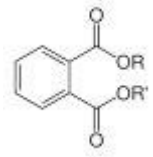
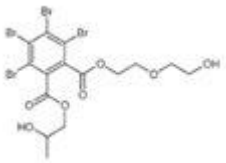
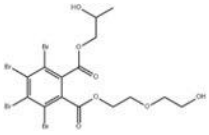
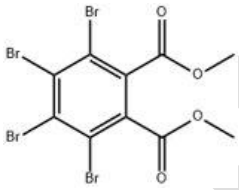
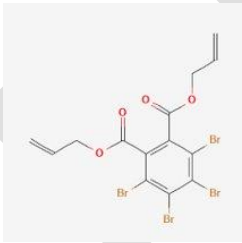
Phthalates identified in the FR Law: CAS# 26040-51-7 TBPH - bis(2-ethylhexyl)-3,4,5,6-tetrabromophthalate **Basic structure:**   Analogue #1  Analogue #2  Analogue #3  Analogue #4	**Relevant endpoints: Persistence, Bioaccumulation, and Developmental/Reproductive Toxicity** 4 Proposed Analogues: • Analogue #1: 2-(2- hydroxyethoxy)ethyl-2- hyroxypropyl-3,4,5,6-tetrabromo phthalate, CAS 20566-35-2 • Analogue #2: 2-(2- hydroxyethoxy)ethyl-2- hyroxypropyl-3,4,5,6-tetrabromo phthalate mixed esters with diethylene and propylene glycol, CAS 77098-07-8 • Analogue #3: Tetrabromophthalic acid dimethyl ester, CAS 55481- 60-2 • Analogue #4: Diallyl tetrabromophthalate, CAS 49693-09-6 The U.S. EPA assessed a group of seven brominated phthalate FRs for problem formulation and data needs assessment (US EPA, 2015). In addition to TBPH, Analogue #1 and Analogue #2 were included in the group. The major use identified for these substances was as flame retardants in polyurethane foams (PUFs) and PUF products. The assessment states that these chemicals have similar physical and chemical properties and environmental fate characteristics. The group members are expected to be persistent, bioaccumulative and potentially hazardous to human health, and to the environment. It was concluded that the available data on the toxicological hazard of these chemicals is incomplete for risk assessment. The Danish EPA has applied a category approach to 67 brominated flame retardants, including TBPH (Wedebye et al., 2016). The chemicals were divided into 15 groups, based on structural similarity. TBPH was assigned to the group of "Phthalates/benzoates" together with Analogue #1 and Analogue #3. All members were predicted to be persistent and to have positive indications for carcinogenicity and weak genotoxicity. TBPH is on EPA 2022 list of 30 OFRs that need more information and that are being assessed for health risks by CPSC. TBPH is on Washington Dept. of Ecology and Vermont Lists of Chemicals of High Concern to Children.
HEALTH HAZARDS	
Developmental and Reproductive Toxicity	See TBPH Toxicology Literature Matrix at the end of this document for summaries of nine studies on male reproductive toxicity, endocrine disruption, liver and thyroid effects, cytotoxicity, obesenogenicity and cardiovascular disease. TBPH induced chromosomal aberrations in mammalian cells in vitro. TBPH did not induce micronuclei in mice in vivo. TBPH, Analogue #1 and Analogue #2 are not mutagenic to bacteria in vitro. (EPA 2015 TSCA Hazard Assessment)

	EPA classified TBPH as a moderate hazard for reproductive, developmental, neurological, and repeated dose toxicities based on rodent toxicity of commercial mixtures, structurally similar chemicals, and professional judgement. TBPH is a brominated analog of phthalate DEHP and may be an endocrine disrupter. A metabolite of TBPH induced proliferative damage in rodent liver and altered serum thyroid hormone (T3) in rats after 2 days exposure to 200 mg/kg per day. A study in Boston, MA, reported house dust concentrations of TBPH were positively associated with higher level of thyroid hormone (T3) in men. (see WA Dept of Ecology 2021, page 87-88 for references).
Toxicokinetics	DEHP has been widely used as a plasticizer but is currently a restricted substance due to its endocrine disrupting properties and reproductive toxicity. Structural similarity to DEHP raised a concern for toxicity of TBPH. However, bromination alters the physical and chemical properties of DEHP. Available data e.g. a 28 d repeated dose toxicity study in which both TBPH and DEHP were tested indicate that the toxicity pattern of DEHP is different from that of TBPH. In photodegradation experiments TBPH has been shown to undergo sequential reductive debromination, possibly down to non-brominated degradation products (Davis and Stapleton, 2009, see section 7.7.1). However, there is limited evidence of debromination of TBPH in vivo. (ECHA 2020) Limited data are available on the toxicokinetics of the Brominated Phthalates Cluster (BPC) members. Phthalic acid is the common final metabolite of phthalic acid esters in rats; the main route of excretion being in urine (Lim et al., 2007). While information for the structural analogue, bis(2- ethylhexyl)phthalate (DEHP; CASRN 117-81-7) can be used to inform the metabolism and potential hazard of some of the BPC members, it is not appropriate for all members due to the differences in metabolites. (EPA 2015: Hazard Assessment) (i.e., *it is NOT appropriate for TBB because it metabolizes into a benzoic acid, not a phthalic acid. It IS appropriate for all other BPC members because they metabolize into a phthalic acid.)*
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
Persistence	In 2023 ECHA included TBPH in the SVHC list as "*bis(2-ethylhexyl) tetrabromophthalate covering any of the individual isomers and/or combinations thereof*" for it's **vPvB** qualities. Results from an inherent degradation test (reliable with restrictions) performed according to OECD guideline 302C (7% degradation in 28 days) indicate that TBPH is persistent. No simulation study is available for TBPH. However, in accordance with REACH Annex XIII Section 3.2.1. (d), a DT50 >200 days from a non-guideline outdoor mesocosm study (reliable with restrictions) is considered in the assessment of P or vP properties of TBPH as part of a weight-of-evidence approach. The study used an artificial sediment with a

	high organic carbon (OC) content and potentially with different microbial communities (e.g., density and diversity of microorganisms) compared to a natural sediment. Many conditions (high temperature compared to EU standard conditions, pre-exposure of micro-organisms to test conditions and exposure to sunlight leading to abiotic degradation (photolysis)) under which the study was conducted favoured dissipation/ degradation. Despite those favourable conditions, there was no dissipation/biodegradation of TBPH in the sediment of this test system. Overall, the study is considered to be relevant for the PBT assessment. The study can be used to show that TBPH is very persistent in the sediment of this test system. Furthermore, the presence of TBPH in all environmental compartments including air, surface water sediment, and in remote areas such as the Tibetan Plateau and the Arctic, gives further support to conclude that the substance is very recalcitrant to degradation. Overall, based on the available information and considering a weight-of-evidence approach, it is concluded that TBPH is very persistent. EPA 2015 Alternatives Assessment for FRs in Flexible Foam classified TBPH and TBB as **High Hazard** with regard to persistence. The primary removal processes of TBPH produce persistent metabolites and degradation products resulting in a high persistence designation. TBPH was reported to have a half-life of 3.5 days in water and 8.5 days in sediment in a confidential shake flask die-away test. In two closed bottle tests <4 or 2% of theoretical oxygen demand in a Closed Bottle test was reported after 28 days. TBPH has an estimated half-life of 120 days in soil where it is mainly expected to partition. TBPH is not expected to undergo hydrolysis at appreciable rates. Hydrolysis rates are expected to be pH dependent and may be limited by low water solubility of this compound. TBPH has the potential to undergo photodegradation, in an experimental study, half-lives of 147 to 220 minutes were obtained in the presence of organic solvents. The vapor phase reaction half-life of TBPH with atmospheric hydroxyl radicals is estimated at <1 day, although it is expected to exist primarily in the particulate phase in air. See excerpted Assessment.
Bioaccumulation	TBPH is **very bioaccumulative**. According to REACH Chapter R.11 (ECHA, 2017a), substances having a log Kow greater than 4.5 screen as potentially (very) bioaccumulative for aquatic organisms. For TBPH a log Kow value of 10.2 has been determined experimentally following an OECD TG 117, HPLC method. As this log Kow value is > 4.5, it is concluded that TBPH screens as potentially (very) bioaccumulative for aquatic organisms. In fish laboratory studies TBPH has a BCF>5000. See details on pages 6 & 7 of the ECHA link in persistence. The available toxicokinetic data (see section 4.1.1.1) indicate that TBPH is poorly absorbed and poorly metabolised and is mainly excreted unchanged via faeces. This is what can be expected for a substance with a log KOW >10. However, a

	small fraction of the substance seems to be accumulating in tissues of the exposed organisms. Studies of repeated oral exposures showed that while only a small amount of TBPH is absorbed, it has the potential to accumulate in adrenal and liver tissue, largely as the parent substance (see section 4.1.1.1.) This is apparent from the available monitoring data that suggests that TBPH accumulates in air breathing animals. TBPH has been detected in liver and eggs from several bird species including raptors preying on terrestrial species as well as birds that feed on aquatic organisms also in the Arctic. It is not possible to derive BMF values for the different bird species from these monitoring studies as the concentrations in their feed is not known. Furthermore, TBPH has been detected in blubber from marine mammals such as finless porpoise and dolphins and in the liver of the arctic species ringed seal and in the plasma of polar bears. To conclude, TBPH is present in a wide range of air breathing birds and mammals including top predators both in more industrialized areas as well as in remote regions, such as the Arctic. For explanation of field data, see pages 33-41 of the above reference. EPA 2015 Alternatives Assessment for FRs in Flexible Foam classified TBPH and TBB as **High Hazard** with regard to bioaccumulation. The bioaccumulation hazard designation is estimated based on TBPH monitoring data reporting detections in many different species including those higher on the food chain. In addition, a stable metabolite and degradation product of TBPH is expected to have a moderate bioaccumulation designation based on an estimated BAF value. Although the experimental BAF is low, the persistence of TBPH and its detection in many species from different habitats and trophic levels indicates potential for a high bioaccumulation designation in aquatic or terrestrial species. See excerpted Assessment.

Cheminformatics data for TBPH, Analogues 1, 3, 4 and metabolic products

		VH - Very High	H - High	M - Medium	L - Low	I - Inconclusive	No Data		Authoritative		Screening	*QSAR Model*	
		Human Health Effects									Ecotoxicity	Fate	
		Acute Mammalian Toxicity						Neurotoxicity		Systemic Toxicity										
CAS	Name	Oral	Inhalation	Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Repeat Exposure	Single Exposure	Repeat Exposure	Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Exposure
26040-51-7	Bis(2-ethylhexyl) tetrabromophthalate named in the law	L		L		VH	*L*	L	H								**VH**	H	*H*	M	*H*
20566-35-2	2-(2-Hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate Analogue #1	L	I	L		*VH*	*L*		*I*					*H*			M	*VH*	*H*	L	*H*
55481-60-2	dimethyl 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate Analogue #3	*VH*				*L*	*L*		*I*								*L*			*L*	
49693-09-6	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, di-2-propenyl ester Analogue #4	*I*				*L*	*L*		*I*					*H*			*VH*	*VH*		*L*	*L*
632-79-1	Tetrabromophthalic anhydride Metabolite	L	I	L		L	*L*		L			H					L		*VH*	H	*H*
13810-83-8	Tetrabromophthalic acid Metabolite																				*L*

Note: Cheminformatics data for TBPH do not include the more recent studies cited by ECHA for bioaccumulation; nor do they include EPA's bioaccumulation "High Hazard" classification from EPA 2015 Alternatives Assessment for FRs in Flexible Foam

Substance	Endpoint	Year	Author	Title	Concentration	Test substance	Effect/ Summary
TBPH	Male reproductive toxicity	2023	Fu	Integrated Studies on Male Reproductive Toxicity of Bis(2-ethylhexyl)-tetrabromophthalate: in Silico, in Vitro, ex Vivo, and in Vivo	0, 0.2, 2, 20, and 200 µM (in vitro) 0, 0.01, 0.1, 1, 10, 60 µM (ex vivo) 0, 0.002, 0.02, 0.2, 2 µM (in vivo)	Leydig cells, zebrafish sperm, male zebrafish (4 mo old)	identified TBPH as male reproductive toxin, classic nuclear receptor-mediated pathway, AR antagonist, in vitro (Leydig cells) significantly prohibited proliferation, ex vivo (zebrafish semen) negatively affected quality, similar to DEHP
TBPH and metabolite (TBMEPH)	Endocrine disruption	2016	Klopcic	Comparison of in vitro hormone activities of novel flame retardants TBB, TBPH and their metabolites TBBA and TBMEPH using reporter gene assays	TBPH exhibited anti-glucocorticoid activity with IC50 value of 0.3 mM. mode of action is by direct competing to the glucocorticoid receptor (GR) with IC50 value of 0.002 mM. Anti-androgenic activities with IC50 values of 0.1 mM and 1.3 mM were found for TBPH and TBMEPH. The anti-thyroid hormonal IC50 values of 0.1 mM and 32.3 mM for TBPH and TBMEPH	gene assays	TBPH showed anti-androgenic, anti-thyroid and anti-glucocorticoid effects as well as competition for binding to the GR. TBMEPH metabolite could have different effects from parent compound. The compounds disrupted the endocrine system, with the TBPH as the most active of all the tested compounds
TBPH and metabolite (TBMEPH)	Reproductive toxicity, thyroid, liver, obesity	2012	Springer	Rodent Thyroid, Liver, and Fetal Testis Toxicity of the Monoester Metabolite of Bis-(2-ethylhexyl) Tetrabromophthalate (TBPH), a Novel Brominated Flame Retardant Present in Indoor Dust	200 and 500 mg/kg TBMEPH for 2 days	pregnant rats; murine FAO and NIH 3T3 L1 cells	Serum liver enzyme levels of the dams were altered and dam livers showed hepatocyte apoptosis and proliferation. Serum T3 levels were significantly decreased in a dose-dependent manner and TBMEHP inhibited deiodinase activity. Testes isolated from the fetuses of exposed dams showed induction of MNGs in the highdose group without significant effects on testosterone production; TBMEHP is a PPARα and PPARγ agonist; thyroid dysfunction, liver dysfunction and obesity are concerns.
TBPH	Liver toxicity	2021	Guo	Nonalcoholic Fatty Liver Disease Development in Zebrafish upon Exposure to Bis(2-ethylhexyl)-2,3,4,5 tetrabromophthalate, a Novel Brominated Flame Retardant	0.02 µM and 2 µM	female zebrafish, 3 mo old	Short-term exposure to TBPH induced NAFLD in zebrafish. TBPH-triggered hepatic TG accumulation seems to be initiated by the modulation of PPARs, provoking downstream genes and causing an imbalance between lipid synthesis and expenditure in the liver, consequently leading to sequential events of hepatic steatosis
TBPH	Liver toxicity	2021	Yin	Effects of bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate on liver injury in Balb/c mice	200 mg/kg, oral (high dose)	balb/c mice	TBPH induces hepatic damage via increasing oxidative stress. Increased ROS, MDA, 8-OH-dG and DPC. Decreased GHS.
TBPH and metabolite (TBMEPH)	Genetic toxicity	2020	Guo	Bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate Affects Lipid Metabolism in Zebrafish Larvae via DNA Methylation Modification	0, 0.2, 2, 20, 200, and 2000 nM	zebrafish	TBPH and TBMEHP are potential PPARγ agonists and interfere with the lipid metabolism via DNA demethylation of the promoter

TBPH and metabolite (TBMEPH)	Cytotoxicity	2020	Chen	Effects of novel brominated flame retardants and metabolites on cytotoxicity in human umbilical vein endothelial cells	0.1, 1, 10, 50, 100, 200 ug/mL for cell viability, 0.8 and 8 ug/L for EC50	human umbilical vein endothelial cells, mice	metabolite (TBMEPH) of TBPH caused higher cytotoxicity and affected gene expression to a greater extent than the parent compounds in HUVECs, indicating a higher potential risk of cardiovascular disease. EC50 = 8.6ug/mL for TBMEPH
TBPH	Obeseno-genicity	2021	Zhou	Bis(2-ethylhexyl)-tetrabromophthalate induces zebrafish obesity by altering the brain-gut axis and intestinal microbial composition	0.02 and 2.0 uM for 6 weeks	zebrafish	Long-term TBPH exposure leads to significant weight gain, adipocyte hypertrophy, and subcutaneous fat accumulation (disrupting brain-gut axis regulation and gut microbial composition)
TBPH and metabolite (TBMEPH)	Cardio-vascular disease	2017	Xiang	Effects of novel brominated flame retardant TBPH and its metabolite TBMEHP on human vascular endothelial cells: Implication for human health risks	1 and 10 ug/mL	human vascular endothilial cells	TBMEHP induced a marked G0/G1 cell cycle arrest and robust cell apoptosis at 1 μg/mL by inducing expression of p53, GADD45α and cyclin dependent kinase (CDK) inhibitors (p21and p27) while suppressing the expression of cyclin D1, CDK2, CDK6, and Bcl-2. TBPH caused early apoptosis after G2/M phase arrest only at 10 μg/mL via upregulation of p21 and down-regulation of CDK2 and CDK4. TBMEHP decreased mitochondrial membrane potential and increased caspase-3 activity at 1 μg/mL, suggesting that activation of p53 and mitochondrial pathway were involved in the cell apoptosis.

Literature studies on metabolite, tetrabromophthalic anhydride

Substance	Endpoint	Year	Author	Title	Concentration	Test substance	Effect/ Summary
tetrabromophthalic anhydride, TBPH	fish mortality, developmental effects	2016	Usenko	Evaluation of Common Use Brominated Flame Retardant (BFR) Toxicity Using a Zebrafish Embryo Model	1.25, 2.5, 5, 10, 20 ppm, observed daily until 168 hpf	zebrafish	Purpose was to test zebrafish as a comparative screening tool. LC50 = 18 ppm. TBPH did not induce mortality up to 20 ppm. Neither altered the rate of spontaneous movement up to 20 ppm.
tetrabromophthalic anhydride	many	1999	Masten	Tetrabromophthalic Anhydride Review of Toxicological Literature - National Institute of Environmental Health Sciences	many	rat, fish, water flea	Oral and dermal toxicity >10,000 mg/kg in rats, rabbits, mice; 4-hour LC50 in rats 10.9mg/L; LC50 in fish >10mg/L; LC50 in water fleas >5.6mg/L; persistent in soils; low bioaccumulation in aquatic soils; symptoms of exposure may include coughing, sneezing, respiratory system irritation, dermatitis, and eye irritation. Many more, mostly corporate, test results, see report.