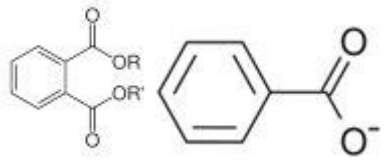
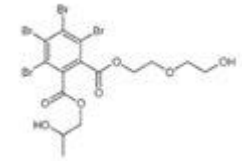
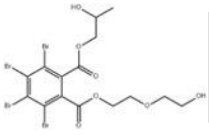
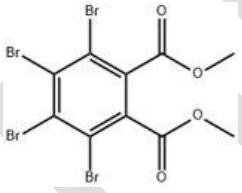
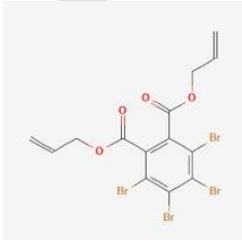
Draft EHS Summary of Phthalates/Benzoates for the MA TURA Science Advisory Board Mtg – September 2023

Phthalates/Benzoates identified in the FR Law:	**Relevant endpoints: Persistence, Bioaccumulation, and to a lesser extent Developmental Toxicity**
CAS# 26040-51-7 TBPH - bis(2-ethylhexyl)-3,4,5,6-tetrabromophthalate CAS# 183658-27-7 TBB - 2-(ethyhexyl-2,3,4,5-tetrabromobenzoate **Basic structure:**   Analogue #1  Analogue #2  Analogue #3  Analogue #4	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 All four analogues are most similar to TBPH, not TBB. However, some of the available data is for a mixture of the two. 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 and TBB, 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 TBB, Analogue #1 and Analogue #3. All members were predicted to be persistent and to have positive indications for carcinogenicity and weak genotoxicity. TBPH & TBB are on EPA 2022 list of 30 OFRs that need more information and that are being assessed for health risks by CPSC. TBPH & TBB are both on Washington Dept. Of Ecology and Vermont Lists of Chemicals of High Concern to Children.
HEALTH HAZARDS	
Developmental Toxicity	(Rat) Maternal: NOAEL = 50 LOAEL =100; Developmental NOAEL=50 LOAEL=100 (Firemaster® BZ-54 – mix of TBPH/TBB) (EPA 2015 TSCA Hazard Assessment) TBPH was not mutagenic in bacteria in vitro but did induce chromosomal aberrations in mammalian cells in vitro. TBPH did not induce micronuclei in

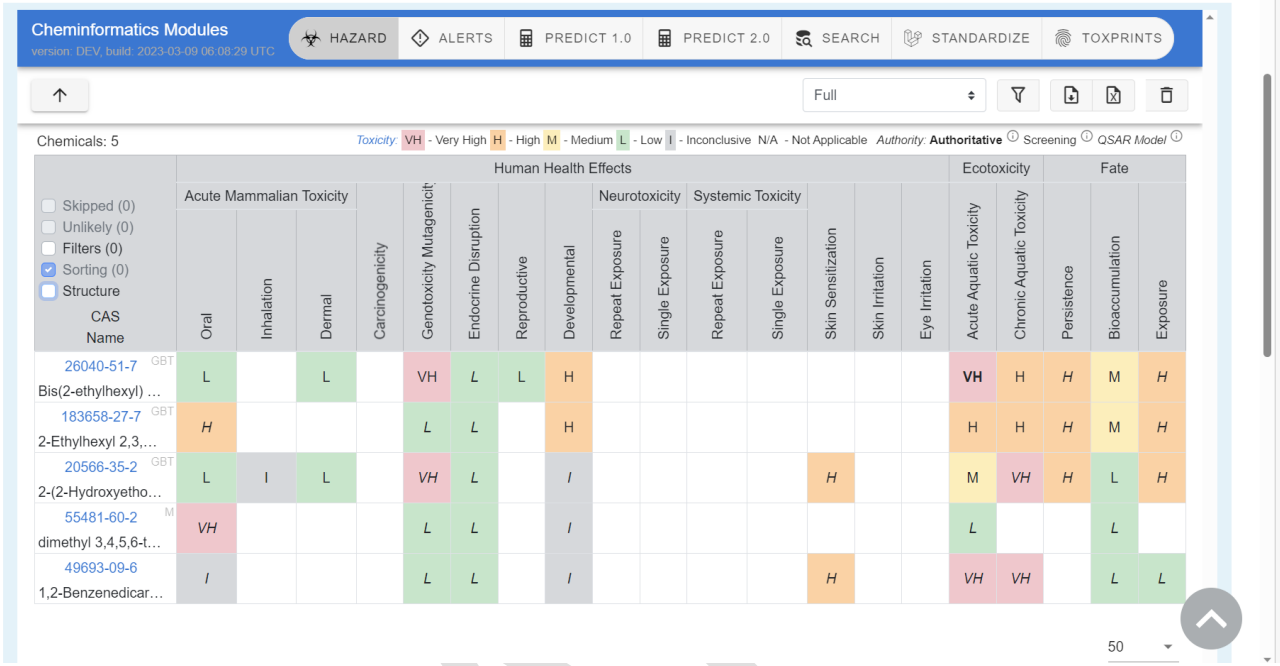
	mice in vivo. No data are available for the reproductive/developmental toxicity endpoint. (EPA 2015 TSCA Hazard Assessment) The effects observed in parental animals in the two-generation reproductive toxicity study with Firemaster® BZ-54 were lower body weights and body weight gains during the premating periods in the parental and first generation females at the highest dose tested. First generation males also had lower body weights in the premating period but body weight gain was unaffected by treatment. At the highest dose tested, both generations of offspring had lower body weights at birth and throughout lactation which resulted in the lower premating body weights of the first female generation. Another effect of treatment was lower spleen weights at lactation day 21 in the first generation male pups and both pup sexes of the second generation. There were no adverse effects on reproductive performance or fertility in rats in this study up to the highest dose tested (165 mg/kg-day). Based on these observations, the NOAEL for parental and neonatal toxicity was designated 50 mg/kg-day; the NOAEL for reproductive toxicity was 165 mg/kg-day (highest dose tested). (EPA 2015 TSCA Hazard Assessment) Analogue #1 and Analogue #2 exhibit low acute toxicity to rats and rabbits via the oral and dermal routes, respectively. They are not mutagenic to bacteria in vitro. No additional data are available on these cluster members. (EPA 2015: 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. Significant data gaps were noted. Lowest-observed-adverse-effect-levels (LOAELs) for developmental effects in rats were 100 mg/kg-day in an oral prenatal study of 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. 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 percent 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. (see WA Dept of Ecology 2021, page 87-88 for references) 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).

Reproductive Toxicity	(Rat; 2-gen) NOAEL=165 (highest dose tested); NOAEL(parental) = 50; LOAEL(parental) = 165; NOAEL(off-spring)=50; LOAEL(off-spring)=165 (Firemaster® BZ-54 – mix of TBPH/TBB) (EPA 2015 TSCA Hazard Assessment) In the prenatal developmental toxicity study with Firemaster®BZ-54 in rats, maternal toxicity included clinical findings (increased incidence of animals with sparse hair in the abdominal region), lower gestation body weights and body weight gain, and lower gestation food consumption at doses greater than or equal to 100 mg/kg-day. Fetal body weights were lower than controls at these doses. At 300 mg/kg-day, examination of the fetuses indicated fused cervical vertebral neural arches which were considered treatment-related (litter incidence of 8%). In addition, there was also an increased litter incidence for fetal ossification variations involving additional ossification centers to the cervical vertebral neural arches, incomplete ossified skull bones (jugal, parietal, and squamosal), and unossified sternebrae. Based on these observations, the NOAEL for maternal and developmental toxicity were designated 50 mg/kgday. (EPA 2015 TSCA Hazard Assessment)
Toxicokinetics	TBPH is the brominated analogue of DEHP. 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 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.

hazard information to evaluate potential health effects of chemicals. These Cheminformatics modules are examples of online platforms being developed by CCTE for EPA Program Offices, EPA Regions, and external stakeholders to use in order to provide feedback early in the development process prior to integration into production systems such as the CompTox Chemicals Dashboard.



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