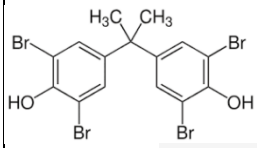
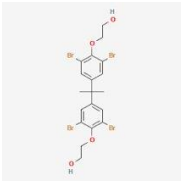
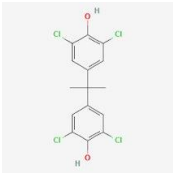
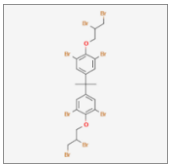
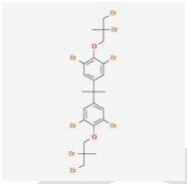
EHS Summary of Polyhalogenated Bisphenol Aliphatics for the MA TURA Science Advisory Board Meeting

Polyhalogenated Bisphenol Aliphatic identified in the FR Law: **Tetrabromobisphenol A (TBBPA)** **CAS #: 79-94-7**   Analogue #1  Analogue #2  Analogue #3  Analogue #4	**Relevant endpoints: PBT, developmental/reproductive toxin, endocrine disruption** TBBPA is one of the most widely used brominated flame retardants globally. Due to the environmental and human health hazards associated with TBBPA (PBT, cancer, endocrine disruption, neurotoxicity, and reproductive toxicity) several alternatives have been developed. **Four Proposed Analogues:** 1. "**Analogue #1**" (CAS #: 4162-45-2) 4,4'-Isopropylidenebis[2-(2,6-dibromophenoxy)ethanol] (BHEE) TBBPA-bis(2-hydroxyethyl) ether addition of two ethyl groups, precursor of TBBPA 2. "**Analogue #2**" (CAS #: 79-95-8) Tetrachlorobisphenol A (TCBPA) substitution of chlorine for bromine 3. "**Analogue #3"** (CAS #: 21850-44-2) TBBPA bis(2,3-dibromopropyl) ether (TBBPA-DBPE) - or 2,2-Bis[3,5-dibromo-4-(2,3-dibromopropoxy)phenyl]propane addition of a 2,3-dibromopropyl group 4. "**Analogue #4**" (CAS #: 97416-84-7) TBBPA-bis brominated ether derivative or 1,1'-(Isopropylidene)bis(3,5- dibromo-4-(2,3-dibromo-2- methylpropoxy)benzene) Government of Canada, 2013: "Given the similarities in the chemical structures of TBBPA and its derivatives (name Analogue #1 specifically), and the common toxicological profiles among the compounds in comparable studies; the TBBPA hazard database was considered adequate to assess the toxicological potential and to characterize risk for TBBPA and its derivatives." From San Antonio Statement on BFRs and CFRs: "Brominated and chlorinated flame retardants as classes of substances are a concern for persistence, bioaccumulation, long-range transport, and toxicity."
Health Hazards	
IARC rating	TBBPA is "Probably carcinogenic to humans" (Group 2A)
Developmental/Reproductive Toxicity	Li (2023) investigated the adverse effects of **Analogue #3** (50 and 1000 µg/kg/day) on postnatal testis development in CD-1 mice and the underlying mechanism. After the first week of maternal exposure, neonatal mice in the high-dose group displayed reduced seminiferous tubule area, fewer Sertoli cells and germ cells, and damaged microtubules in Sertoli cells; microtubule damage was also observed in the low-dose group. Exposure into adulthood resulted in male offspring in the high-dose group presented more remarkable alterations in reproductive parameters, such as reduced sperm count; in the low-dose group, microtubule damage was also observable, along with blood–testis barrier impairment. Huang (2017) studied the effects of BPA and its derivates on the reproduction and development of Oryzias melastigma. BPA, **TBBPA,** and

	Analogue #2 induced the acceleration of embryonic heartbeat. TBBPA and TCBPA resulted in delayed hatching and decreased hatching rate. The expressions of hatching enzyme decreased after exposure and TCBPA was found to be more toxic than TBBPA. "Healthy adult frogs were exposed to 0, 0.001, 0.01, 0.1, and 1mg/L of **TBBPA** and TCBPA (Analogue #2) for 14 days. Sperm numbers were counted by erythrometry. Sperm mobility and deformities were observed under a light microscope (400). We used commercial ELISA kits to determine the serum content of testosterone (T), estradiol (E2), luteinizing hormone (LH) and follicle stimulating hormone (FSH). Expression of androgen receptor (AR) mRNA was detected using real-time qPCR. Sperm numbers and sperm mobility were significantly decreased and sperm deformity was significantly increased in a concentration dependent manner following exposure to TBBPA and TCBPA. Sperm deformity was significantly greater in the 1mg/L TCBPA (0.549) treatment group than in the 1mg/L TBBPA (0.397) treatment group. Serum T content was significantly greater in the 0.01, 0.1 and 1 mg/L TBBPA and TCBPA experimental groups compared with controls, while E2 content was significantly greater in only the 1 mg/L TBBPA and TCBPA experimental groups. Expression levels of LH and FSH significantly decreased in the 1 mg/L TBBPA and TCBPA treatment groups. AR mRNA expression decreased markedly in all the treated groups. Our results indicated that TBBPA and TCBPA induced reproductive toxicity in a dose-dependent manner, with TCBPA having greater toxicity than TBBPA. Furthermore, changes in T, E2, LH, and FSH levels induced by TBBPA and TCBPA exposure, which led to endocrine disorders, also caused disturbance of spermatogenesis through abnormal gene expressions of AR in the testes." (Zhang 2018) "TCBPA (Analogue #2) induces hus-1-mediated DNA damage and further causes apoptosis via a cep-1- dependent pathway. Our data provide evidence that TCBPA causes reproductive toxicity via DNA damage induced apoptosis." (Yu 2022) "TBBPA and TCBPA (Analogue #2) exposure induced ROS generation and activated oxidative stress, induced apoptosis, damaged the tissues and function of the liver, and decreased the liver weight of frogs. Namely, TBBPA and TCBPA induced ROS dependent mitochondria-mediated apoptosis and caused oxidative damage in the liver of R. nigromaculata. The hepatotoxicity of TCBPA is similar to or even more toxic than that of TBBPA." (Jia 2022) From NAS 2019: The data on the four best-studied chemicals in the subclass are discordant for the developmental toxicity endpoint. (p. 35-39).
Genotoxicity/Mutagenicity	"**Analogue #3 and its derivative** were mutagenic to Salmonella typhimurium in one assay, while it was negative in other assays in S. Typhimurium and E. coli. This substance was also negative for mutagenicity in mouse lymphoma cells. TBBPA bis(2,3-dibromopropyl) ether is also estimated to have potential

	for genotoxicity based on the potential for alkylation. TBBPA bis(2,3-dibromopropyl) ether did not cause chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary (CHO) cells (in vitro), was negative in an in vivo micronucleus assay in mice and did not produce unscheduled DNA synthesis in rats." (EPA 2014 HBCD Alternatives)
Endocrine Disruption	TBBPA is known for its endocrine disrupting potential, specifically to the thyroid hormone. An 2023 found that the daily exposure to low concentrations of **TBBPA** activated the thyroid hormone signaling pathway in the HepG2 cells, which was counterbalanced by the thyroid hormone receptor antagonist. The gene regulation of Ras was also counteracted, implying the influence of the thyroid hormone signaling pathway on the activation of the Ras signaling pathway. TBBPA was found to disrupt the content of thyroid hormones and mRNA expression of thyroid hormone synthesis-related enzymes, probably related to the upregulation of insulin-like growth factor homolog (IGF). "Based on four in vitro assays, **Analogue #3** can interact with the endocrine system. Analogue #3 may have potential estrogenic and transthyretin-binding effects; it appears to inhibit sulfation of estradiol (E2), but does not exhibit estrogenic activity via interference with estrogen receptors (ER); it does not appear to interfere with aryl hydrocarbon receptor (AhR)-mediated, androgenic or progestagenic pathways. Analogue #3 competed with thyroid hormone precursor thyroxine (T4) for binding to human transthyretin (TTR), but did not exhibit thyroid hormone (T3) mimicking activity." (EPA 2014) **TBBPA and Analogue #3 are listed on the** TEDx List of Endocrine Disrupting Chemicals **TBBPA, Analogue #3, and Analogue #4** are under assessment as Endocrine Disrupting (ECHA ED List)
Metabolites	As TBBPA is the basic structure for the brominated analogues, it is suspected that they will break down into TBBPA.
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
Persistence	TBBPA and all proposed analogues are expected to have a high potential to persist in the environment. **TBBPA** is classified as a PBT under Washington State Department of Ecology and EPA's Toxic Release Inventory PBTs. The Oregon Department of Environmental Quality classifies **TBBPA** as a priority persistent pollutant as part of its water quality program based on concerns related to persistence and chronic toxicity to fish.

	Minnesota lists **TBBPA** and **Analogue #3** as chemicals of high concern based on persistence, bioaccumulation and toxicity (MDH 2022 Chemicals of High Concern). **TBBPA and Analogue #3** are listed as flame retardant substance class of concern for PB&T & long range transport -EHP San Antonio Statement on BFRs & CFRs "High persistence of **Analogue #3** is expected as a result of located biodegradation studies and the absence of other expected likely removal processes under environmental conditions. In the course of a 28-day Japanese Ministry of International Trade and Industry (MITI) test, only 1% of TBBPA bis(2,3-dibromopropyl) ether was degraded. TBBPA bis(2,3-dibromopropyl) ether will exist primarily in the particulate phase in the atmosphere and is not expected to undergo removal by gas phase oxidation reactions. It is also not anticipated to undergo removal by hydrolysis." (EPA 2014) High persistence of **Analogue #4** is expected. Aerobic biodegradation is not expected to be an important removal process, based on analog data. Although anaerobic biodegradation (by dehalogenation) may occur, the rate is likely to be low, and any such transformation will only lead to intermediate products that have essentially the same environmental properties. In other words, if emission to the environment occurs at any rate greater than negligible, this substance will accumulate. TBBPA-bis brominated ether derivative will exist primarily in the particulate phase in the atmosphere and is not expected to undergo removal by gas-phase oxidation reactions; however due to its properties, it is not expected to be released or transported to the atmosphere to a significant degree. TBBPA-bis brominated ether derivative is not anticipated to undergo removal by hydrolysis, since it does not contain hydrolyzable functional groups. (EPA 2014)
Bioaccumulation	Several reports have demonstrated that TBBPA is absorbed quickly and accumulates in a variety of aquatic organisms, such as zebrafish, bluegill sunfish, whelks and scallops (Yang 2022, Zhao 2020, Wu 2018); their bioaccumulation rate is about 19.33%, while the rate of metabolism is 8.88% (Liu, 2018). **Analogue #3** and **Analogue #4** both have a high potential for bioaccumulation based on an estimated BAF of 12,000 and 1,600 respectively. **Analogue #3** has also been detected in Great Lakes Herring gull eggs (EPA 2014).
Environmental Fate and Transport	"Evaluation of **Analogue #3 and Analogue #4** transport is based entirely on estimations from quantitative structure activity relationships. TBBPA bis(2,3-dibromopropyl) ether is expected to have low mobility in soil based on estimations indicating strong absorption to soil. If released to the

	atmosphere, TBBPA bis(2,3-dibromopropyl) ether is likely to exist solely as particulate. As a particulate, atmospheric oxidation is not expected to be a significant route of environmental removal. Based on the Henry's Law Constant, volatilization from water or moist soil is not expected to occur at an appreciable rate. Level III fugacity models indicate that TBBPA bis(2,3-dibromopropyl) ether will partition predominantly to sediment and soil." (EPA 2014)

Notes:

- EPA/OPPT included **Analogue #3, TBBPA-bis(2,3-dibromopropyl) ether (CAS # 21850-44-2)** in the TBBPA related chemicals cluster because of an initial prioritization exercise due to additive flame retardant uses; EPA/OPPT assumes that additive uses will lead to higher potential for exposure.

Cheminformatics Summary Table of TBBPA and Potential Analogues:

Chemicals: 5 — Toxicity: VH - Very High, H - High, M - Medium, L - Low, I - Inconclusive, N/A - Not Applicable. Authority: **Authoritative**, Screening, QSAR Model

CAS / Name	Human Health Effects: Acute Mammalian Toxicity: Oral	Acute Mammalian Toxicity: Inhalation	Acute Mammalian Toxicity: Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurotoxicity: Repeat Exposure	Neurotoxicity: Single Exposure	Systemic Toxicity: Repeat Exposure	Systemic Toxicity: Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Ecotoxicity: Acute Aquatic Toxicity	Ecotoxicity: Chronic Aquatic Toxicity	Fate: Persistence	Fate: Bioaccumulation	Fate: Exposure
79-94-7 HGBTM 3,3',5,5'-Tetrabro...	L	M	L	VH	L	H	H	H			L		H			VH	VH	VH	M	H
97416-84-7 GBT 1,1'-(Isopropylide...	L	L	L		L	L	L	I						H		VH			H	
21850-44-2 GBT Tetrabromobisph...	L	L	L	H	VH	H	L							H		L		VH	L	VH
4162-45-2 GBT Tetrabromobisph...	L	I	L	I	VH	L	I	I	I	I	I	I	H	L	L	VH	VH	VH	M	L
79-95-8 GBTM 2,2',6,6'-Tetrachlo...	L				H	H		H					H			H	VH		H	M

Additional information:

IARC

- 2,3-dibromo-1-propan-1-ol (Added chain to Analogue #3; contaminant/metabolite/breakdown product) (Group 2B)
- Trichlorophenol (contaminant of Analogue #2) (Group 1)

References:

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