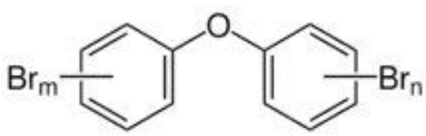
Polybrominated diphenyl ethers identified in the FR Law: **CAS # 32534-81-9** **Pentabromodiphenyl Ether** **CAS # 32536-52-0** **Octabromodiphenyl Ether** 8 proposed analogues – deca, nona, hepta, hexa, tetra, tri, di, mono – congeners of the bromodiphenyl ethers identified in the law differing by the number of bromines Approx 41 positional isomers **Basic structure:** 	**Relevant endpoints: Neurotoxicity (intelligence, learning, memory, ADHD, attention-related behaviors), endocrine alterations, persistence, bioaccumulative properties** “The class is comprised of 209 congeners that share a brominated diphenyl ether molecule with up to 10 bromine atoms attached. Three classes of commercial formulations of PBDE mixtures were produced—the pentaPBDEs, octaPBDEs, and decaPBDEs—but they are no longer produced or used in newly manufactured products in the US.” From Dorman et al (2018) “Polybrominated diphenyl ether (PBDE) neurotoxicity: a systematic review and meta-analysis of animal evidence” They are ubiquitous in the environment; they have been shown to be persistent and to bioaccumulate; and human exposure to them has been well documented. Excerpted from NASEM (2019) A Class Approach to Hazard Assessment of Organohalogen Flame Retardants: The National Academies concluded that with respect to **effects on intelligence** “there was sufficient animal and human evidence to allow the committee to conclude that BDE-47 (**tetra**) is a potential hazard to human health”. The hazard conclusions reached on the other congeners were equivalent to or weaker than the one reached for BDE-47. The present committee concludes that because the data are concordant for the well-studied members of the subclass, a designation of “potentially hazardous” can be applied to the entire subclass. (The following congeners are listed individually in the NAS subclass “polyhalogenated diphenyl ethers” – **deca, octa, hepta, hexa, penta, tetra, tri**.)
HEALTH HAZARDS	
Neurotoxicity/Developmental Toxicity	**“Brominated Diphenyl Ethers” are identified as a chemical group known to cause developmental neurotoxicity in human beings**. Grandjean 2014: “Neurobehavioural effects of developmental toxicity*” The Lancet Neurology, 2014; 13: 330–38.* Positive associations for **tetra/hexa** and attention at age 4, increase cord concentration for **tetra** showed decrease in social domain developmental quotient, prenatal exposure to **tetra/penta/hexa** associated with poorer attention at ages 9-12, house dust exposures to **hexa/penta/deca** were positively associated with depressive behavior problems and lower social development quotients, prenatal exposure to tetra associated with lower MDI scores, decreased FSIQ and externalizing behavior, postnatal **PBDE** exposure associated with decreased FSIQ, increased hyperactivity and aggressive behaviors,

	prenatal exposure to hexa associated with decreased FSIQ and externalizing problems, prenatal exposure to hexa decreased sustained auditory attention, maternal serum concentrations of tetra was associated with more externalizing behaviours among infants, increased prenatal exposure to **PBDEs** was associated with more negative vocalizations in infants, exposure to prenatal **PBDEs** associated with increased global efficiency in an area of the brain associated with more executive functioning problems, cord **PBDEs** associated with increase in aggressive behaviors, emotional reactivity and externalizing, inverse association with prenatal **PBDEs** and global efficiency of the reading network. Vuong 2020: "Flame retardants and neurodevelopment: An updated review of epidemiological literature" *Current Epidemiological Reports*. 2020 December; 7(4): 220–236. Article summarizes the results of 15 studies between 2015-2020 examining neurodevelopmental effects of exposure to certain flame retardants, among them PBDEs. A table edited to include only data for PBDEs is available here. "**Brominated diphenyl ethers**" (CAS 90193-67-2) as a group are on the EPA CompTox list of "Chemicals Triggering Developmental Neurotoxicity in Vivo" (33 total). This is a (non-exhaustive) list of compounds documented to trigger developmental neurotoxicity (DNT) in at least two different laboratories, described in Table 5 of Aschner et al 2017
Endocrine Disruption/Thyroid	PBDEs, mainly those with lower molecular weight, are structurally similar to thyroid hormones. Therefore, they may disrupt the endocrine system by interfering with hypothalamic pituitary-thyroid axis homeostasis. BDE-71 (**tetra**) and -79 (**tetra**) decrease thyroid hormone serum levels and induce liver enzyme biotransformation, as shown in studies carried out with mice and rats. Moreover, **many PBDE congeners** damage mitochondria, increasing reactive oxygen species (ROS) production and oxidative stress, exerting genotoxicity, and inducing apoptotic cell death in isolated rat mitochondrial and hepatocarcinoma cells (HepG2). From Miranda 2022: "Flame Retardants: New and Old Environmental Contaminants*"* chapter in Junqueira Dorta D and Palma de Oliveira D (eds) (2022) The Toxicity of Environmental Pollutants. IntechOpen. DOI: 10.5772/intechopen.98127. **Tri, tetra, penta, hepta, hexa, octa, nona, deca** BDEs all listed as 'potential endocrine distruptors' on *TEDx the Endocrine Disruption Exchange, updated 2019*
Reproductive Toxicity	**Hepta, hexa, penta, tetra, tri**-bromodiphenyl ether have all been shown to have either a "robust" or "moderate" effect on male reproduction in human studies. Arowolo 2022: "Mechanisms of Male

	Reproductive Toxicity of Polybrominated Diphenyl Ethers," International Journal of Molecular Sciences, 2022, 23, 14229.
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
Persistence	**Deca, hepta, hexa, penta, tetra** on Stockholm POP list for elimination PBDE congeners with four to ten bromine atoms are highly persistent based on several lines of evidence, but especially by a large body of environmental monitoring data in both the United States and abroad (Environment Canada, 2009a; Shaw and Kannan, 2009; Vonderheide et al., 2008). USEPA PBDE TSCA Action Plan 2009
Bioaccumulation	**Hexa**bromodiphenyl ether and **hepta**bromodiphenyl ether are the main components of commercial **octa**bromodiphenyl ether. Commercial mixture of **octaBDE** is highly persistent, has a high potential for bioaccumulation and food-web biomagnification, as well as for long-range transport. The only degradation pathway is through debromination (i.e. the replacement of bromine on the aromatic ring with hydrogen) and producing other bromodiphenyl ethers. **Higher bromodiphenyl ether congeners may be converted to lower, and possibly more toxic, congeners. The higher congeners might therefore be precursors to the tetraBDE, pentaBDE, hexaBDE, or heptaBDE.** UNEP 2007: "Risk profile on commercial octabromodiphenyl ether" **Tetra**bromodiphenyl ether and **penta**bromodiphenyl ether are the main components of commercial **penta**bromodiphenyl ether. Commercial mixture of **pentaBDE** is highly persistent in the environment, bioaccumulative and has a high potential for long-range environmental transport. These chemicals have been detected in humans in all regions. There is evidence of its potential for toxic effects in wildlife, including mammals. UNEP 2006: "Risk profile on commercial pentabromodiphenyl ether" The commercial mixture of **deca**BDE consists primarily of the fully brominated decaBDE congener in a concentration range of 77.4-98 %, and smaller amounts of the congeners of **nona**BDE (0.3-21.8 %) and **octa**BDE (0-0.04 %). The **decaBDE mixture is highly persistent, has a high potential for bioaccumulation and food-web biomagnification**, as well as for long-range transport. Adverse effects are reported for soil organisms, birds, fish, frog, rat, mice and humans. UNEP 2014: "Risk profile on commercial decabromodiphenyl ether" Available data also indicate that **tetra-, penta-**, and **hexa**-BDE are

	highly bioaccumulative (Environment Canada, 2006). After reviewing the available information, EPA has concluded that decaBDE likely contributes to the formation of bioaccumulative and/or potentially bioaccumulative transformation products such as lower brominated PBDEs in organisms and in the environment. Studies have shown that that photodegradation of **decaBDE** may result in PBDEs from **tri- to nona**- and biodegradation of **decaBDE** may result in **nona-, octa- and heptaBDE**s (as reviewed in Environment Canada 2009 a). USEPA PBDE TSCA Action Plan 2009

Notes:
The deca and penta members of this subclass have been shown to have carcinogenic properties. Deca: Under the USEPA Guidelines for Carcinogen Risk Assessment, the database for decabromodiphenyl ether provides suggestive evidence of carcinogenic potential. The weight of evidence of human carcinogenicity of decaBDE is based on (1) no studies of cancer in humans exposed to decaBDE; (2) statistically significant increases in incidence of neoplastic nodules in the liver of low- and high-dose male rats and high-dose female rats; (3) significantly increased incidences of hepatocellular adenoma or carcinoma (combined) in male mice at the low dose and marginally increased incidences at the high dose; (4) nonsignificantly increased incidences of hepatocellular adenoma or carcinoma (combined) in female mice; (5) slightly greater (but not statistically significant) incidences of thyroid gland adenomas or carcinomas (combined) in dosed male and female mice; (6) significantly increased incidences in male mice, at both doses, of follicular cell hyperplasia, considered by many as a precursor to thyroid tumors; and (7) an apparent absence of genotoxic potential. USEPA 2008, Integrated Risk Information System (IRIS) U.S. Environmental Protection Agency Chemical Assessment Summary National Center for Environmental Assessment.

Penta: NTP 2016 Clear evidence of carcinogenic activity in rats and mice for DE-71 mixture (penta, tetra, hexa cogeners). On Proposition 65 list for cancer.

This subclass of chemicals has also shown hepatotoxicity and immunological toxicity.

Comparison using EPA Cheminformatics[1]:

The Hazard Comparison Dashboard is a prototype tool and a compilation of information sourced from many sites, databases and sources including U.S. Federal and state sources and international bodies that saves the user time by providing information in one location. The data are not reviewed by USEPA – the user must apply judgment in use of the information. The results do not indicate EPA's position on the use or regulation of these chemicals.

			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									
DTXSID	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
DTXSID9020376	1163-19-5	2,2',3,3',4,4',5,5',6,6'-Decabromodip	L	L	L	VH	L	H	H	H			M	M	L	L	M	L	H	VH	VH	L
DTXSID30451985	437701-79-6	2,2',3,3',4,4',5,6,6'-Nonabromodiph	I				VH	L		I								VH		VH	VH	L
DTXSID30881107	63387-28-0	2,2',3,3',4,4',5,5',6-Nonabromodiph	I				VH	L		I								VH		VH	VH	
DTXSID3074789	446255-39-6	2,2',3,3',4,4',5,6'-octabromodiphen	I				VH	L		I								L		VH	VH	L
DTXSID9074775	117964-21-3	2,2',3,3',4,4',6,6'-octabromodiphen	I				VH	L		I								L		VH	VH	L
DTXSID8052693	207122-16-5	2,2',3,4,4',5',6-Heptabromodipheny	I				VH	H		I								L		VH	VH	L
DTXSID40873972	446255-26-1	BDE-180 (hepta)	I				VH	L		I								L		VH	VH	
DTXSID80873971	446255-19-2	BDE-171 (hepta)	I				VH	L		I								L		VH	VH	
DTXSID3052692	207122-15-4	2,2',4,4',5,6'-Hexabromodiphenyl e	I				VH	L		I								L		VH	VH	L
DTXSID4030047	68631-49-2	2,2',4,4',5,5'-Hexabromodiphenyl e	I			I	VH	H		I								L	VH	VH	VH	L
DTXSID60879951	446255-03-4	BDE-148 (hexa)	I				VH	L		I								L		VH	VH	
DTXSID4052685	182346-21-0	2,2',3,4,4'-Pentabromodiphenyl etl	VH				VH	H		I								VH		VH	VH	L
DTXSID4052689	189084-64-8	2,2',4,4',6-Pentabromodiphenyl etl	VH				VH	H		I								L		VH	VH	L
DTXSID9030048	60348-60-9	2,2',4,4',5-Pentabromodiphenyl etl	VH			I	VH	H		I								VH	H	VH	VH	L
DTXSID7074749	337513-72-1	1,2,3,4,5-Pentabromo-6-(2,4,5-tribi	I				VH	L		I								L		VH	VH	L
DTXSID3030056	5436-43-1	2,2',4,4'-Tetrabromodiphenyl ether	VH			I	VH	H		I								VH	VH	VH	VH	L
DTXSID5024348	147217-78-5	2',3,4-Tribromodiphenyl ether	VH				VH	L		I								L		H	VH	
DTXSID9024015	2050-47-7	4,4'-Dibromodiphenyl ether	L			I	VH	L		I					H			L	VH	H	VH	L
DTXSID8023927	101-55-3	p-Bromodiphenyl ether	L			I	VH	L		L					H			VH	VH	M	H	H

Note: Due to the ambiguities of the structures for CAS 32534-81-9 (penta) and 32536-52-0 (octa) these CAS numbers do not yield any hazard data in Cheminformatics. The table shows hazard data for all discretely defined congeners.

Monobromodiphenyl ether on TURA list, never reported – CERCLA chemical RY 1991

[1] Cheminformatics analysis modules provide information on chemicals including high-quality chemical structures, experimental and predicted physicochemical properties, environmental fate and transport information, and appropriately linked toxicity data. This research improves the understanding of chemical fate and activity in both organisms (humans and wildlife) and the environment to support chemical safety decision making. The Cheminformatics analysis modules, including a Hazard Comparison Dashboard, enable users to search and compare a variety of chemical and 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.