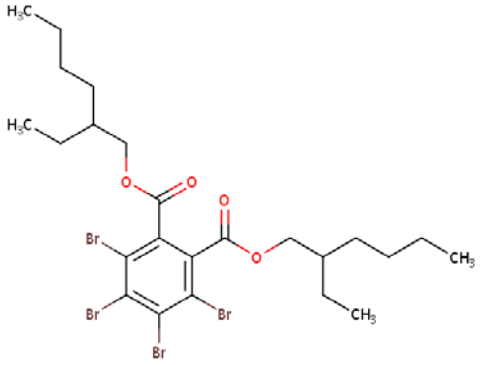
CAS RN 26040-51-7

Substance Name Bis (2-ethylhexyl) 2,3,4,5-tetrabromophthalate (TBPH, also BEH-TEBP)



Source: EPA Chemistry Dashboard

Uses

TBPH is an additive flame-retardant and plasticizer used in polyvinylchloride (PVC), neoprene and certain rubbers (styrene butadiene rubber and ethylene propylene diene monomer). PVC containing TBPH is used in electrical equipment such as wire and cable insulation and PVC films and sheeting. It's an additive flame retardant in flexible polyurethane foam and is also used in construction materials (such as adhesives, coatings, coated fabric, and wall coverings) [1, 2]. TBPH has been detected in foam baby products [3] and U.S. residential furniture [4].

Domestic manufacturers (including importers) reported to U.S. Environmental Protection Agency (EPA) in 2016 that TBPH was used industrially in plastic product manufacturing and had commercial and consumer uses as a flame retardant in fabric, textile, and leather products; electrical and electronic products, foam seating and bedding, and plastic and rubber products [5]. These included products intended for children. Maximum concentration was reported as 30% by weight for electrical and electronic products and for foam bedding and seating. Maximum concentrations in consumer plastic and rubber products was reported to be less than 1% by weight [5].

Manufacturers

Three domestic TBPH manufacturing sites were reported to EPA in 2016[1]. None were in Washington State. National Production Volume for TBPH was in the range of 1-10 million pounds/year for the years 2011-2015 [5].

[1] Manufacturers of chemicals listed on the TSCA Inventory were required to report to EPA in 2016 if they produced or imported the chemical in volumes ≥25,000 pounds at a US site during any of the calendar years 2012, 2013, 2014, or 2015. https://www.epa.gov/chemical-data-reporting/2016-chemical-data-reporting-results#overview

Toxicity

EPA classified TBPH as a moderate hazard for reproductive, developmental, and neurological toxicities based on laboratory testing of commercial mixtures in rodents, the toxicity of structurally similar chemicals, and professional judgement [6]. Significant data gaps were noted. A lowest observed adverse effect level (LOAEL) for developmental effects in rats was 100 mg/kg-day in an oral prenatal study of a Firemaster® BZ 54, a commercial mixture of TBB and TBPH. A LOAEL of 1 mg/kg- day was reported in a second perinatal oral study with another commercial mixture, Firemaster® 550, which contains TBB and TBPH plus two non-brominated phosphate flame retardants [6]. The latter study, published by Patisaul et al. 2013, found that pregnant rats exposed to the Firemaster® 550 mixture during gestation and lactation had altered thyroid function and produced offspring that were 30–60% heavier by weaning, an effect that persisted into adulthood. Female offspring of treated rats entered puberty sooner and had glucose intolerance and elevated anxiety behaviors in maze testing [7]. Firemaster® 550 produced lipid accumulation in 3T3-L1 preadipocytes *in vitro* as did TBPH alone. The mechanism by which TBPH produced mild lipid accumulation was not determined [8].
TBPH is a brominated analog of phthalate DEHP, a confirmed endocrine disrupter. A potential mammalian metabolite of TBPH, mono-ethylhexyl tetrabromophthalate (TBMEHP), induced proliferative damage in the liver and a marked decrease in serum thyroid hormone (T3) in pregnant rats following two days of oral exposure to 200 mg/kg per day on gestation days 18 and 19. Examination of fetal testes found increased multinucleated germ cells at the high dose of 500 mg/kg [9]. *In vitro* investigation with rat hepatic (liver) microsomes indicated that TBMEHP inhibits thyroid hormone deiodinase, which mediates the conversion of T4 to T3 in peripheral tissues [9]. In a further experiment with pooled and commercially available human liver microsomes, TBMEHP inhibited deiodinase only at high levels unlikely to result from environmental exposure [10]. *In vitro* experiments in 3T3 L1 cells revealed that TBMEHP activates peroxisome proliferator-activated receptors, PPARα- and PPARγ-mediated gene transcription and stimulates PPARγ-mediated adipocyte differentiation [9]. TBPH did not activate PPARγ or PPARα in 3T3-L1 preadipocytes [8, 9]. These findings were consistent with results from another assay system (transfected HepG2 cells) reporting weak activation of PPARα and PPARγ by TBMEHP (at 10 µM) but not by TBPH [11].

Both TBPH and TBMEHP were agonists of the pregane X receptor (PXR) and induced transcription of gene products (CYP3A4 mRNA) *in vitro* [11]. Activation of PXR helps detoxify foreign toxic substances but can also cause endocrine disruption through enhanced metabolism of endogenous hormones.

TBMEHP was 10x more potent than TBPH in inhibiting cell viability and growth of human vascular endothelial cells *in vitro* in a screening test for adverse effects in cardiac tissue. TBMEHP's effect on cell cycle arrest and apoptosis was concentration-dependent [12]. Klopčič et al. 2016, investigated potential endocrine activity of TBPH and the TBMEPH metabolite in three reporter gene assays. TBPH but not TBMEPH had potent anti-thyroid hormone activity and anti-glucocorticoid activity. TBPH and the TBMEPH metabolite also had anti-androgenic activity [13]. TBPH was also active in Tox21 screening for

chemicals active in the glucocorticoid receptor signaling pathway and the androgen receptor signaling pathway [14].

It is unclear how much metabolism to TBMEHP occurs in humans. In rodent testing by the National Toxicology Program, TBPH was poorly absorbed by the gut and the skin and most of the absorbed fraction was detected unchanged in the feces. Following a single oral administration, less than 0.3% was recovered in the urine. When investigators bypassed normal routes of exposure and administered TBPH to rats by IV, there was considerable metabolism to TBMEHP. The majority of the TBPH dose (78%) was recovered in feces: 70% as the metabolite TBMEHP, 30% as TBPH [15].

Exposure

TBPH is used as an additive flame retardant and plasticizer and can escape everyday products in the indoor environment. TBPH has been measured with high frequency in residential indoor dust in the United States [9, 16-19] and Canada [20, 21]. It was found in 100% of indoor dust samples from California childcare centers studied in 2010-2011 [22]. Across these studies, mean levels in indoor dust ranged from 144-734 ng/g dust and the maximum level reported was 47,110 ng/g. In a study of pregnant women in North Carolina, levels of TBPH in dust correlated positively with levels in hand wipes [23]. TBPH was also detected in 100% of office dust and 90% of car dust in a Boston study [9]. TBPH was measured in 100% of car interiors in Greece that included American-made cars. Mean concentration of TBPH in car dust was 233 ng/g and maximum detection was 1553 ng/g [24].

Furniture may be a significant contributor to TBPH in indoor dust. TBPH in residential indoor dust was significantly associated with presence or absence of the commercial flame retardant Firemaster 550® in the sofa in the same room [25]. In a study of North Carolina adults, TBPH levels in hand wipes correlated positively with levels in indoor dust indicating that dust levels contribute to human exposure [26]. TBPH and TBB levels in hand wipes between mothers and their three year old children were highly correlated in samples collected from New York City participants in 2012-13. Median concentration of TBB +TBPH on toddler's hands (0.86 ng/cm^2) was nearly twice as high as the median concentrations measured on mother's hands (0.48 ng/cm^2) [27].

TBPH has also been measured in indoor air. Venier et al. 2016, collected air samples in 64 homes in Indiana and Toronto in 2013. TBPH was detected in 100% of home air samples, the mean concentration in air was 16 pg/m^3 in U.S. homes and 6.8 pg/m^3 in Canadian homes, and the maximum concentration reported was of 109 pg/m^3 [28]. Two smaller studies collected indoor air samples in the Seattle area [29, 30]. Mean concentration of TBPH in inhalable particulate (>4 μm) was 34.3 ng/m^3 in gymnastic facilities, 8.61 ng/m^3 in gym coaches homes, and 2.97 ng/m^3 in other homes and offices. Mean concentration of TBPH associated with smaller respirable particles (<4 μm) was 5.41, 6.93 and 0.57 ng/m^3 for gyms, coaches homes, and other homes and offices, respectively [31]. Larger inhalable particulate is typically trapped in the lining of the upper respiratory tract and swallowed, adding to the total ingested. Authors calculated daily adult inhalation intake including the ingestion of larger particulates for the three settings. TBPH intake ranged 3.27 -0.51 ng/kg-day [31]. The much higher air concentrations reported in

the Seattle studies is likely related to different study design and sampling method. Venier et al. 2016, used foam samplers installed in a corner of the home's living room to passively collect flame retardants in air over 28 days. Participants were asked to refrain from vacuuming. Schreder and La Guardia used active personal air monitors to capture flame retardants in the breathing zone. Participants were encouraged to engage in all their normal activities over 24hrs. This latter study design would have better captured personal activities that re-suspend particles into the breathing zone.

TBPH was recently detected in 16% of human serum samples, 94% of hair samples and 80-86% of finger and toe nail samples in a 2014 Indiana study of 50 adults aged 19-38 [32]. Median serum concentrations of samples with detectable quantities was 40 ng/g lipid weight (range 19−69 ng/g lipid). Maternal serum and breast milk was collected in a 2008-2009 study of nursing women living in Québec, Canada [33]. TBPH was detected in 16.7% of serum samples. The 95th percentile was 33 ng/g lipid and the maximum concentration was 164 ng/g lipid. TBPH was detected in 32.4% of milk samples, the 95th percentile was 4.0 ng/g lipid and the maximum detected was 6.6 ng/g lipid. TBPH was detected in 15% of breast milk samples collected in the Netherlands in 2011-14. Median concentration of TBPH in samples with detectable quantities was 0.99 ng/g lipid.

TBPH was detected with high frequency in atmospheric particulate samples collected from six sites around the Great Lakes over a two year period. Over 90% of the samples in Chicago, Il and Cleveland, OH were positive for TBPH; detections ranged from 0.17 – 290 pg/m^3. More remote sites had 0.11–32 pg/m^3 of TBPH [34].

In testing by the National Toxicology Program (NTP), TBPH was very poorly absorbed in rats and mice when administered orally by gavage at environmentally relevant doses. Repeated daily oral doses resulted in bioaccumulation of TBPH in the adrenal glands and in liver [15]. About 8% of TBPH was absorbed into the skin in a dermal rat study. TBPH was not metabolized and only 1.2% of the total dose applied to clipped fur penetrated into systemic circulation. Based on these results and further *in vitro* experiments with human and rat skin, the NTP authors conservatively predict that 7.8±7.6% of TBPH may be absorbed into human skin *in vivo*; with only 0.8±0.4% of the parent chemical reaching systemic circulation after 24 hours of continuous exposure [35].Excretion of TBPH occurred primarily in feces of rats, not urine, which makes urinary biomarkers unsuitable for this compound. Hair and nails may offer a promising alternative to more invasive biomarkers such as serum and breastmilk [32].

Environmental Fate and Transport

TBPH is classified by EPA as having high persistence and high bioaccumulation based on modelling [6].

Summary from National Library of Medicine, Hazardous Substances Databank [36] and a 2016 Environment Canada review [2]

If released to air	• TBPH declines rapidly in gas phase of air (predicted half-life 5.9 hrs) but may persist in the air compartment via sorption to fine particulates. • TBPH was frequently detected in ambient air studies in the Great Lakes and Toronto. Ma et al. 2012, provided evidence that airborne TBPH in Great Lakes area was rapidly increasing overtime. TBPH is detected in remote environments, likely due to long-range transport on airborne particulate.
If released to soil	• TBPH has very low water solubility, very low vapor pressure, and high to very high octanol-water partition coefficient. TBPH is expected to strongly sorb to solid phases in various media (e.g., biosolids, sediments, aerosols, soil). • TBB is expected to be persistent. Predicted half-lives in soil are approximately 600-1000 days. 2-3% biodegradation of TBPH was reported after 28 days for a TBB/TBPH mixture in an inoculated mineral media. • TBPH is not expected to be mobile in soil and is not expected to volatilize significantly from dry or moist soil surfaces.
If released into water	• TBPH has been detected at low levels in surface water but it is highly lipophilic and is expected to adsorb to organic fractions in suspended solids and sediment. • Hydroloysis and photo-degradation are pathways of degradation in the aquatic environment. Tribromo anhydride is a reported aqueous photo-degradation product. • In a field pond study, the dissipation half-lives in suspended solids and sediment were reported as 25 and >200 days, respectively. There was very little dissipation of TBPH in sediment overtime.
Bioconcentration and bioaccumulation	• An estimated BCF of 13 was calculated in fish for bis(2-ethylhexyl) tetrabromophthalate(SRC), using an estimated log Kow of 11.95 and a regression-derived equation (EPA, EPI Suite). • TBPH did not bioconcentrate in fathead minnows at any point of in a 72 day experiment (exposed for 42 days and moved to clean water for 28 days). • Empirical data suggest that bioaccumulation is likely to be limited.

Physical-Chemical Properties for TBPH from EPA Chemistry Dashboard [37]

Property	Predicted Average	Predicted Median	Predicted Range	Unit
LogP: Octanol-Water	9.64 (5)	9.47	7.57 to 12.0	-
Water Solubility	1.54e-08 (4)	1.73e-08	2.81e-15 to 2.73e-08	mol/L
Density	1.76 (2)	1.76	1.53 to 2.00	g/cm^3
Flash Point	283 (2)	283	259 to 307	°C
Melting Point	113 (4)	83.9	55.0 to 229	°C
Boiling Point	492 (5)	513	393 to 585	°C
Surface Tension	41.3 (1)	-	-	dyn/cm
Thermal Conductivity	127 (1)	-	-	mW/(m*K)
Vapor Pressure	4.37e-09 (4)	1.26e-09	1.16e-13 to 1.50e-08	mmHg
LogKoa: Octanol-Air	11.7 (1)	-	-	-
Henry's Law	8.92e-07 (1)	-	-	$atm\text{-}m^3/mole$
Index of Refraction	1.54 (1)	-	-	-
Molar Refractivity	145 (1)	-	-	cm^3
Molar Volume	462 (1)	-	-	cm^3
Polarizability	57.6 (1)	-	-	$Å^3$

Numbers in parentheses indicate the number of measurements or model predictions identified by EPA.

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