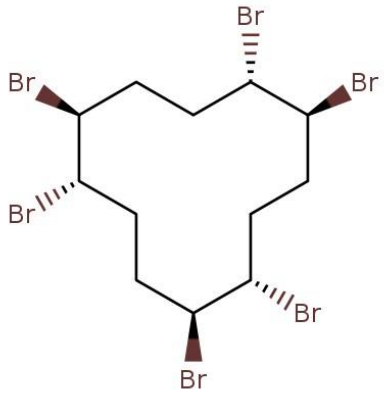
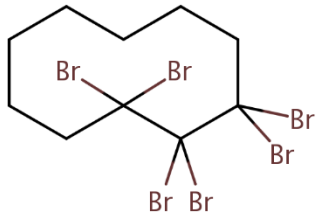
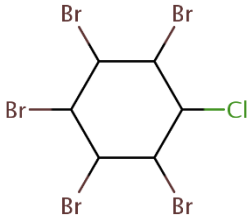
Polyhalogenated Alicyclics identified in the FR Law: **Hexabromocyclododecane (HBCDD)** **CAS #: 25637–99–4; 3194-55-6**  	**Relevant Endpoints: PBT, reproductive/developmental toxicity, neurotoxicity, endocrine disruption (thyroid), and aquatic toxicity** "HBCDD is a brominated flame retardant found world-wide in the environment and wildlife. Human exposure is evidenced from its presence in breast milk, adipose tissue and blood. It bioaccumulates and biomagnifies in the food chain. It persists and is transported long distances in the environment, and highly toxic to aquatic organisms. It also presents potential human health concerns based on animal test results indicating potential reproductive, developmental and neurological effects. (EPA Action Plan, 2010)" **Proposed Analogues:** Analogue #1: Hexabromocyclodecane (CAS #: 25495-98-1)  Analogue #2: Pentabromochlorocyclohexane (PBCC) (CAS #: 87-84-3) 
HEALTH HAZARDS	
Chronic or Sub-chronic Toxicity	
Neurotoxicity	The developing brain has been determined to be a target organ for HBCDD exposure. Effects range from spontaneous behavior and habituation, brainstem auditory evoked potential, catalepsy, and effects on memory and learning ability (Encyclopedia of Toxicology, 2015).
Developmental/Reproductive Toxicity	HBCDD is suspected of damaging fertility or the unborn child and may cause harm to breast-fed children. In EPA's 2022 Unreasonable Risk Determination for HBCDD, they identified offspring loss as the most concerning endpoint for acute HBCDD exposures for all conditions of use. They also noted additional hazards associated with

	other adverse effects for acute and chronic exposures including reproductive and developmental effects. UNEP's HBCDD Risk Profile, page 4 "In mammals, studies have shown reproductive, developmental and behavioral effects with some of the effects being trans-generational and detectable even in unexposed off-spring. Besides these effects, data from laboratory studies with Japanese quail and American kestrels indicate that HBCDD at environmentally relevant doses could cause eggshell thinning, reduced egg production, reduced egg quality and reduced fitness of hatchlings." Page 25: "HBCDD exerts reproductive, developmental and neurotoxic effects in mammals and birds with a NOEC/NOAEL in the order of 1 mg/kg/day. In vivo data include: • Decreased pup survival and fewer primordial follicles in rats at 100 mg/kg/day, NOAEL 10 mg/kg/day (Ema et al. 2008). • Decreased pup weight, decreased testis and prostrate weights, impaired hearing, and reduction in female bone mineral density in rat offspring at 30-100 mg/kg/day (van der Ven et al. 2009, Lillienthal et al. 2009). • TH imbalance and impaired oligodendroglial development in the brain cortex of rat offspring at 1,000 ppm (81-213 mg/kg/day), NOAEL 8-21 mg/kg/day (Saegusa et al. 2009). • Behavioral effects in mice exposed to 13.5 mg/kg/day at day 10, NOAEL 0.9 mg/kg/day (Eriksson et al. 2006). • Bird egg/chick survival was decreased in quails exposed via the feed to 15 ppm HBCDD (2.1 mg/kg/day), NOEC 5 ppm (0.7 mg/kg/day) (Ministry of the Environment, Japan, 2009). • Differences in courtship behavior, earlier egg-laying, and a slower growth rate were observed in American kestrels exposed daily to 800 ng/g HBCDD, internal dose of 164 ng/g ww α-HBCDD (Dioxin 2010b and Dioxin 2010c)." EPA Federal Register 2016: "HBCDD has been shown to cause developmental effects at doses as low as 146.3 mg/kg/day (LOAEL) in male rats. Developmental effects have also been observed with a BMDL of 0.056 mg/kg/day (BMD of 0.18 mg/kg/day) based on effects in female rats and a BMDL of 0.46 mg/kg/day (BMD of 1.45 mg/kg/day) based on effects in male rats. HBCDD also causes reproductive toxicity at doses as low 138 mg/kg/day (LOAEL) in female rats. Based on the available developmental and reproductive toxicity, EPA believes that HBCDD can be reasonably anticipated to cause moderately high to high chronic toxicity in humans. Therefore, EPA believes that the evidence is sufficient for listing the HBCDD category on the EPCRA section 313 toxic chemical list pursuant to EPCRA section 313(d)(2)(B) based on the available developmental and reproductive toxicity data." HBCDD is considered a substance of very high concern (SVHC) under ECHA.

	(Suspected to be toxic to reproduction).
Endocrine Disruption	HBCDD is on the TEDx List.
Thyroid	In EPA's 2022 Risk Determination of HBCDD thyroid effects were determined to be the most sensitive and robust endpoint for noncancer adverse effects for all conditions of use.
Other organ toxicity	Page 22 EPA PPR Tox Values for PBCC **(1999): "In the subchronic-duration studies of FR-651A, FR-651G, and FR-651 "slurry dried" described above (Dow Chemical Co, 1980a, b, c), bromine content of the adipose tissue, liver, and kidney of treated and control rats was measured at termination. In all three studies, increased bromine levels were detected in treated animals relative to controls. Bromine concentrations were higher in the kidney than liver or adipose (kidney > liver > adipose tissue). Concentrations increased across dose groups in a dose-related manner. No sex differences in bromine concentrations were evident. The authors estimated that about 1–2% of the total bromine ingested was in these tissues at termination (Dow Chemical Co, 1980a, b, c)."** **Additional data in original study, EPA ORD 1985 Health and Environmental Effects Profile for PBCC. Presumably these were all considered in the 1999 EPA PPR Tox Values.**
Carcinogenesis	Page 25 EPA PPR Tox Values for PBCC(1999): **"Suggestive evidence of carcinogenic potential" Two chronic-duration studies of F344 rats orally exposed to mixtures in which PBCC was the primary constituent have shown increased incidences of intestinal tumors (Keys et al.(1982) as cited in U.S. EPA (1985); Dow Chemical Co (1983a, 1983b)**
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
PBT	HBCDD and its various isomers may be susceptible to long-range transport. Elevated concentrations have been found in animals and environmental samples in remote areas including the Arctic. These substances are considered to be highly persistent in the environment as HBCDD binds strongly to sediment and is immobile in soil (EPA Action Plan, 2010). HBCDD is widely accepted as a Persistent, Bioaccumulative and Toxic Substance and is a listed as a Persistent Bioaccumulative and Toxic Chemical Category under EPA's Toxics Release Inventory. HBCDD is on Washington State's Persistent Bioaccumulative Toxic List HBCDD is listed as Persistent, Bioaccumulative and Toxic and Persistent Organic Pollutants under ECHA. HBCDD is listed as a Persistent Organic Pollutant (POP) under UNEP's Stockholm Convention on POPs
Bioaccumulation	"HBCDD has been measured in air and sediment in Scandinavian countries, North America and Asia (Covaci, et al., 2006, Arnot, et al., 2009). HBCDD has been measured in marine and arctic mammals, freshwater and marine

	fish, aquatic invertebrates, birds and bird eggs, and one plant species (Covaci, et al., 2006; Arnot, et al., 2009). HBCDD has been detected in Arctic air in northern Scandinavia and in Arctic birds and bird eggs, Arctic fish, ringed seals and polar bears (UNEP, 2009). It has been detected in freshwater, marine, and avian organisms, and in upper trophic-level mammals (polar bears and seals)." (EPA Action Plan, 2010) BCF for HBCDD average of 16 experimental data points = 26900 (ECOTOX) **EPA ORD 1985 pages 9-11, McCarty et al. (1978) estimated a BCF of 2400 for PBCC in trout muscle based on its log octanol-water partition coefficient. Three additional calculated BCF values are 618, 8470 and 15000, leading to the conclusion that PBCC is likely to bioaccumulate significantly in aquatic organisms.**
Aquatic Toxicity	EPA's 2022 Risk Evaluation of HBCDD delayed hatching and reduced growth of offspring were the most concerning endpoints for pelagic organisms from acute and chronic exposures of HBCDD. Reduced reproduction was identified as the most sensitive endpoint for benthic organisms as a result of chronic exposure to HBCDD. Soil organisms also experienced reduced reproduction and survival after chronic exposure to HBCDD. Usenko 2016: LC50 = 7.7ppm in zebrafish
Breakdown/degradation /combustion products	HBCDD degradation observed under abiotic conditions was attributed to abiotic reductive dehalogenation (Refs. 44, 76, and 95). Degradation proceeded through a stepwise process to form tetrabromocyclododecene, dibromocyclododecadiene (DBCD), and 1,5,9-cyclododecatriene (Refs. 44 and 95). Further degradation of 1,5,9-cyclododecatriene was not observed. In this study, HBCDD degradation occurred faster in sediment than in soil and faster under anaerobic conditions compared to aerobic conditions (Refs. 44 and 95). (EPA Federal register, 2016)

Chemiformatics Table for HBCDD and Analogues

Chemicals: 3

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

Skipped (0)
Unlikely (0)
Filters (0)
Sorting (0)
Structure

CAS Name	Human Health Effects															Ecotoxicity		Fate		
	Acute Mammalian Toxicity								Neurotoxicity		Systemic Toxicity									
	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
3194-55-6 HIGBT 1,2,5,6,9,10-Hex…	*L*				*VH*	H	M	H								VH	VH	*H*	VH	*L*
25495-98-1 Cyclodecane, he…	*M*				*I*	*L*		*I*								*VH*			*L*	*L*
87-84-3 GBTPS Pentabromochlor…	L			**VH**	L	*L*		*I*								L	*VH*		M	*L*

1. HBCDD
2. HBCyD
3. PBCC