Tetrabromobisphenol A
[79-94-7]

Review of Toxicological Literature

June 2002

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Prepared for

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Executive Summary

Basis for Nomination
Tetrabromobisphenol A (TBBPA) was nominated by the NIEHS for toxicological characterization including neurodevelopmental toxicity studies and carcinogenicity. The nomination is based on its high production volume, widespread human exposures, and suspicion to cause thyroid toxicity and thyroid tumors.

Nontoxicological Information
TBBPA contains 58.7% bromine. When pyrolyzed in open quartz tubes for ten minutes, TBBPA produces polybrominated dibenzo-*p*-dioxins (PBDDs) and -furans (PBDFs) at 700 °C. When used as a flame retardant, TBBPA contains <0.01 to 0.05 µg/kg PBDDs and <0.01 to 0.02 µg/kg PBDFs. TBBPA can be detected by chromatographic methods coupled with mass spectrometry (MS) or other detectors. Gas chromatography (GC) and GC/MS are used after conversion of TBBPA to the diethyl derivative by ethylation. The Occupational Safety and Health Administration (OSHA) air sampling method for TBBPA is high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. TBBPA has been determined in human plasma using solid-phase extraction (SPE) and GC with electron-capture MS (ECMS) detection in the concentration range of 4-200 pg/g plasma; the estimated detection limit was 0.8 pg/g plasma.

TBBPA is commercially available as an epoxy resin grade and a higher quality polycarbonate grade. It is produced by Albemarle Corporation (Magnolia, AR) and Great Lakes Chemical Corporation (El Dorado, AR) by the bromination of bisphenol A. TBBPA is a high volume chemical with U.S. annual production exceeding 1 million pounds. In 2001, a U.S. import volume for consumption of 1,132,750 kg (2,497,286 lb) was reported for TBBPA; all was imported from Israel. As mixtures of TBBPA-carbonate oligomers, dibromoneopentyl glycol, polydibromophenylene oxide, and electroplating chemical and electroless, a world total of 1,319,393 kg (2,908,764 lb) was reported.

The primary use of TBBPA is as a reactive flame retardant in epoxy resin circuit boards and more recently in electronic enclosures made of polycarbonate-acrylonitrile-butadiene-styrene (PC-ABS). Other applications of TBBPA include its use as a flame retardant for plastics, paper, and textiles; as a plasticizer; in adhesives and coatings; and as a chemical intermediate for the synthesis of other flame retardants (e.g., TBBPA allyl ether). It is also used as a fire-retardant additive (ABS, phenolic, unsaturated polyester resins) and as a fire-retardant polycarbonate co-monomer and has been applied to carpeting and office furniture.

TBBPA is expected to adsorb to sediment and organic matter in the soil. It is partly degraded under both aerobic and anaerobic conditions in soil, in river sediment, and in water. In soil, TBBPA is expected to be immobile, while in moist and dry soil surfaces, volatilization is not expected. Volatilization from water surfaces is also not expected. Photodegradation of TBBPA in water by UV radiation had the following half-lives: 10.2 days in spring, 6.6 days in summer, 25.9 days in autumn, and 80.7 days in winter. If released to air, TBBPA is expected to exist solely in the particulate phase. Bioconcentration factors (BCFs) ranging from 20 to 3200 suggest that bioconcentration is generally moderate to high in aquatic organisms. In 2000, off-site release for TBBPA totaled 537,549 lb (67..4% of total releases). On-site releases were reported as 197,529 lb (24.8%) to the land (other than Resource Conservation and Recovery Act [RCRA] subtitle C landfills) and 62,387 lb (7.8%) to the air. Production-related waste of TBBPA totaled 804,166 lb, of which 787,143 lb (97.9%) was released on- and off-site. Transfers off-site for further waste management and disposal totaled 546,096 lb.

TBBPA is listed in the Environmental Protection Agency (EPA) Toxic Substances Control Act (TSCA) Section 8(b) Chemical Inventory. Under Section 8(d) of TSCA, manufacturer, importers, and processors of TBBPA are required to submit to EPA copies and lists of unpublished health and safety studies (40 CFR 716.120). In addition, persons who manufacture or import TBBPA must report the results of tests showing that the chemical substance has been tested for the presence of halogenated dibenzodioxins (HDDs) or dibenzofurans (HDFs) (40 CFR 766.35). The reporting threshold for TBBPA for the Toxic Release Inventory (64 FR 58666, October 29, 1999; EPCRA Section 313) is 100 lb. Waste solids from TBBPA production are not listed as hazardous; wastewaters from the process, however, meet the existing listing description for K131 (Wastes from the Production of Methyl Bromide). As particulates not otherwise regulated (PNOR), the OSHA permissible exposure level time-weighted average (PEL TWA) is 15 mg/m^3 TBBPA; as particulates not otherwise specified (PNOS), the American Conference of Governmental Industrial Hygienists threshold limit value (ACGIH TLV) TWA is 10 mg/m^3.

Human Exposure

For the general population, exposure to TBBPA is possible from inhalation of ambient air and dermal contact with the compound (e.g., products made from polymers incorporating the TBBPA). Ingestion of TBBPA is also a possible exposure route. In commercial drinking water stored in reusable polycarbonate containers, native TBBPA as well as brominated derivatives of the ^{13}C-bisphenol A (BPA) were detected. Additionally, TBBPA has been found in fish and shellfish.

Occupational exposure to TBBPA may occur via dermal contact during its production or use in the workplace or via inhalation of dusts. In its National Occupational Exposure Survey (NOES) (1981-1983), the National Institute for Occupational Safety and Health (NIOSH) estimated that 224 workers were potentially exposed to TBBPA in the United States.

An ongoing increase in human exposure to brominated flame retardants, including TBBPA, has been observed. Analysis of archived samples from Norway (spanning the years 1986 to 1999) showed that serum levels of TBBPA ranged from 0.34-0.71 ng/g (0.63-1.3 pmol/g) lipid. The following TBBPA levels in plasma have been found in different occupational groups: up to 0.52 ng/g lipid in laboratory personnel; up to 0.80 ng/g lipid in circuit board producers; up to 1.8 ng/g lipid in computer technicians; 0.76 ng/g lipid in smelter workers; and 1.1-3.8 ng/g lipid in electronics dismantlers.

Toxicological Data

Human Studies: In several patch tests with human subjects, TBBPA was non-irritating and non-sensitizing. In one study, TBBPA (3-5 mg [6-9 µmol]) was applied ten times to the upper arms of 54 volunteers during a sensitization phase, followed by a modified Draize multiple insult test ten to 14 days later. In a similar study, 50 human subjects were patch-tested nine times with Firemaster® PHT4 (dose not provided) on the upper arm (males) or the upper back, shoulder area (females), followed 12 days later by a single challenge patch on a site adjacent to the induction site. When TBBPA as a 1% mixture with Vaseline® petroleum jelly was applied under occlusion to the skin of three individuals for two days, no skin reaction occurred.

Chemical Disposition, Metabolism, and Toxicokinetics: In Sprague-Dawley rats, ^{14}C-TBBPA (single oral dose; 6.51-7.55 mg/kg [0.0120-0.0139 mmol/kg] body weight) was poorly absorbed from the gastrointestinal tract. At 72 hours, ~95% was eliminated in the feces and <1.1% in the urine. The highest concentrations were found in the liver and the gonads; maximum half-life in any tissue was less than three days. Recent studies using bile-duct cannulated rats have shown that TBBPA is readily absorbed. Oral administration of ^{14}C-TBBPA (2.0 mg/kg [3.7 nmol/kg]) for three days produced three conjugated metabolites in the bile—a diglucuronide, a monoglucuronide, and a glucuronide-sulfate ester (34, 45, and 21%, of the radioactivity excreted during the first 24 hours, respectively). Within 72 hours, 71.3% of the administered dose was excreted in the bile and 26.7% in the feces. In uncannulated rats, 91.7% was

excreted in the feces as TBBPA, and about 2% remained after 72 hours. In pregnant rats, oral administration of ^{14}C-TBBPA (dose not provided) on gestation days 10 through 16 resulted in the excretion of 79.8% of radioactivity in feces. In dams 0.83% of the total administered dose was found in the tissues, while in fetuses the amount was 0.34%. Highest maternal levels were seen in the carcass (0.37%) and liver (0.26%).

In another rat study, a single intraperitoneal dose of ^{14}C-TBBPA (250 or 1000 mg/kg [0.460 or 1.839 mmol/kg] body weight) produced a radioactivity level in erythrocytes that was ten times higher than in plasma after 72 hours. Within the first hour after administration, highest concentrations were found in the fat tissue, followed by liver, sciatic nerve, muscles, and adrenals. After 72 hours, 51-65% of the dose was excreted in the feces and 0.3% in the urine, while about 20% was retained.

Acute Toxicity: The high LD_{50} and LC_{50} values for mice, rats, guinea pigs, and rabbits indicate that the acute toxicity of TBBPA is low. For the mouse and guinea pig, LC_{50} values were >500 mg/m^3 (22.5 ppm), while for the rat, it was >10,920 mg/m^3 (490.88 ppm). Oral LD_{50} values for mice and rats were >2000 mg/kg, while an LD_{50} >50,000 mg/kg (92 mmol/kg) was calculated for the rat via intubation. Dermal LD_{50} values >1000 mg/kg (2 mmol/kg) were reported for rabbits and guinea pigs. The intraperitoneal LD_{50} values were ≥3200 mg/kg (5.883 mmol/kg) for the mouse and rat.

Short-term or Subchronic Toxicity: In mice, oral administration of TBBPA (up to 4900 mg/kg [9.009 mmol/kg]) in the diet for three months caused no adverse effects. A higher dose (15,600 mg/kg [28.681 mmol/kg] caused decreases in body weight, hemoglobin, hematocrit, red blood cells, serum proteins, and serum triglyceride and an increase in spleen weight.

In rats, inhalation of micronized TBBPA (up to 18 mg/L [810 ppm]) for four hours per day, five days per week for two weeks produced excess salivation, excess lacrimation, and nasal discharge. Females exhibited decreased relative liver weights; at 8 mg/L (360 ppm) they had increased relative adrenal and thyroid weights.

TBBPA (375, 750, or 1125 mg/kg [0.689, 1.38, or 2.068 mmol/kg]) administered intragastrically daily for seven days produced a decreased glutathione (GSH) level at the mid and high doses in female rats and an increased malondialdehyde (MDA) level at the high dose in male rats. In contrast, the activity of 5-aminolevulinate dehyratase (ALA-D) was affected oppositely for both sexes. A 28-day study using TBBPA (10, 50, or 250 mg/kg [0.018, 0.092, 0.460 mmol/kg]) daily on females only caused a systemic increase in GSH and MDA at the medium dose, while 5-aminolevulinate synthase (ALA-S) activity had a decreasing tendency at the high dose during the observation period. Significant changes with regard to indicators of porphyrogenic action suggested that TBBPA is capable of disturbing the heme metabolism in the animals. Oral administration of TBBPA (up to 1000 mg/kg [1.839 mmol/kg] per day for up to 90 days) produced no adverse effects.

TBBPA (up to 2500 mg/kg [4.596 mmol/kg] body weight) applied for three weeks to the clipped and abraded skin of rabbits produced slight erythema. At double the dose (5000 mg/kg [9.193 mmol/kg]), moderate desquamation and loss of body weight prior to death occurred. Pale liver, accentuated liver lobulation, and gastric irritation were also observed in several animals in this group. In the rabbit ear assay, TBBPA (0.5-50% in Polylan) applied for four weeks was not chloracnegenic.

Reproductive and Teratological Effects: TBBPA (doses up to 2.5 g/kg [4.6 mmol/kg] body weight) given to rats via gavage on gestation days 0-19 produced no signs of toxicity, including no abnormalities. Oral administration of TBBPA as SAYTEX®111 (2.5, 10.0, or 25.0 mg/kg [4.6, 18.4, or 46.0 µmol/kg]) on gestation days 6-15 was more toxic to the conceptus than to the dam. The embryo/fetal no-effect level was 2.5 mg/kg/day, while the maternal no-effect level was >25.0 mg/kg/day. At ≥10 mg/kg/day, dose-

dependent effects on the conceptuses were observed (e.g., increased resorption and delayed skeletal ossification). At the high dose, the effects were statistically significant, as compared with control. In another study, TBBPA as Firemaster® BP4-A (up to 10 g/kg [18.385 mmol/kg]) was not teratogenic in rats similarly exposed. Slight decreases in body weight gains were seen at the highest dose. The green-colored stools suggested an effect on bile pigment formation metabolism. When given to pregnant mice, TBBPA accumulated in the brains of unborn mice by passing through blood barriers to the fetus.

Genotoxicity: TBBPA (up to ≥10,000 µg/plate [18.385 µmol/plate]) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strain D4 in the presence and absence of metabolic activation. In human peripheral lymphocytes, TBBPA (1.5-200 µg/mL [2.8-368 µM]) failed to induce chromosome aberrations with and without metabolic activation.

Immunotoxicity: In several studies using guinea pigs, TBBPA was not a sensitizer. In one experiment, TBBPA (0.1% in 0.9% NaCl solution) was injected intradermally in the back and flanks of guinea pigs every other day three times per week for up to ten doses, followed by a challenge dose two weeks later.

No information regarding chronic toxicity, synergistic/antagonistic effects, cytotoxicity, or carcinogenicity was located.

Structure-Activity Relationships

2,2′,6,6′-Tetrabromo-3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl (TTDB)

In rats and rabbits, TTDB (doses not provided) is a possible irritant but is not a primary skin irritant, and is not toxic when applied dermal or orally (LD_{50} = 5 g/kg). In a 28-day oral study with rats, TTDB (1, 10, 100, and 1000 ppm) produced no changes in behavior, appearance, body weight or organ weights, food consumption, or gross or microscopic pathologic lesions.

Other TBBPA Structural Analogs

Unpublished health and safety studies of TBBPA bis(2-hydroxyethyl ether) have been submitted to EPA (i.e., Toxic Substances Control Act Test Submissions [TSCATS]). Reports include acute toxicity studies in mice, rats, guinea pigs, and rabbits; subchronic oral toxicity studies in rats; genetic toxicology studies in bacteria *in vitro*; and dermal exposure in humans of the substance either as the single chemical or a component of a mixture (e.g., Emery diol 1608-62R) tested separately from the mixture. TSCATS are also available for TBBPA allyl ether. The oral LD_{50} was >5 g/kg in rats, and the dermal LD_{50} was >2 g/kg in rabbits. The chemical was a mild irritant on the skin (at 500 mg) and in the eyes (at 100 mg) of rabbits.

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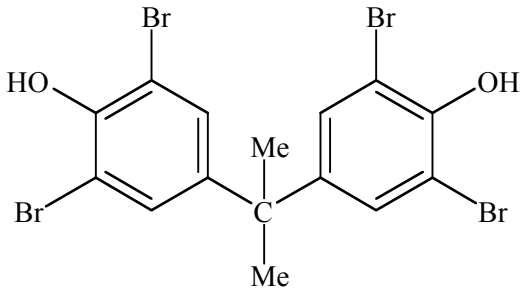
1.0 Nomination

Tetrabromobisphenol A (TBBPA) was nominated by the NIEHS for toxicological characterization including neurodevelopmental toxicity studies and carcinogenicity. The nomination is based on its high production volume, widespread human exposures, and suspicion to cause thyroid toxicity and thyroid tumors.

2.0 Introduction

Tetrabromobisphenol A (TBBPA)
[79-94-7]



2.1 Chemical Identification and Analysis

TBBPA ($C_{15}H_{12}Br_4O_2$, mol. wt. = 543.91) is also called the following:

BA59	Phenol, 4,4´-(isopropylidene(2,6-dibromo-
2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane	Phenol, 4,4´-(1-methylethylidene)bis(2,6-dibromo- (9CI)
2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane	Saytex 111
Bromdian	Saytex RB-100
FG 2000	Saytex RB-100 ABS
Fire Guard 2000	Saytex RB 100PC
Firemaster BP 4A	Tetrabrom
FR-1524	2,2´,6,6´-Tetrabromobisphenol A
Great Lakes BA-59P	3,3´,5,5´-Tetrabromobisphenol A
4,4´-Isopropylidenebis(2,6-dibromophenol)	3,5,3´,5´-Tetrabromobisphenol A
4,4´-Isopropylylidenebis(2,6-dibromophenol)	Tetrabromodian
4,4´-(1-Methylethylidene)bis(2,6-dibromophenol)	Tetrabromodiphenylopropane

Sources: HSDB (2001); IPCS/WHO (1995); RTECS (2000)

TBBPA can be detected by chromatographic methods coupled with mass spectrometry (MS) or other detectors. Brominated organic compounds from air, collected by use of a glass fiber filter and a high-volume air sampler, can be analyzed by gas-liquid chromatography (GLC)/MS/computer, GLC/electron capture detection (ECD), or thin-layer chromatography (TLC) (HSDB, 2001). Gas chromatography (GC) and GC/MS are used after conversion of TBBPA to the diethyl derivative by ethylation (IPCS/WHO, 1995). The Occupational Safety and Health Administration (OSHA) air sampling method for TBBPA is high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection (OSHA, 2001). TBBPA has been determined in human plasma using solid-phase extraction (SPE) and GC with electron-capture MS (ECMS) detection in the concentration range of 4-200 pg/g plasma; the estimated detection

limit was 0.8 pg/g plasma. The method has been applied in the analysis of plasma samples from potentially occupationally exposed individuals (Thomsen et al., 2001a).

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	White (colorless) crystalline powder	IPCS/WHO (1995)
Melting Point (^oC)	181-182	IPCS/WHO (1995)
Boiling Point (^oC)	~316	IPCS/WHO (1995)
Vapor Pressure (mm Hg @ 20 °C)	<1	IPCS/WHO (1995)
Specific Gravity	2.18	IPCS/WHO (1995)
Log P_{OW}	4.5	IPCS/WHO (1995)
Water Solubility (mg/L)	0.72 @ 15 °C 4.16 @ 25 °C 1.77 @ 35 °C	IPCS/WHO (1995)
Soluble in:	Methanol, ether, acetone, methylene chloride, toluene, benzene, and methyl ethyl ketone	CRCS, Inc. (1984); IPCS/WHO (1995)

TBBPA contains 58.7% bromine (IPCS/WHO, 1995). Under basic conditions, both hydroxyl groups of TBBPA react with epichlorohydrin to give the diglycidyl ether, which is widely used in epoxy resin formulations. When pyrolyzed in open quartz tubes for ten minutes, TBBPA produces polybrominated dibenzo-*p*-dioxins (PBDDs) and -furans (PBDFs) at 700 °C. At 800 °C the levels of the pyrolysis products increase; however, at 900 °C a decrease is found (HSDB, 2001). When used as a flame retardant, TBBPA contains <0.01 to 0.05 µg/kg PBDDs and <0.01 to 0.02 µg/kg PBDFs (Kurz, 1998).

2.3 Commercial Availability

TBBPA is commercially available as an epoxy resin grade and a higher quality polycarbonate grade (HSDB, 2001). It is produced by Albemarle Corporation (Magnolia, AR) and Great Lakes Chemical Corporation (El Dorado, AR) (SRI Int., 2001). In 1999, Albemarle Corporation's 50,000-metric ton plant produced TBBPA under the trade name SAYTEX® RB-100 flame retardant (58.5% bromine). Proprietary continuous process technology, which does not yield methyl bromide during production, is used to give a product with six sigma quality. The facility also makes the company's new SAYTEX CP-2000 flame retardant (Albemarle Corp., 1997, 1998; Chem. Mark. Rep., 1999b). By the end of 2002, Albemarle, through its joint venture with Arab Potash, will have added an annual TBBPA capacity of 37,500 metric tons (Mg) (82.7 million lb) to its facility in Safi, Jordan (Lerner, 2001).

3.0 Production Processes

TBBPA is produced by the bromination of bisphenol A in the presence of solvents, such as a halocarbon, water, 50% hydrobromic acid, aqueous alkyl monoethers, or aqueous acetic acid. When methanol is used, methyl bromide is formed as a co-product (IPCS/WHO, 1995).

4.0 Production and Import Volumes

TBBPA is a high production volume (HPV) chemical with U.S. annual production exceeding 1 million pounds (Environ. Defense, 2001). In 1997, a lower limit of 34,550 Mg and an upper limit of 48,140 Mg were reported (U.S. EPA, 1998b). Under the 1998 Inventory Update Rule

(IUR), an aggregate production volume ranging between >100 million lb (45,400 Mg) to 500 million lb (227,000 Mg) was reported (U.S. EPA, 2000b). In 1999, an estimated rise in demand of 8 to 9% per year was projected for TBBPA (a 145,000-metric ton market globally) (Chem. Mark. Rep., 1999a).

In 2001, a U.S. import volume for consumption of 1,132,750 kg (2,497,286 lb) was reported for TBBPA; all was imported from Israel. As mixtures of TBBPA-carbonate oligomers, dibromoneopentyl glycol, polydibromophenylene oxide, and electroplating chemical and electroless, a world total of 1,319,393 kg (2,908,764 lb) was reported. The two leading exporter countries were Canada and the Federal Republic of Germany, who exported 710,566 and 420,858 kg (1,566,530 and 927,833 lb), respectively, to the United States (ITA, 2001).

5.0 Uses

TBBPA is primarily used as a reactive flame retardant in epoxy resin circuit boards and more recently in electronic enclosures made of polycarbonate-acrylonitrile-butadiene-styrene (PC-ABS); approximately 90% is used in the manufacture of the resins (HSDB, 2001; IPCS/WHO, 1995). In encapsulations for integrated circuit chips, TBBPA is incorporated into the epoxy polymer structure after curing, resulting in no free TBBPA in the finished product (Philips Semiconductors, 2001). In addition to its use in polymers, general applications of TBBPA include its use as a flame retardant for plastics, paper, and textiles; as a plasticizer; in adhesives and coatings; and as a chemical intermediate for the synthesis of other flame retardants (e.g., TBBPA allyl ether, TBBPA bis(2-hydroxyethyl ether), TBBPA carbonate oligomers, and TBBPA diglycidyl ether). It has also been used as a fire-retardant additive (ABS, phenolic, unsaturated polyester resins) and as a fire-retardant polycarbonate comonomer (HSDB, 2001; IPCS/WHO, 1995). Additionally, TBBPA is applied to carpeting and office furniture (Gain, 1997).

6.0 Environmental Occurrence and Persistence

Production and use of TBBPA as a reactive flame retardant in epoxy resin circuit boards and electronic enclosures made of PC-ABS may result in the compound's release to the environment through waste streams. If released into water, TBBPA is expected to adsorb to suspended solids and sediment (based upon an estimated K_{OC} of 56,000). Volatilization from water surfaces, however, is not expected (based upon an estimated Henry's Law constant of 7.0×10^{-11} atm-m^3/mol). If released to air, TBBPA is expected to exist solely in the particulate phase (based on estimated vapor pressure of 1.8×10^{-11} mm Hg at 25 °C), which may then be removed by wet and dry deposition (HSDB, 2001). TBBPA has persistence half-life values ranging from 44-179 days in soil, 48-84 days in water, and 1-9 days in air (U.S. EPA, 1999a; cited by U.S. EPA, 2002a).

In soil, TBBPA is expected to be immobile (based upon the estimated K_{OC}), while in moist and dry soil surfaces, volatilization is not expected (based upon the estimated Henry's Law constant and estimated vapor pressure, respectively). Under anaerobic conditions, TBBPA is expected to undergo rapid primary degradation and slow mineralization in some soils. In three different anaerobic soils, biodegradation of TBBPA (10 mg/kg [0.018 mmol/kg]) resulted in 44 to 91% of the parent after 64 days (depending on the type and composition of the soil, temperature, and humidity). Only 0.03 to 0.35% of the radioactive compound was recovered as carbon dioxide.

In a sediment/water microbial test system using natural river sediment and water, a 56-day aerobic test showed biodegradation of TBBPA; half-lives ranged from 48 (10 µg/L [0.018 µM]) to 84 days (1000 µg/L [1.839 µM]). As above, mineralization was much slower with <8% mineralized during the period (HSDB, 2001; IPCS/WHO, 1995). A sequential anaerobic-aerobic process may completely degrade TBBPA (Ronen and Abeliovich, 2000). Under sewage treatment conditions, no biodegradation has been detected (IPCS/WHO, 1995).

Sediment collected from the Neya River in Japan contained ~20 µg/kg (0.037 µmol/kg) (dry weight) TBBPA, while marine sediments from estuaries in Osaka Bay contained 0.5-4.5 ppb (0.9-8.3 nmol/kg) TBBPA and river sediments from the bay contained 22-140 ppb. Marine sediments from other estuaries had levels between <0.5-1.8 ppb (HSDB, 2001). The sediment upstream and downstream from a Swedish plastics factory using TBBPA contained levels of 50 and 430 µg/kg, respectively; the dimethylated compound was found at concentrations of 36 and 2400 µg/kg, respectively (IPCS/WHO, 1995). In sewage sludge from treatment plants, TBBPA ranged from 2.9 to 76 ng/g dry weight (de Wit, 2000).

Photodegradation of TBBPA in water by UV radiation had the following half-lives: 10.2 days in spring, 6.6 days in summer, 25.9 days in autumn, and 80.7 days in winter; cloud cover increased the times by a factor of two (IPCS/WHO, 1995). In the absence and presence of hydroxyl radicals, the main breakdown product of TBBPA photodegradation was 2,4,6-tribromophenol. Other decomposition products have been tentatively identified as di- and tri-bromobisphenol A; dibromophenol; 2,6-dibromo-4-(bromoisopropylene)phenol; 2,6-dibromo-4-(dibromoisopropyl-ene)phenol; and 2,6-dibromo-1,4-hydroxybenzene (Eriksson and Jakobsson, 1998; cited by de Wit, 2000).

Bioconcentration factors (BCFs) ranging from 20 to 3200 suggest that bioconcentration is generally moderate to high in aquatic organisms. In fish, a half-life of less than one day was observed, while in oysters, it was less than five days. During depuration, the majority of accumulated TBBPA and its metabolites was eliminated within three to seven days (HSDB, 2001; IPCS/WHO, 1995).

In 2000, off-site release for TBBPA totaled 537,549 lb (67..4% of total releases). On-site releases were reported as 197,529 lb (24.8%) to the land (other than Resource Conservation and Recovery Act [RCRA] subtitle C landfills) and 62,387 lb (7.8%) to the air. Production-related waste of TBBPA totaled 804,166 lb, of which 787,143 lb (97.9%) was released on- and off-site. Transfers off-site for further waste management and disposal totaled 546,096 lb, of which 537,549 lb (98.4%) was off-site transfers to disposal (U.S. EPA, 2002a).

7.0 Human Exposure

For the general population, exposure to TBBPA is possible from inhalation of ambient air and dermal contact with the compound (e.g., products made from polymers incorporating the TBBPA). In Southern Arkansas, a level of 1.8 µg/m^3 TBBPA was detected in air near production facilities (IPCS/WHO, 1995). From barber shops in El Dorado and Magnolia, AR (production sites), samples of human hair contained levels up to 2-5 µg/kg (HSDB, 2001). In the analysis of dust samples from Parliament buildings in eight countries, TBBPA was not a significant contaminant. Only in samples from a Dutch Parliament building was it present above

detection limits at 0.05 ppm (Santillo et al., 2001). In a study of samples of waste electric appliances, TV waste consisting of 420 µg/g TBBPA/ABS resin contained 2.4-1300 µg/g TBBPA in the casing and 500-520 µg/g TBBPA in the circuit board. In waste PC, the casing contained 2900 µg/g TBBPA, and in waste cellular phone, the amount of TBBPA was 28 µg/g (Sakai et al., 2001). In filings from a printed circuit board, approximately 700 ppm unreacted TBBPA per gram circuit board was found, corresponding to ~4 mg free TBBPA per gram of TBBPA used (Sellström and Jansson, 1995).

Ingestion of TBBPA is also a possible exposure route. In commercial drinking water stored in reusable polycarbonate containers, native TBBPA as well as brominated derivatives of the ^{13}C-bisphenol A (BPA) were detected. In two single carboy samples, ^{13}C-TBBPA was the major ^{13}C-BPA constituent (>85%) (Peterman et al., 2000). Additionally, TBBPA has been found in fish and shellfish. Samples from the Osaka area contained 0.8 and 4.6 µg/kg (wet weight) methylated TBBPA, respectively. TBBPA was not detected in any other fish samples collected from other locations in Japan. The dimethylated metabolite of TBBPA, however, was not found in fat samples collected from residents of Osaka (IPCS/WHO, 1995). The median level of TBBPA was 4500 pg/g lipid in the blood of Japanese adults; the maximum level was 12,000 pg/g lipid (Nagayama et al., 2001).

Occupational exposure to TBBPA may occur via dermal contact during its production or use in the workplace or via inhalation of dusts. The compound was found in the blood of computer technicians with a half-life of two days (Hagmar et al., 2000a,b; cited by Santillo et al., 2001). The following TBBPA levels in plasma have been found in different occupational groups: up to 0.52 ng/g lipid in laboratory personnel; up to 0.80 ng/g lipid in circuit board producers; up to 1.8 ng/g lipid in computer technicians; 0.76 ng/g lipid in smelter workers; and 1.1-3.8 ng/g lipid in electronics dismantlers (Hagmar et al., 2000a,b; cited by Hagmar and Bergman, 2001; Thomsen et al., 2001b). An ongoing increase in human exposure to brominated flame retardants, including TBBPA, has been observed. Analysis of archived samples from Norway (spanning the years 1986 to 1999) showed that serum levels of TBBPA ranged from 0.34-0.71 ng/g (0.63-1.3 pmol/g) lipid (Thomsen et al., 2002). In rooms containing computers and other electrical equipment, all air particulate samples contained TBBPA (Bergman et al., 1997; cited by de Wit, 2000). From the dismantling hall at a recycling plant for electronic products such as computer, TV sets, microwaves, and printers, an average concentration of 30 ng/m^3 (55 pmol/m^3) was detected in the air. Near the shredder at the dismantling plant, significantly higher levels (mean=140 ng/m^3 [257 pmol/m^3]) were detected. Other measurements were taken at an assembly of circuit boards (mean=0.20 ng/m^3 [0.37 pmol/m^3]), an office with computers (0.035 ng/m^3 [0.066 pmol/m^3]), a computer repair facility (0.035 ng/m^3 [0.064 pmol/m^3]), and a teaching hall (0.093 ng/m^3 [0.171 pmol/m^3]) (Sjödin et al., 2001). In its National Occupational Exposure Survey (NOES) (1981-1983), the National Institute for Occupational Safety and Health (NIOSH) estimated that 224 workers were potentially exposed to TBBPA in the United States (HSDB, 2001).

No significant concentrations of dioxins and furans have been found from TBBPA-containing plastics before and after the recycling process (Riess et al., 1999; cited by Miguel and Laboa, 2001). Studies have shown that printed circuit boards can also be recycled; circuit boards under

thermal stress in an oven generated low amounts of PBDDs/PBDFs (0.74-4.51 ng/g) (Lorenz and Bahadir, 1993).

8.0 Regulatory Status

TBBPA is listed in the Environmental Protection Agency (EPA) Toxic Substances Control Act (TSCA) Section 8(b) Chemical Inventory (RTECS, 2000). Under Section 8(d) of TSCA, manufacturers, importers, and processors of TBBPA are required to submit to EPA copies and lists of unpublished health and safety studies (40 CFR 716.120) (HSDB, 2001). In addition, persons who manufacture or import TBBPA must report the results of tests showing that the chemical substance has been tested for the presence of halogenated dibenzodioxins (HDDs) or dibenzofurans (HDFs) (40 CFR 766.35) (U.S. EPA, 2001). The reporting threshold for TBBPA for the Toxic Release Inventory (64 FR 58666, October 29, 1999; EPCRA Section 313) is 100 lb (U.S. EPA, 1999a,b, 2000a). Waste solids from TBBPA production are not listed as hazardous; wastewaters from the process, however, meet the existing listing description for K131 (Wastes from the Production of Methyl Bromide) (U.S. EPA, 1994). Although removed in 1994 when TSCA Section 4 Final Rule Making (FRM) testing was completed, TBBPA remains of Master Testing List concern with respect to monitoring and product analysis for poly-HDDs and -HDFs (U.S. EPA, 1996). As particulates not otherwise regulated (PNOR), the OSHA permissible exposure level time-weighted average (PEL TWA) is 15 mg/m^3 TBBPA; as particulates not otherwise specified (PNOS), the American Conference of Governmental Industrial Hygienists threshold limit value (ACGIH TLV) TWA is 10 mg/m^3 (Great Lakes Chem. Corp., 1999).

Under the 1990, 1994, and 1998 IUR, Ameribrom, Inc. and Great Lakes Chemical Corporation reported manufacture or importation of TBBPA. Additionally, Ethyl Corporation and Albermarle Corporation reported the data in 1990 and 1994, respectively. The chemical was available for sponsorship in the HPV Challenge Program (U.S. EPA, 1998a). However, because a complete set of Screening Information Data Sheet (SIDS)-level data is currently available, no testing is planned under the program (U.S. EPA, 2002b).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

TBBPA (3-5 mg [6-9 µmol]), as a thick paste-like slurry when mixed with water, applied ten times to the upper arms of 54 volunteers (13 males and 41 females; ages 18 to 74 years) during a sensitization phase, followed by a modified Draize multiple insult test (48-hour application of dose to a different site) 10 to 14 days later, did not produce skin irritation nor contact sensitization (U.S. EPA, 1978a). In a similar study, 50 human subjects (2 males and 48 females; ages 24 to 65 years) were patch-tested nine times with Firemaster® PHT4 (dose not provided; chemical evaluated as received) on the upper arm (males) or the upper back, shoulder area (females), followed 12 days later by a single challenge patch on a site adjacent to the induction site. Neither irritation reactions nor skin sensitization was observed (Ind. Bio-Test Labs, Inc., 1976). When TBBPA as a 1% mixture with Vaseline® petroleum jelly was applied under occlusion to the skin of three individuals for two days, no skin reaction occurred (Du Pont, 1972a).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In Sprague-Dawley rats, ^{14}C-TBBPA (single oral dose; 6.51-7.55 mg/kg [0.0120-0.0139 mmol/kg] body weight) was poorly absorbed from the gastrointestinal tract. At 72 hours, ~95% was eliminated in the feces and <1.1% in the urine. The highest concentrations were found in the liver and the gonads; maximum half-life in any tissue was less than three days (Brady, 1979; cited by IPCS/WHO, 1995). However, recent studies using bile-duct cannulated rats showed that TBBPA was readily absorbed. Oral administration of ^{14}C-TBBPA (2.0 mg/kg [3.7 nmol/kg] body weight) for three days produced three conjugated metabolites in the bile—a diglucuronide, a monoglucuronide, and a glucuronide-sulfate ester (34, 45, and 21%, of the radioactivity excreted during the first 24 hours, respectively). Within 72 hours, 71.3% of the administered dose was excreted in the bile and 26.7% in the feces. In uncannulated rats, 91.7% of the dose was excreted in the feces as TBBPA, and about 2% remained after 72 hours. Highest levels were found in the large intestine (1%), small intestine (0.6%), lung (0.2%), and carcass (not otherwise specified) (0.2%). Levels of TBBPA in the liver were <0.1% (Hakk et al., 2000; Larsen et al., 1998 [cited by de Wit, 2000]).

Oral administration of ^{14}C-TBBPA (dose not provided) to pregnant rats on gestation days 10 through 16 resulted in the excretion of 79.8% of radioactivity in feces. In dams 0.83% of the total administered dose was found in the tissues, while in fetuses the amount was 0.34%. Highest maternal levels were seen in the carcass (not otherwise specified) (0.37%) and liver (0.26%) (Meerts et al., 1999; cited by de Wit, 2000).

In another rat study, a single intraperitoneal dose of ^{14}C-TBBPA (250 or 1000 mg/kg [0.460 or 1.839 mmol/kg] body weight) produced a radioactivity level in erythrocytes that was ten times higher than in plasma after 72 hours. Within the first hour after administration, highest concentrations were found in the fat tissue, followed by liver, sciatic nerve, muscles, and adrenals. After 72 hours, 51-65% of the dose was excreted in the feces and 0.3% in the urine, while about 20% was retained in the rat (Szymanska et al., 2001).

9.1.3 Acute Exposure

Numerous companies have submitted studies with TBBPA under Section 8(e) of TSCA under the name Firemaster® PHT-4 (or FM PHT4) as well as the common trade name Firemaster® BP4-A. The use of the first term has led to confusion regarding the actual identity of the chemical substance with this name. For example, Velsicol Chemical Corporation identified Firemaster® PHT-4 as tetrabromophthalic anhydride in a pilot teratology study and used Firemaster® BP4-A for TBBPA in a separate identical study. In a letter to Velsicol, U.S. EPA (1979) noted that "the implication in the submitter's transmittal letter that all of the submitted information concerns FM PHT4 (tetrabromo bisphenol A) is incorrect" (regarding 8EHQ-0678-0185). In the following sections, the actual compound name reported by the authors was used.

Acute toxicity values for TBBPA are presented in **Table 1**.

Table 1. Acute Toxicity Values for TBBPA

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
inh	Mouse (sex and strain n.p.)	LC_{50} >500 mg/m^3 (22.5 ppm)	RTECS (2000)
	Rat (sex and strain n.p.)	LC_{50} >10,920 mg/m^3 (490.88 ppm)	
	Guinea pig (sex and strain n.p.)	LC_{50} >500 mg/m^3 (22.5 ppm)	
oral	Mouse (M, B6C3F$_1$)	LD_{50} = 4.4 g/kg (8.1 mmol/kg)	Sekizawa (1994 [personal communication]; cited by IPCS/WHO, 1995)
	Mouse (F, B6C3F$_1$)	LD_{50} = 4.5 g/kg (8.3 mmol/kg)	
	Mouse (sex and strain n.p.)	LD_{50} = 10 g/kg (18 mmol/kg) bw	IPCS/WHO (1994)
	Mouse (sex and strain n.p.)	LD_{50} = 3.2 g/kg (5.9 mmol/kg) bw	Eastman Kodak Co. (1973); Gustafsson and Wallen (1988; cited by IPCS/WHO, 1995)
	Rat (sex and strain n.p.)	LD_{50} >2 g/kg (4 mmol/kg) bw	
	Rat (sex and strain n.p.)	LD_{50} >5 g/kg (9 mmol/kg) bw	Hardy (1994; cited by IPCS/WHO, 1995)
int	Rat (M and F, Wistar)	LD_{50} >50,000 mg/kg (92 mmol/kg)	Great Lakes (1984; cited by CRCS, Inc., 1984)
dermal	Guinea pig (sex and strain n.p.)	LD_{50} >1 g/kg (2 mmol/kg) bw	Bayer (1990; cited by IPCS/WHO, 1995)
	Rabbit (sex and strain n.p.)	LD_{50} >2000 mg/kg (4 mmol/kg)	Hardy (1994; cited by IPCS/WHO, 1995)
	Rabbit (sex and strain n.p.)	LD_{50} >3160 mg/kg (5.810 mmol/kg)	RTECS (2000)
i.p.	Mouse (sex and strain n.p.)	LD_{50} >3200 mg/kg (5.883 mmol/kg)	Eastman Kodak Co. (1973)
	Rat (sex and strain n.p.)	LD_{50} = 3200 mg/kg (5.883 mmol/kg)	

Abbreviations: bw = body weight; F = female; h = hour(s); inh = inhalation; int = intubation; i.p. = intraperitoneal(ly); LC_{50} = concentration lethal to 50% of test animals; LD_{50} = lethal dose for 50% of test animals; M = male; n.p. = not provided

Inhalation

Mice, rats, and guinea pigs exposed to TBBPA aerosol (up to 0.5 mg/L [22 ppm]) for up to eight hours showed no symptoms of local or systemic toxicity and no gross findings at autopsy (Dow Chem. Co., 1975; Great Lakes, 1984 [cited by CRCS, Inc., 1984]; Sterner, 1967 [cited by IPCS/WHO, 1995]). When exposed to a higher concentration of TBBPA (10.92 mg/L [10,920 mg/m^3 or 490.88 ppm]) for four hours, rats displayed decreased motor activity, eye squint, and slight dyspnea and erythema (Velsicol, 1978c; cited by CRCS, Inc., 1984). [This study is identical to that using FM PHT4 (micronized) by IRDC (1974a).]

Oral Administration

In rats, a single oral dose of TBBPA (5000 mg/kg [9.193 mmol/kg]) produced no mortality and no gross lesions at necropsy (Hardy, 1994; cited by IPCS/WHO, 1995). Rats intubated with TBBPA as a 50% suspension in 0.25% aqueous methyl cellulose (50,000 mg/kg [91.927 mmol/kg]) also exhibited no significant pathological lesions (Great Lakes, 1984; cited by CRCS, Inc., 1984).

Dermal Application
In rats and rabbits, TBBPA (up to 500 mg [0.919 mmol]) applied to the intact, shaven, and/or abraded skin for 24 hours was not a primary irritant (Bayer, 1990; Hardy, 1994 [both cited by IPCS/WHO, 1995]; Velsicol, 1978c [cited by CRCS, Inc., 1984]). When applied to the clipped intact skin of rabbits and guinea pigs at concentrations up to 3.16 g/kg (5.81 mmol/kg) for 24 hours, no local or systemic symptoms of toxicity were found (Great Lakes, 1984; cited by CRCS, Inc., 1984). However, at a dose of 2000 mg/kg (3.677 mmol/kg), one rabbit had slight erythema and edema on day 1 (Hardy, 1994; cited by IPCS/WHO, 1995). At 200 mg/kg (0.368 mmol/kg), female rabbits showed reddening of the skin, which disappeared within 48 hours. At 4640 and 10,000 mg/kg (8.531 and 18.385 mmol/kg) body weight, weight loss was seen, and at 1000 and 4640 mg/kg (1.839 and 8.531 mmol/kg), one rabbit from each group died (Bayer, 1990; cited by IPCS/WHO, 1995).

Studies using undiluted material on intact or abraded skin of rabbits found TBBPA not irritating. A 10% solution in Dowanol DPM on abraded skin was also nonirritating; however, erratic hyperemia occurred during week 1 and exfoliation during week 2 in the ear and slight to moderate hyperemia and exfoliation manifested during week 2 of application to the belly (Dow Chem. Co., 1975).

A 24-hour topical application of TBBPA (moistened slightly with water; dose not provided) to the skin of guinea pigs produced slight skin irritation; the LD_{50} of skin absorption was >1 g/kg (2 mmol/kg) (Eastman Kodak Co., 1973).

Eye Application
A single application of TBBPA (dose given as 3 mg [6 µmol] in one study) into the conjunctival sac of the eyes of albino rabbits had no effects on the cornea, iris, or conjunctiva. In addition, no effects on appearance, behavior, and body weight gain were found, as well as no signs of systemic toxicity nor any gross findings at autopsy (Greak Lakes, 1984 [cited by CRCS, Inc., 1984]; Hardy, 1994; Sterner, 1967 [both cited by IPCS/WHO, 1995]). At a higher dose, TBBPA (100 mg [0.184 mmol]) was an eye irritant in the animals (Velsicol, 1978c; cited by CRCS, Inc., 1984). In another study, TBBPA (dose not provided) produced slight irritation (slight erythema on the nictitating membrane) (Eastman Kodak Co., 1973). FM PHT4 (micronized) was an eye irritant in albino rabbits (IRDC, 1974b).

9.1.4 Short-term and Subchronic Exposure

Details of the following studies are presented in **Table 2**.

In mice, oral administration of TBBPA (up to 4900 mg/kg [9.009 mmol/kg]) in the diet for three months caused no adverse effects. A higher dose (15,600 mg/kg [28.681 mmol/kg], however, caused decreases in body weight, hemoglobin, hematocrit, red blood cells, serum proteins, and serum triglyceride and an increase in spleen weight (Tobe et al., 1986; cited by IPCS/WHO, 1995).

In rats, inhalation of micronized TBBPA (up to 18 mg/L [810 ppm]) for four hours per day, five days per week for two weeks produced excess salivation, excess lacrimation, and nasal discharge. At all doses, females exhibited decreased relative liver weights; at 8 mg/L (360 ppm),

Table 2. Short-term and Subchronic Exposure to TBBPA (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, outbred IMP:Wist, age n.p., 4-5F per group	TBBPA, purity n.p.	i.g.; 10, 50, or 250 mg/kg (0.018, 0.092, or 0.460 mmol/kg) per day for 7, 14, 21, or 28 days; killed 24 h after last dose	At the high dose, body weight was lowered by 5% compared to controls during the first 2 wk and by 10% in the next 2 wk; this was insignificant. GSH levels initially decreased after the first 7 days and then increased throughout the rest of the exposure period. At the low and high doses, MDA increased beginning on day 14. For the mid dose, the increase was seen throughout the experiment. ALA-D activity increased during the first 2 wk and then decreased. In contrast, ALA-S activity had a decreasing tendency, while □-GT activity and ALT levels fluctuated. ALA-U concentration in the urine significantly increased in wk 2 with the high dose. HO_x activity doubled in wk 1 and 3; at the low dose, the lowest activity occurred on day 14. Urinary porphyrin concentrations had an increasing tendency in a rather irregular fashion. Individual porphyrins were excreted in the following order: hexa- < penta- < hepta- < octa- <tetracarbosyporphyrins.	Szymanska et al. (2000)
Rats, Charles River CD, age n.p., 25M and 25F	TBBPA, purity n.p.	oral; 1, 10, 100, or 1000 mg/kg (0.002, 0.018, 0.184, 1.839 mmol/kg) (corresponding to 0.05, 0.5, 5, or 50 mg/kg bw/day, respectively) for 28 days. After 4 wk, 5 rats/sex/group were sacrificed; the remaining rats were placed on control diets for 2, 6, or 12 wk	No effects on behavior, appearance, food consumption, and bw gain, and no gross or microscopic abnormalities were observed. No differences in bromine contents in the liver and fat from the high-dose group and control group were seen. At 10 mg/kg, 1F died during the experiment.	Goldenthal and Geil (1972; cited by IPCS/WHO, 1995); Great Lakes (1984; cited by CRCS, Inc., 1984)
Rats, Sprague-Dawley, 6- to 7-wk old, 7M and 7F per dose group, except 3 mg/kg group which had 21M and 21F	TBBPA, purity n.p.	oral; 0.3, 3, 30, or 100 mg/kg (0.6, 6, 55, or 184 µmol/kg) per day in the diet for 90 days; killed on day 90	No toxicological effects (e.g., appearance, behavior, bw gain, hematology, and gross and microscopic examinations) were observed. In F given the high dose, a slight but statistically significant decrease in PCV and SGPT activity were seen; these changes were not regarded as toxicologically significant. There were no differences in total bromine content in tissues (liver, kidneys, skeletal muscle, fat, and serum) of rats receiving 3 mg/kg/day and the controls.	Dow Chem Co. (1975)

Table 2. Short-term and Subchronic Exposure to TBBPA (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rabbits, New Zealand white, age n.p., 4M and 4F per group	TBBPA, purity n.p.	dermal; 100, 500, or 2500 mg/kg (0.184, 0.919, or 4.596 mmol/kg) bw to the clipped, abraded skin of the back for 6 h/day, 5 days/wk for 3 wk	At the low dose, occasional very slight erythema was observed. At ≥500 mg/kg, almost all rabbits showed erythema for various lengths of time.	Goldenthal et al. (1979; cited by IPCS/WHO, 1995)
Rabbits, New Zealand white, age n.p., 3M and 3F per group	TBBPA (called FM PHT4 [micronized] in IRDC report), purity n.p.	oral, 50, 500, or 5000 mg/kg (0.092, 0.919, or 9.193 mmol/kg) per day 5 days/wk for 4 wk	In all rabbits, very slight to moderate erythema was observed. At the high dose, moderate desquamation was noted in 3 rabbits, and all had loss of bw prior to death. On day 14, 1 rabbit of this group showed a moderate increase in urea nitrogen. On day 26, the 1 surviving rabbit at the high dose showed a neutrophilia with a lymphopenia, nucleated erythrocytes, significant increases in glucose and urea nitrogen, and albumin in the urine. Pale liver, accentuated liver lobulation, and gastric irritation were also observed in several animals in the high-dose group. Microscopically, a slight hyperkeratosis at the application site was found in 1 rabbit given the mid dose.	IRDC (1975a); Velsicol (1978c; cited by CRCS, Inc., 1984)
Rabbits, strain n.p., age n.p., 2M and 2F	TBBPA, purity n.p.	inuncted in one ear; 0.5, 5, or 50% in Polylan 1x/day, 5 days/wk for 4 wk; observed at time 0 and on days 7, 14, 21, and 28	At 5 and 50%, no chloracnegenic activity was seen. At the low dose, 1 rabbit showed a slight response (grade 1) on day 7. No gross lesions were found at necropsy.	Hardy (1994; cited by IPCS/WHO, 1995)

Abbreviations: ALA-D = 5-aminolevulinate dehyratase; ALA-S = 5-aminolevulinate synthase; ALA-U = 5-aminolevulinic acid; ALT = alanine aminotransaminase; bw = body weight; F = female(s); GSH = glutathione; -GT = gamma-glutamyltransferase; h = hour(s); HO_x = heme oxygenase; i.g. = intragastric; inh = inhalation; M = male(s); MDA = malondialdehyde; mo = month(s); n.p. = not provided; PCV = packed cell volume; SGPT = serum glutamic pyruvic transaminase; wk = week(s)

they had increased relative adrenal and thyroid weights (Goldenthal et al., 1975 [cited by IPCS/WHO, 1995]; Great Lakes, 1984; Velsicol, 1975b [both cited by CRCS, Inc., 1984]; IRDC, 1975b).

TBBPA (375, 750, or 1125 mg/kg [0.689, 1.38, or 2.068 mmol/kg]) administered intragastrically to rats daily for seven days produced a decreased glutathione (GSH) level at the mid and high doses in females and an increased malondialdehyde (MDA) level at the high dose in males. In contrast, the activity of 5-aminolevulinate dehyratase (ALA-D) was affected oppositely for both sexes. A 28-day study using TBBPA (10, 50, or 250 mg/kg [0.018, 0.092, 0.460 mmol/kg]) daily on female rats only caused a systemic increase in GSH and MDA at the medium dose, while 5-aminolevulinate synthase (ALA-S) activity had a decreasing tendency at the high dose during the observation period. Significant changes with regard to indicators of porphyrogenic action suggested that TBBPA is capable of disturbing the heme metabolism in the animals (Szymanska et al., 2000).

Oral administration of TBBPA to rats (up to 1000 mg/kg [1.839 mmol/kg] per day for up to 90 days) produced no adverse effects (Dow Chem. Co., 1975; Goldenthal and Geil, 1972 [cited by IPCS/WHO, 1995]; Great Lakes, 1984 [cited by CRCS, Inc., 1984]).

TBBPA (up to 2500 mg/kg [4.596 mmol/kg] body weight) applied for three weeks to the clipped and abraded skin of rabbits produced slight erythema (Goldenthal et al., 1979; cited by IPCS/WHO, 1995). At double the dose (5000 mg/kg [9.193 mmol/kg]), moderate desquamation and loss of body weight prior to death occurred. Pale liver, accentuated liver lobulation, and gastric irritation were also observed in several animals in this group (IRDC, 1975a; Velsicol, 1978c [cited by CRCS, Inc., 1984]). In the rabbit ear assay, TBBPA (0.5-50% in Polylan) applied for four weeks was not chloracnegenic (Hardy, 1994; cited by IPCS/WHO, 1995).

9.1.5 Chronic Exposure
No data were available.

9.1.6 Synergistic/Antagonistic Effects
No data were available.

9.1.7 Cytotoxicity
No data were available.

9.2 Reproductive and Teratological Effects
The details of the following studies are presented in **Table 3**.

TBBPA (doses up to 2.5 g/kg [4.6 mmol/kg] body weight) given to rats via gavage on gestation days 0-19 produced no signs of toxicity, including no abnormalities (BFRIP, 2001; Noda, 1985 [cited by IPCS/WHO, 1995]). Oral administration of TBBPA as SAYTEX®111 (2.5, 10.0, or 25.0 mg/kg [4.6, 18.4, or 46.0 µmol/kg]) on gestation days 6-15 was more toxic to the conceptus than to the dam. The embryo/fetal no-effect level was 2.5 mg/kg/day, while the maternal no-effect level was >25.0 mg/kg/day. At ≥10 mg/kg/day, dose-dependent effects on the conceptuses were observed: reduced average fetal body weight, increased resorption, fetal malformation, and

Table 3. Reproductive Toxicity and Teratology Studies with TBBPA

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, CD®, age and number n.p., F	TBBPA, purity n.p.	Oral (via gavage); 100, 300, or 1000 mg/kg [0.184, 0.552, or 1.839 mmol/kg] per day on gd 0-19	No toxicological effects were observed. The NOAEL for maternal and developmental toxicity was 1000 mg/kg day.	BFRIP (2001)
Rats, strain, age, and number n.p., F	TBBPA, purity n.p.	oral (via gavage); 0.28, 0.83, or 2.5 g/kg (0.51, 1.5, or 4.6 mmol/kg) bw on gd 0-19	Birth rate was not impaired. Embryo and fetus had no toxic effects; there were no skeletal or visceral abnormalities. Postnatal development was not impaired.	Noda (1985; cited by IPCS/WHO, 1995)
Rats, Charles River Crl:COBS®CD®(SD)BR, ~113-days old (at gd 0), 25 F per group	SAYTEX®111, purity n.p.	oral (via gavage); 2.5, 10.0, or 25.0 mg/kg (4.6, 18.4, or 46.0 µmol/kg) per day (given at a dosage volume of 5 mL/kg/day [0.5, 2.0, or 5.0 mg/mL]) on gd 6-15, sacrificed on gd 20	At the high dose, overall average maternal bw gain was significantly decreased during gd 0-20 compared to controls (100.9 g vs. 129.9 g, respectively). There was a significant increase in resorption (embryo and fetal death) and a significant decrease in average live litter size, compared with control values. At the high dose, there were significant increases in the litter incidences of fetuses with enlarged heart and rear limb malformation (shortened, bent, and/or incompletely ossified femur, tibia, and/or fibula); with significant delays in ossification of the skull, vertebrae, ribs, and pelvis; with delayed brain development (slight dilation of the lateral ventricles); and with malformed and incompletely ossified scapulae. There were also significant delays in the average number of ossified sacral and caudal vertebrae, manubrium, sternal and xiphoid centers, metacarpals, metatarsals, and forepaw and hindpaw phalanges. At ≥10.0 mg/kg/day, average fetal bw per litter were decreased; fetal bw averaged 3.38, 3.34, 3.25, and 2.10 g at 0, 2.5, 10.0, and 25.0 mg/kg/day. At all doses, M fetuses weighed more than F fetuses.	ICI Americas, Inc. (1985)
Rats, Charles River CD, ~15-wk-old (time of mating), 5F per group	TBBPA (called Firemaster® BP4-A by Velsicol), purity n.p.	oral (via gavage); 30, 100, 300, 1000, 3000, or 10,000 mg/kg (0.055, 0.184, 0.552, 1.839, 5.516, or 18.385 mmol/kg) per day (volumes of 10 mL/kg/day for all except the high dose, which was 20 mL/kg/day) on gd 6-15; sacrificed on gd 20	At ≤3000 mg/kg/day, no effects in appearance, behavior, or bw were observed. At all doses, there were no differences in the mean number of viable or nonviable fetuses, resorptions, implantation, or corpora lutea when compared to controls. At the high dose, slight decreases in bw gains occurred between gd 6 and 15. Rats had green, soft stool and an increase in matted hair in the anogenital area. Three rats died at this dose. [U.S. EPA (1978b) found the study "deficient."]	IRDC (1978); Velsicol Chem. Corp. (1978b)

Table 3. Reproductive Toxicity and Teratology Studies with TBBPA (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Charles River CD, ~12-wk-old (time of mating), 5F per group	Firemaster® PHT-4 (identified as tetrabromophthalic anhydride in report), purity n.p.	oral (via gavage); 30, 100, 300, 1000, 3000, or 10,000 mg/kg (0.055, 0.184, 0.552, 1.839, 5.516, or 18.385 mmol/kg) per day (given at a dose volume of 25 mL/kg/day) on gd 6-15; sacrificed on gd 20	At ≤3000 mg/kg/day, there were no changes in appearance, behavior, or maternal bw. There were no effects on the number of viable or nonviable fetuses, resorptions, implantations, and corporal lutea. At the high dose, all rats had staining of the anogenital area and red nasal and/or oral discharge after day 3 of treatment. By gd 14, 4 of 5 rats were dead; the surviving rat was pregnant at sacrifice.	Velsicol Chem. Corp. (1978a)

Abbreviations: bw = body weight(s); F = female(s); gd = gestation day(s); M = male(s); NOAEL = no observable adverse effect level; n.p. = not provided; TD_{Lo} = toxic dose, low; wk = week(s)

delayed skeletal ossification. At the high dose, the effects were statistically significant, as compared with control. At ≥100 mg/kg/day, maternal body weight gain was inhibited, while doses ≥500 mg/kg/day resulted in death (ICI Americas, Inc., 1985).

In another study, TBBPA as Firemaster® BP4-A (up to 10 g/kg [18.385 mmol/kg]) was not teratogenic in rats exposed on gestation days 6-15. Slight decreases in body weight gains were seen at the highest dose. The green-colored stools suggested an effect on bile pigment formation metabolism (IRDC, 1978; Velsicol Chem. Corp., 1978a,b).

When given to pregnant mice, TBBPA accumulated in the brains of unborn mice by passing through blood barriers to the fetus by binding to a carrier protein in the blood [study details not provided] (Brouwer, 1998a).

9.3 Carcinogenicity
No data were available.

9.4 Initiation/Promotion Studies
No data were available.

9.5 Anticarcinogenicity
No data were available.

9.6 Genotoxicity
TBBPA (up to ≥10,000 µg/plate [18.385 µmol/plate]) was not mutagenic in *Salmonella typhimurium* strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strains D3 or D4 in the presence and absence of metabolic activation (Brusick, 1976; Great Lakes Chem. Corp., 1986 [both cited by IPCS/WHO, 1995]; Dow Chem. Co., 1976a; Ethyl Corp., 1981a,b; Litton Bionetics, Inc., 1976, 1977a,b; Mortelmans et al., 1986; SRI Int., 1976; Velsicol Chem. Corp., 1978c). In human peripheral lymphocytes, TBBPA (1.5-200 µg/mL [2.8-368 µM]) failed to induce structural and numerical chromosome aberrations in the presence and absence of an Aroclor-induced S9 activation system (BFRIP, 2001).

9.7 Cogenotoxicity
No data were available.

9.8 Antigenotoxicity
No data were available.

9.9 Immunotoxicity
TBBPA (0.1% in 0.9% NaCl solution) injected intradermally in the back and flanks of guinea pigs every other day three times per week for up to ten doses, followed by a challenge dose two weeks later, produced no sensitization (Dean et al., 1978b; cited by IPCS/WHO, 1995). [Note: This study appears to be the report cited as Velsicol (1978c) by CRCS, Inc. (1984), which stated that based upon the results, TBBPA was considered a "probable sensitizing agent in man."] Other studies (details not provided) using guinea pigs also showed that TBBPA was not a sensitizer (Eastman Kodak Co., 1973; Hardy, 1994 [cited by IPCS/WHO, 1995]).

9.10 Other Data

Effects on Cellular Membranes

Incubation of erythrocytes with TBBPA (25-250 µM [14-136 µg/mL]) resulted in K^+ release from normal to cup-formed cells and then spherocytes; hemolysis of the cells occurred when the permeability of the membranes was altered. It also induced K^+ release from isolated mitochondria. At >50 µM (27 µg/mL), it increased state 4 respiration and decreased state 3 respiration, resulting in a decrease of respiratory control and oxidative phosphorylation. At <100 µM (54.4 µg/mL), it acted as a respiratory inhibitor. TBBPA inhibited Ca^{2+} accumulation in isolated mitochondria accompanied by oxygen uptake and stimulated mitochondrial latent ATPase activity (Inouye et al., 1979; cited by HSDB, 2001 and IPCS/WHO, 1995).

Effects on Liver Microsomes

TBBPA caused a slight but significant increase in cytochrome P450 of liver microsomes (Lundberg, 1980; cited by HSDB, 2001). In a comparative *in vivo* study of rat liver aryl hydrocarbon hydrocylase (AHH) activity induction, TBBPA (500 mg/kg [0.919 mmol/kg]) generated an AHH activity level of 615 pmol of hydroxylated products (3-hydroxy-benz[a]pyrene) formed/mg protein (Clayton and Clayton, 1994; cited by HSDB, 2001).

Effects on Thyroid Hormones

TBBPA is structurally similar to the thyroid hormone thyroxine (T4) (Peterman et al., 2000). TBBPA has been observed to compete with the thyroid hormone T4 for transthyretin (TRR) binding sites and to reduce overall serum levels of thyroid hormones (Darnerud and Sinjari, 1996; Meerts et al., 1998 [both cited by Santillo et al., 2001]; Brouwer, 1998a; Meerts et al., 2000). TBBPA had the highest potency of all brominated and chlorinated substances tested so far; it was up to 25 times more potent in binding to human transthyretin than T4 (Brouwer, 1998b; cited by de Wit, 2000). When pregnant rats were given ^{14}C-labelled TBBPA on days 10 to 16 of gestation, no effects were seen on total T4, free T4, or total triiodothyronine (T3) levels in dams or fetuses. In the fetuses, thyroid-stimulating hormone increased significantly in the plasma by 196%, but in dams, no such effect was seen. Therefore, TBBPA was concluded to not bind to transthyretin *in vivo* (Meerts et al., 1999; cited by de Wit, 2000).

Estrogen-like Properties

In the estrogen-dependent human breast cancer cell line MCF-7, TBBPA competed with 17β-estradiol for binding to the estrogen receptor. When cells were incubated in 100% serum, TBBPA had a significantly lower access to the estrogen receptors versus incubation in serum-free medium, indicating the compound's strong binding to serum proteins. Furthermore, TBBPA induced proliferation in the cells; however, it did not induce maximal cell growth, signifying cytotoxic effects at high concentrations (Samuelsen et al., 2001). The estrogenic potency of TBBPA was five to six orders of magnitude lower than that of 17β-estradiol (Koerner et al., 1998; cited by HSDB, 2001).

In avian embryos, TBBPA caused high embryo mortality at up to 45 µg/g egg in quail and chicken but no estrogen-like effects. Maternal transfer of labeled TBBPA to the egg was low (Berg et al., 2001; Halldin et al., 2001).

Miscellaneous Studies

In NMRI male mice, TBBPA (0.75 or 11.5 mg/kg [1.4 or 21.2 µmol/kg] body weight) given orally as a single dose on postnatal day 10 produced no clinical signs of dysfunction and no significant changes in body weight gain. At two and four months after neonatal exposure, no significant changes in locomotion, rearing, and total activity were seen, as compared with controls. There were also no changes in habituation capability and no effect on learning and memory functions (Eriksson et al., 2001).

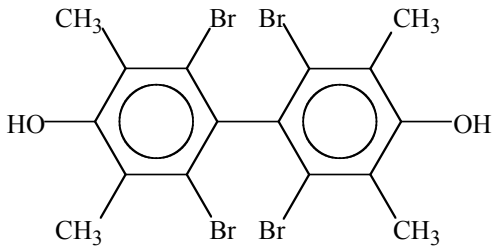
In SPD8 and SP5 assay systems, TBBPA (study details, including doses, not provided) produced no statistically significant increases in recombination frequency (Helleday et al., 1999).

TBBPA Derivatives

IPCS/WHO (1995; available at http://www.inchem.org/documents/ehc/ehc/ehc172.htm) provides general information and toxicological studies regarding the following TBBPA derivatives: TBBPA dimethyl ether [37853-61-5], TBBPA dibromopropyl ether [21850-44-2], TBBPA bis(allyl ether) [25327-89-3], TBBPA bis(2-hydroxyethyl ether) [4162-45-2], TBBPA brominated epoxy oligomer [no CASRN available], and TBBPA carbonate oligomers [94334-64-2 for BC-52 and 71342-77-3 for BC-58].

10.0 Structure-Activity Relationships

2,2′,6,6′-Tetrabromo-3,3′,5,5′-tetramethyl-4,4′-dihydroxybiphenyl (TTDB)



In rats and rabbits, TTDB (doses not provided) is a possible irritant but is not a primary skin irritant, and is not toxic when applied dermal or orally (LD_{50} = 5 g/kg). In a 28-day oral study with rats, TTDB (1, 10, 100, and 1000 ppm) produced no changes in behavior, appearance, body weight or organ weights, food consumption, or gross or microscopic pathologic lesions (Liepins and Pearce, 1976).

Other TBBPA Structural Analogs

Other compounds structurally related to TBBPA, ranked by chemical similarity by the ChemIDplus System (http://chem.sis.nlm.nih.gov/chemidplus/), are the following:

Compound	Common Name(s)	CASRN	% Similarity
Tetrachlorodian	Tetrachlorobisphenol A	79-95-8	96.58
Phenol, 2,6-dibromo-4-(1-(3-bromo-4-hydroxyphenyl)-1-methylethyl)-	Tribromobisphenol A	6386-73-8	95.44

Compound	Common Name(s)	CASRN	% Similarity
Benzene, 1,1´-(1-methylethylidene)bis(3,5-dibromo-4-methoxy-	TBBPA dimethyl ether; TBBPA methyl ether; Tetrabromobisphenol B	37853-61-5*	85.88
2,2´-Isopropylidenebis(4,6-dibromophenol)		97890-15-8	81.50
Phenol, 4,4´-(1-methylethylidene)bis(2-chloro-	2,2´-Dichlorobisphenol A; 3,3´-Dichlorobisphenol A; Dichlorodian	79-98-1	81.21
Ethanol, 2,2´-((1-methylethylidene)bis((2,6-dibromo-4,1-phenylene)oxy))bis-	Ethoxylated TBBPA; TBBPA bis(2-hydroxyethyl ether)	4162-45-2*	79.83
Phenol, 4,4´-isopropylidenebis(2,3,5,6-tetrachloro-	Isopropylidene bistetrachlorophenol	16669-42-4	78.83
Benzene, 1,1´-(1-methylethylidene)bis(3,5-dibromo-4-(2,3-dibromopropoxy)-	TBBPA bis(2,3-dibromopropyl ether)	21850-44-2*	77.29
Benzene, 1,1´-(1-methylethylidene)bis(3,5-dibromo-4-(2-propenyloxy)-	TBBPA allyl ether; TBBPA diallyl ether	25327-89-3* 37769-31-6	75.35
Phenol, 4,4´-(1-methylethylidene)bis(2,6-dibromo-, diacetate	3,3´,5,5´-TBBPA diacetate	33798-02-6	69.62
2-Propenoic acid, (1-methylethylidene)bis((2,6-dibromo-4,1-phenylene)oxy-2,1-ethanediyl) ester	Bis(*p*-acryloxyethoxy)-TBBPA	66710-97-2	65.75
Phenol, 4,4´-(1-methylethylidene)bis(2,6-dimethyl-	Bisxylenol A; Tetramethyl-bisphenol A	5613-46-7	65.75
2-Propenoic acid, (1-methylethylidene)bis(26-dibromo-4,1-phenylene) ester	TBBPA diacrylate	55205-38-4	64.65

*As mentioned above (in Section 9.10), these are in the review by IPCS/WHO (1995).
Additional sources for columns 2 and 3 include CIS Files and Registry (2002).

The following organizations have submitted unpublished health and safety studies of TBBPA bis(2-hydroxyethyl ether) to EPA (i.e., Toxic Substances Control Act Test Submissions [TSCATS]): Great Lakes Chemical Corporation, the Interagency Testing Committee, Eastman Kodak Company, Dow Chemical Company, and E.I. DuPont Denemours and Company, Inc. Reports include acute toxicity studies in mice, rats, guinea pigs, and rabbits; subchronic oral toxicity studies in rats; and genetic toxicology studies in bacteria *in vitro* either as the single chemical or a component of a mixture (e.g., Emery diol 1608-62R) tested separately from the mixture. In addition, several studies regarding dermal exposure of the substance (in Dacron fibers) have been conducted in humans. TSCATS are also available for TBBPA allyl ether; acute toxicity studies (routes: orally, dermally, or applied topically to the eye) in rats and rabbits and genetic toxicology studies in bacteria *in vitro* were performed. The oral LD_{50} was >5 g/kg in rats, and the dermal LD_{50} was >2 g/kg in rabbits. The chemical was a mild irritant on the skin (at 500 mg) and in the eyes (at 100 mg) of rabbits (RTECS, 1999).

11.0 Online Databases and Secondary References

11.1 Online Databases

Chemical Information System (CIS) Files
SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

STN International Files

BIOSIS	LIFESCI	PROMT
CA	MEDLINE	Registry
EMBASE	NIOSHTIC	RTECS
HSDB	NTIS	TOXLINE

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet
Code of Federal Regulations (CFR), National Archives and Records Administration
RTK Net (Right-To-Know Network) database

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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Appendix: Units and Abbreviations
°C = degrees Celsius
μg/L = microgram(s) per liter
μg/m^3 = microgram(s) per cubic meter
μg/mL = microgram(s) per milliliter
μM = micromolar
bw = body weight
EPA = Environmental Protection Agency
F = female(s)
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
HPV = high production volume
HSDB = Hazardous Substances Data Bank
i.p. = intraperitoneal(ly)
IPCS/WHO = International Programme on Chemical Safety/World Health Organization
IUR = Inventory Update Rule
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)

mol. wt. = molecular weight
n.p. = not provided
OSHA = Occupational Safety and Health Administration
ppb = parts per billion
ppm = parts per million
s = second(s)
TBBPA = tetrabromobisphenol A
TSCA = Toxic Substances Control Act
TWA = time-weighted average
wk = week(s)
yr = year(s)