPA ranged between 13 and 200 mg/kg (nominal).

The test systems achieved and maintained equilibrium between sediment and water for the duration of the tests. The highest mean interstitial water concentrations of TBBPA were measured in the nominal 200 mg/kg treatments where midges were continuously exposed to interstitial water concentrations of 0.046 mg/L (HOC), 0.045 mg/L (MOC) and 0.039 mg/L (LOC) TBBPA.

Sediment/interstitial water partitioning coefficients ( $K_d$ ) were 7,349; 5,378 and 5,816, in the HOC, MOC, and LOC groups, respectively, at the highest dose tested. These  $K_d$  values indicate TBBPA preferentially partitions to sediment rather than water.

Midge survival and growth in all TBBPA-treated sediments was statistically comparable to control organisms. The no effect sediment concentrations were 228 to 341 mg TBBPA/kg sediment, corresponding to 0.039 to 0.046 mg TBBPA/L interstitial water. The NOEC in interstitial water was greater than TBBPA's estimated water solubility. The NOECs in both sediment and interstitial water were independent of the total organic carbon content of the sediments. (*Breteler, R., 1989, Study No. 90-08-3067A; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.*)

#### 4.2.5.4 Amphibian Thyroid Hormone System

The potential for TBBPA to adversely affect the amphibian thyroid hormone system was investigated using the tadpole (*Xenopus*) tail regression assay. Tadpoles were microinjected with TBBPA at developmental stage 58 (hind limbs emerged; forelimbs formed, but not emerged) at doses up to 60 ug/tadpole. Tail resorption was not affected by TBBPA. Positive controls showed delayed tail resorption. (*Balch and Metcalfe, Proceedings of the 3<sup>rd</sup> Annual Workshop on BFRs in the Environment, August 2001, Burlington, Ontario.*)

#### 4.2.6 Bioconcentration Studies

Several biocentration studies have been performed. Bioconcentration studies in fish produced bioconcentration factors (BCF) ranging from 20 to 1200. The half-life in fish was < 1 day, and plateau levels were reached in appr. 4 days. During depuration, TBBPA and its metabolites were eliminated within 3-7 days.

TBBPA's bioconcentration factor in oysters was 720 and its depuration half-life was 3- 5 days. TBBPA's BCF in sediment midges was  $\approx$  1000, except when tested in low (<1%) organic carbon sediments.

#### 4.2.6.1 Carp Bioconcentration

The bioconcentration of TBBPA was evaluated in Japanese carp following an 8 week exposure period at concentrations of 8 or 80 ug/L. The BCF was 30~341 at 80 ug/L and 52~485 at 8 ug/L. The LC50 in killifish was determined to be 8.2 mg/L at 48 hours. (*Data of Existing Chemicals Based on the CSCL Japan, CITI, 1992, Tokyo; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.2.6.2 Fathead Minnow Bioconcentration ( $^{14}\text{C}$ -TBBPA) (BFRIP)

Fathead minnows were exposed to 4.7 ug/L  $^{14}\text{C}$ -TBBPA (flow through conditions) for a 24-day exposure period followed by a 6-day depuration period.  $^{14}\text{C}$ -activity remained below the limit of radiometric detection in water during depuration. The concentration of  $^{14}\text{C}$ -activity in fish tissue reached a steady-state level on day 4 of exposure. The mean steady-state concentration on a whole body basis was 5,800 ug/Kg or a BCF of 1200 (mean equilibrium tissue concentration = 5800 ug/kg; mean water concentration = 4.7 ug/L). This BCF value was based on  $^{14}\text{C}$ -residues and therefore represents the sum total of parent compound, any retained metabolites and assimilated carbon. The BCF of the parent compound (TBBPA) may be lower.

Rapid elimination of the radiolabel was observed. The whole-body half-life in the fish was < 1 day. 98% of the  $^{14}\text{C}$ -activity was eliminated by 6 days of depuration; elimination of 95% occurred between day 1 and 4 of depuration.  $^{14}\text{C}$ -TBBPA residues did not persist in fish tissue. (*Fackler, P., 1989, SLS No. 89-3-2952; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.*)

The results of this study indicated ready uptake in continuously exposed fathead minnows with steady-state reached within 4 days. Extending the period of continuous exposure up to 24 days did not increase the levels in fish. During depuration, the fathead minnows rapidly and nearly completely eliminated the  $^{14}\text{C}$ -residue. The whole body half- life was < 24 hours and by day 6 of the elimination period only 2% of the  $^{14}\text{C}$ -residue remained in the exposed fish. Therefore, these residues should not persist once the fish are no longer continuously exposed. Intermittent exposures should not result in any significant TBBPA tissue residues because of the short half-life (<24 hours) of TBBPA and its metabolites.

#### 4.2.6.3 Blue Gill Sunfish Bioconcentration (<sup>14</sup>C-TBBPA)

Blue gill sunfish were exposed to <sup>14</sup>C-TBBPA for 28 days to 0.0098 mg/L (flow-through) followed by a 14-day withdrawal period. The bioconcentration factor (BCF) in edible tissue was 20 and 170 in visceral tissue. These BCF values were based on <sup>14</sup>C-residues and therefore represent the sum total of parent compound, any retained metabolites and assimilated carbon. Plateau levels were reached within 3-7 days. The whole body half-life was < 24 hours. The radiocarbon dissipation to <0.01 mg/kg in fish tissue occurred within 3-7 days of the beginning of the withdrawal phase. TBBPA did not show accumulation potential in this test. (Nye, D., 1978, Project 780241; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.2.6.4 Bioconcentration in Eastern Oysters (<sup>14</sup>C-TBBPA) (BFRIP)

Eastern oysters were exposed to nominal concentration of 1 ug/L of <sup>14</sup>C-TBBPA for 20 D followed by a 14-day depuration period. The concentration of <sup>14</sup>C-residues in the aquaria water remained constant throughout the 20-day exposure period. During depuration <sup>14</sup>C-residues in the water remained ≤ 0.34 ug/L, the limit of radiometric detection. <sup>14</sup>C-residues reached steady-state in oyster tissues by day 5. The mean steady-state bioconcentration factor was 720. The depuration half-life was between 3-5 days (Fackler, P. 1989, SLS Number 89-1-2918; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

#### 4.2.6.5 Chironmid (BFRIP)

The subchronic effects of TBBPA on the survival and growth of the sediment midge, *Chironomus tentans*, were evaluated in a 14 day continuous exposure via treated sediments under flow-through conditions. As a part of the study, bioconcentration factors were calculated (ratio of the body concentration and interstitial water). In the high (>4%) organic carbon sediment, the BCF ranged from 240-520. In the mid (1.5-3%) organic carbon sediment, the BCF ranged from 490-1100. In the low (<1%) organic carbon sediment, the BCF ranged from 650 to 3200. TBBPA accumulated substantially less in high organic than in low organic sediment, indicating that bioavailability was significantly affected by the total organic carbon content in the sediment. In the high and mid organic carbon sediments, TBBPA's BCF was ≤ 1,000. Only in the low (<1%) organic carbon sediment at the highest dose tested, 200 mg/kg sediment, was the BCF > 1,500 (Breteler, R., 1989, SLS No. 89-08-3067; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

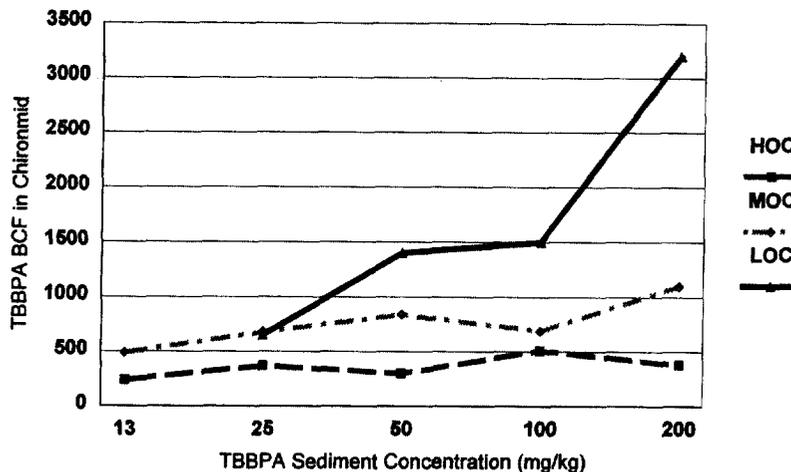


Figure 2. TBBPA BCF in *Chironomid* following a 14-day sediment exposure.

### 4.3 Mammalian Toxicology Data

TBBPA produced minimal effects in mammals when tested in acute and subchronic studies. TBBPA was not acutely toxic or irritating to the skin or eye. TBBPA did not induce chloracne on skin exposure and did not induce skin sensitization in guinea pigs. Testing in human volunteers showed no evidence of irritation or induction of skin sensitization. TBBPA was negative in the Ames Salmonella mutagenicity test and in the *in vitro* chromosome aberration test. Pharmacokinetic studies demonstrate TBBPA has a short half-life and is readily metabolized and excreted, as would be expected of a chemical possessing two hydroxyl groups suitable for metabolic conjugation.

#### 4.3.1 Acute Toxicity Data

The oral LD50 in the rat is >5,000 mg/kg and the dermal LD50 in rabbits is > 2,000 mg/kg. TBBPA was also not acutely toxic by inhalation; the inhalation LC50 in rats is >2550 mg/m<sup>3</sup> for a 2 hour exposure. TBBPA is not irritating to the skin or eye. These acute studies were reported in the Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995.

#### 4.3.2 Repeated Dose Toxicology

##### 4.3.2.1 14-Day Rat Inhalation

In a 14-day inhalation study, no systemic toxicity was observed in rats treated with up to 18 mg/L. Rats were exposed to an atmosphere of 0, 2, 6 or 18 mg micronized TBBPA/L air (0, 2000, 6000, or 18,000 mg/m<sup>3</sup>) for 4 h daily, 5 days/week for 2 weeks. Mortality, body weight gain, food consumption, hematological, biochemical or urinary parameters were not affected by treatment. No gross or microscopic lesions were detected in any

dose level. (Goldenthal et al. 1975; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.3.2.2 21 Day Rat Dermal

In a 21-day dermal study, no systemic toxicity was observed in rabbits treated with 0, 100, 500, or 2,500 mg TBBPA/kg body weight for 6 hours/day, 5 days/week for 3 weeks. No mortality or overt signs of toxicity were observed. Body weight gain, hematological parameters, urinalysis, organ weights, and gross and microscopic examinations did not reveal any compound-related changes. (Goldenthal et al., 1979; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.3.2.3 28-Day Rat Oral

In a 28-day oral study, no toxicity was observed in rats treated with up to 1,000 ppm TBBPA in the diet. Rats were fed at dietary dose levels of 0, 1, 10, 100 or 1000 ppm TBBPA for 28 days after which one group was sacrificed and the remaining rats placed on untreated diets for 2, 6 or 12 weeks. No effects on general appearance, behavior, body weight, food consumption or mortality were observed. No compound related gross or microscopic lesions or variations in organ weights were observed at any dose level. Liver and adipose bromine levels were similar in rats of the control and high dose groups sacrificed at the end of the 28 day treatment period. (Goldenthal and Geil, 1972; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

#### 4.3.2.4 90-Day Rat Oral

In a 90-day oral study, no toxicity was found in rats treated with up to 100 mg/kg in the feed. Rats were fed a diet supplying 0, 0.3, 3, 30 or 100 mg TBBPA/kg body weight for 90 days. No toxicological effects were detected at any dose level for appearance, demeanor, body weight gain, food consumption, hematology, clinical chemistry values, urinalysis, organ weights, and gross and microscopic examinations. The total bromine content in liver, kidney, skeletal muscle, fat and serum of rats in the 3 mg/kg dose group did not differ from that of the controls. (The 3 mg/kg group was the only group tested for total bromine content.) (Quast et al. 1975; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

#### 4.3.2.5 90-Day Rat Oral

In another 90-day study, a no adverse effect level of 4,900 mg/kg diet (~700 mg/kg body weight) was determined in mice (Tobe et al., 1986; reported in *Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

### 4.3.3 Genetic Toxicity – Mutation

#### 4.3.3.1 Ames Salmonella

TBBPA has been tested in multiple Ames assays. All results were negative for mutagenicity (*reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

#### 4.3.3.2 Intragenic recombination

The Sp5 and SPD8 cell lines were developed by the paper's authors. The clones used in this study exhibit spontaneous partial duplication of the hprt gene, resulting in a non-functional hgpRT protein. These mutants revert spontaneously to a functional hprt gene phenotype by recombination with a frequency of  $1 \times 10^5$  reversions/cell generation. This reversion frequency is said to increase by exposure to chemical or physical agents. Treatment with the test substance was for 24 hr.

In the SPD8 cells, TBBPA concentrations of 0, 5, 10, 20, 30, and 40 ug/ml resulted in a reversion frequency of 1.0, 1.1, 1.4, 1.3, 1.3, and 1.0, respectively. Cytotoxicity was not observed at the doses tested. In the Sp5 cells, TBBPA concentrations of 0, 10, 20, 40, 70 ug/ml resulted in a reversion frequency of 1.0, 0.8, 0.8, 1.0 and 0.7, respectively. Cytotoxicity was observed at 70 ug/ml. None of these reversion frequencies were statistically different from the control (Student's t test,  $p < 0.05$ ). Thus, TBBPA had no effect in either the SPD8 or Sp5 recombination assay (*Helleday et al. Brominated flame retardants induce intragenic recombination in mammalian cells. Mutation Research 439 (1999) 137-147*).

#### 4.3.4 Genetic Toxicity – Chromosome Aberration (BFRIP)

TBBPA was tested in the *in vitro* mammalian chromosome aberration test using human peripheral lymphocytes (HPBL) in both the absence and presence of an Arochlor-induced S9 activation system. Dose levels in the definitive assay in absence of exogenous metabolic activation (4 hr treatment, 20 hr harvest) were 6.25, 25, 100 ug/ml, and for a 20 hr treatment, 20 hr harvest were 6.25, 25, 75 ug/ml. In the presence of metabolic activation (4 hr treatment, 20 hr harvest), test article concentrations were 3.125, 12.5, 50 ug/ml.

The test article was soluble in treatment medium at all concentrations tested. Toxicity (mitotic inhibition) was appr. 54 and 59% at the highest dose level evaluated for chromosome aberrations, 100 ug/ml and 75 ug/ml in the non-activated 4 hr and 20 hr exposure groups, respectively. Toxicity (mitotic inhibition) was 58% at the highest dose level evaluated for chromosome aberrations, 50 ug/ml, in the S9 activated study.

No statistically significant increases in structural and numerical chromosome aberrations were observed in the non-activated or the S9 activated 4 hr exposure groups relative to the solvent control group, regardless of dose level ( $p > 0.05$ , Fisher's exact test). In the absence of a positive response in the non-activated 4 hr exposure group, the non-activated 20 hr continuous exposure group was evaluated for structural and numerical chromosome

aberrations. No statistically significant increases in structural and numerical chromosome aberrations were observed in the non-activated 20 hr continuous exposure group relative to the solvent control group, regardless of dose level ( $p > 0.05$ , Fisher's exact test). The positive controls performed as expected.

TBBPA was negative for the induction of structural and numerical chromosome aberrations in the in vitro chromosome aberration test using human peripheral lymphocytes (*Gudi, R. and Brown, C. In vitro chromosome aberration test. Test Article: Tetrabromobisphenol A (TBBPA). Study Number: AA47PV.341.BTL. 2001. BioReliance, Rockville, MD*).

#### 4.3.5 Developmental Toxicity Data

Several studies have evaluated the potential of TBBPA to induce developmental effects. None were observed.

##### 4.3.5.1 Rat Oral Prenatal Developmental Toxicity (BFRIP)

TBBPA is not a developmental toxicant (not teratogenic) in rats. TBBPA was administered by gavage at dose levels of 0, 100, 300, or 1,000 mg/kg body weight on gestation days 0-19 to pregnant rats. No signs of toxicity were observed at any dose level. No effect of treatment was evident from gestational parameters (body weight, body weight gain, or food consumption), uterine implantation data, liver weights or necropsy findings. No effect of treatment was evident from fetal body weights, fetal sex distribution, or from fetal external, visceral, or skeletal examinations (*Schroeder, R. An oral prenatal developmental toxicity study with tetrabromobisphenol A in rats. Study No. 474-005. 2001. MPI Research, Mattawan, MI*).

##### 4.3.5.2 Rat Oral Developmental Toxicity

TBBPA was administered by gavage at dose levels of 0, 30, 100, 300, 1,000, 3,000, or 10,000 mg/kg body weight on gestation days 6-15 to pregnant rats. No signs of toxicity were observed in rats receiving doses of 3,000 mg/kg or less. No differences in the mean numbers of viable or nonviable fetuses, resorption, implantations, or corpora lutea were detected between treated and control rats (*Goldenthal et al., 1978; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*).

##### 4.3.5.3 Rat Oral Developmental Toxicity

Female rat were treated with TBBPA at doses of 0, 280, 830, or 2,500 mg/kg body weight from day 0-19 of gestation. Birth rate was not impaired by treatment. No toxic effects were observed on the embryo or fetus. No skeletal or visceral abnormalities were detected. Postnatal development (21 days post-birth) was not impaired (*Noda, et al. 1985. Annual Report, Osaka City Institute of Public Health and Environmental Sciences*).

#### 4.3.6 Reproductive Toxicity Data

Several developmental toxicity studies on TBBPA are available, one of which was recently completed under current guidelines and Good Laboratory Practices using the TBBPA in commercial production and use at a top dose of 1,000 mg/kg/d. All studies are negative for developmental toxicity.

Several repeated dose studies, in more than one mammalian species, are also available and none show evidence of an effect on the reproductive tract.

According to the SIDS Manual, when teratology and 90 day studies show no effects on the reproductive system then the requirement for the reproductive endpoint are met.

#### 4.3.7 Other

In the rat, TBBPA was readily absorbed, metabolized and eliminated within 72 hours after oral dosing. Recovery of <sup>14</sup>C-activity in the conventional and bile-cannulated rat administered a single oral dose of <sup>14</sup>C-TBBPA was 92 and 98.5% of the dose, respectively, by 72 hours post-dosing. Owing to the extensive elimination, total tissue retention at 72 hours was limited. In the conventional rat, 2% of the dose was retained in the tissues, but <1% in the cannulated rat at 72 hours. Essentially no deposition of TBBPA was detected in adipose tissue, heart, spleen, testis or thymus (<0.0005% of dose). The primary route of elimination was the feces; only negligible amounts were detected in urine. Glucuronic acid and sulphate ester conjugates were detected in bile; however the parent molecule was the predominant form found in species due to deconjugation by intestinal bacteria (*Haak et al., Xenobiotica, 2000, 30,9,881-890; Larsen, G. et al, Organohalogen Compounds, 31, 413-416, 199).*

Earlier work concluded that in rats, after oral dosing, approximately 95 percent of the administered material was found in the feces and less than 1.1 percent in the urine within 72 hours. Blood and tissue levels were extremely low at all time points measured. The half-life in the blood was about 20 hours; the maximum half life in any tissue was less than 3 days. Because of the short half-life, the small amounts of TBBPA absorbed would have relatively little persistence or accumulation in mammalian systems. (*Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995*)

## 5 TBBPA TEST PLAN

A complete set of SIDS-level data currently exists on TBBPA (Table 3), and the results are described in the attached robust summaries. Therefore, no testing is planned under this program.

**Table 3. TBBPA HPV Test Plan.**

<b>Study Type</b>	<b>Data Available</b>	<b>Data Acceptable</b>	<b>Estimation</b>	<b>Testing Required</b>
<b>Physical/Chemical</b>				
Melting Point	Y	Y	-	N
Boiling Point	N	-	-	N
Vapor Pressure	Y	Y	-	N
Water Solubility	Y	Y	-	N
<b>Environmental Fate</b>				
Photodegradation	Y	-	Y	N
Stability in Water	N	-	Y	N
Biodegradation	Y	Y	-	N
Transport (Fugacity)	N	-	Y	N
<b>Ecotoxicity</b>				
Acute Toxicity to Fish	Y	Y	-	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	N
Toxicity to Aquatic Plants	Y	Y	-	N
<b>Toxicology Data</b>				
Acute Toxicity	Y	Y	-	N
Repeated Dose Toxicity	Y	Y	-	N
Genetic Toxicity – Mutation	Y	Y	-	N
Genetic Toxicity – Chromosome Aberration	Y	Y	-	N
Developmental Toxicity	Y	Y	-	N
Reproductive Toxicity	Y	Y	-	N