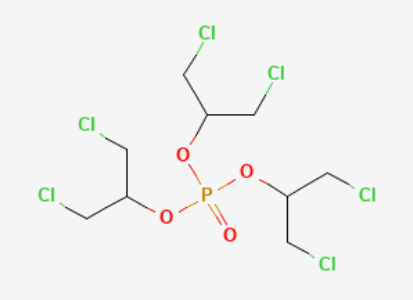
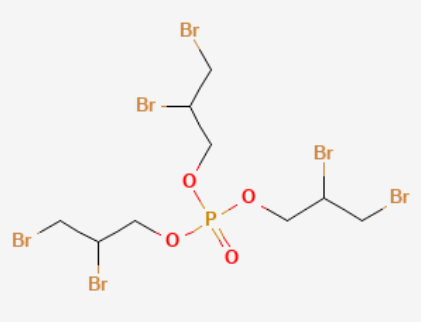
Updated EHS Summary of Tris(1,3-dichloro-2-propyl) Phosphate and Analogues for the MA TURA SAB Meeting – June 20, 2024

Tris(1,3-dichloro-2- propyl)phosphate (TDCPP) (CAS#: 13674-87-8)

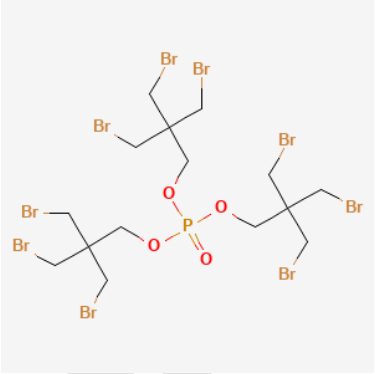


Analogue #1: Tris(2,3-dibromopropyl) phosphate (TDBPP) (CAS#: 126-72-7)

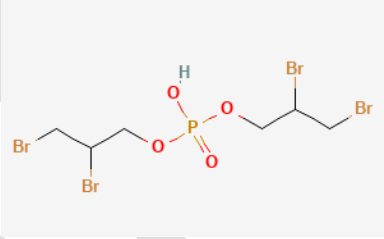


Primary hazards include cancer, genotoxicity, endocrine disruption (thyroid), nephrotoxicity, reproductive, developmental toxicity and persistence.

Analogue #2: Tris(tribromoneopentyl) phosphate (TTBNP) (CAS#: 19186-97-1)



Analogue #3: Bis(2,3-dibromopropyl) phosphate (BDBPP) (CAS#: 5412-25-9)



Analogue #3 is a hydrolysis product of **Analogue #1.**

TDCPP, Analogue #1, and Analogue #2 are all listed on the TSCA List of 30 Organophosphate Flame Retardants, and all are identified in the Polyhalogenated Organophosphate Subclass of the Consumer Product Safety Commission 2018 report.

PHYSICAL CHARACTERISTICS	
Primary Use	**TDCPP** is used as an additive flame retardant in resins, latexes, and polyurethane foams.
HEALTH HAZARDS	
Chronic or Sub-chronic Toxicity	
IARC rating	**Analogue #1 (TDBPP):** Probably carcinogenic to humans (Group 2A) based on sufficient evidence in experimental animals (IARC 1987).
Carcinogenicity	**TDCPP:** High hazard for carcinogenicity based on sufficient evidence of carcinogenicity in a two-year combined chronic toxicity and carcinogenicity assay in rats. It is also included as a substance known to cause cancer on the California Proposition 65 list of chemicals (EPA, 2015). The EU classified **TDCPP** as a Category 2 Carcinogen.

	Analogue #1 (TDBPP) is reasonably anticipated to be a human carcinogen based on sufficient evidence from studies in experimental animals (NTP, 1981). **Analogue #2: (TTBNP):** There is potential for **carcinogenicity** based on a consideration of the mechanistic potential for alkylation and crosslinking (EPA, 2015). **Analogue #3 (BDBPP):** "Four groups of 40 Wistar rats of each sex per dose level were fed diets containing 0, 80, 400 or 2000 ppm of the magnesium salt of bis(2,3-dibromopropyl)phosphate (Bis-BP) for 24 months. A high incidence of tumours was induced, in both sexes, in the digestive system. Tumours included papillomas and adenocarcinomas of the tongue, esophagus and forestomach, adenocarcinomas of the intestine and hepatocellular adenomas (neoplastic nodules) and carcinomas. Pre-terminal mortalities were associated with an increased incidence of forestomach papillomas in both sexes, adenocarcinomas of the small intestine in male rats and increased incidence of hepatocellular carcinomas in females. The data suggest that Bis-BP is a more potent proximate carcinogen than tris-(2,3-dibromopropyl)phosphate (Tris-BP)" (Takada, 1991).
Neurotoxicity	**TDCPP** has an affinity for the nervous system and is commonly associated with neurotrophic inhibition (Gu, 2018). **TDCPP** has shown neurotoxic effects in several animal or animal-derived cell-based models. Examples of adverse effects include decreased neurobehavioral responses, progressive degenerative changes in responses, changes in acetylcholinesterase (Ache) activity, neurotransmitter levels, reduced serotonin and dopamine levels, expression levels for mRNAs and proteins related to central nervous system development (Wang, 2020). **TDCPP and Analogue #1 (TDBPP):** "The greatest similarities were observed between compounds with similar halogenation substitution patterns, suggesting the presence of a structure activity relationship. Across all tested measures, the effects of **TDCPP** and **TDBPP**, which differ only by the type of halogen substituent, were nearly identical, with each promoting differentiation into both the cholinergic and dopaminergic phenotypes. TCEP and TCPP, however, which differ from TDCPP and TDBPP most notably by the number halogen substituents, showed distinct effects on neurodifferentiation; these OPFRs promoted emergence of the cholinergic phenotype without affecting dopaminergic expression. Thus, the results of these studies suggest that the difference in molecular size due to the presence of two different halogen atoms (i.e. bromine and chlorine) had little effect. Rather, differences in the halogen substitution patterns appear to be an important factor in determining the effect of OPFRs on phenotypic fate" (Dishaw, 2011).

	Analogue #2 (TTBNP) has a high potential for neurotoxicity based on the potential for the neopentyl alcohol groups acting as leaving groups (EPA, 2014).
Developmental/Reproductive Toxicity	**TDCPP:** High hazard for reproductive toxicity based on an oral two-year combined chronic toxicity and carcinogenicity assay in rats. Effects included atrophy and decreased secretory product of the seminal vesicle and damage to the testes and epididymis. Moderate hazard for developmental toxicity based on two prenatal developmental toxicity studies in rats (EPA, 2015). **TDCPP** exposure may cause adverse effects to the reproductive systems. Effects seen in animals include, decreased zebrafish hating rate, reduced egg production, promotion of oocyte maturation in females, and retardation of spermiation in males, as well as an increased severe malformation ratio and decreased egg quality, and overall decrease in reproduction performance (Wang, 2020). **TDCPP** has been shown to cause developmental toxicity in experimental animal studies. Adverse effects include organ malformations in Japanese medaka, body and heartrate changes in zebrafish, mortality, spinal curvatures, and other malformations in zebrafish, body size, short tail, and other developmental abnormalities in zebrafish (Wang, 2020). **Analogue #2 (TTBNP):** Moderate potential for reproductive and **neurodevelopmental effects** based on presence of alkylating groups and cholinesterase inhibition (EPA, 2014).
Genotoxicity/Mutagenicity	**TDCPP:** Moderate hazard for genotoxicity based on a weight of evidence including positive test results in in vitro chromosomal aberration and gene mutation tests (EPA, 2015). **Analogue #1 (TDBPP)** is mutagenic in bacteria and results in genetic damage in cultured mammalian cells, *Drosphila melanogaster* and mice, probably via metabolism to various intermediates of which 2-bromoacrolein may be particularly important (IARC 1987). **"TDCPP** was metabolized to products which were mutagenic for Salmonella typhimurium TA100 in the presence of liver microsomes from phenobarbital (PB)-pretreated rats and NADPH. Effects of various inhibitors and inducers of cytochrome P-450 on Tris-CP mutagenicity were in accordance with PB-inducible forms of this enzyme system being responsible for the formation of mutagenic product(s). A comparison was made between the toxic potential of the two halogenated flame retardants TDCPP and **Analogue #1 (TDBPP)** in 5 in vitro tests. **TDCPP was much less potent than TDBPP** with respect to bacterial (Salmonella/microsome or Salmonella/hepatocyte assay) and mammalian (V79

	cells) mutagenicity, as well as DNA repair synthesis in hepatocytes. On the other hand, **TDCPP** and **TDBPP** were both equally effective in transforming Syrian hamster embryo cells in vitro. TDCPP was not nephrotoxic to rats after a single dose of 500 mg/kg intraperitoneally, whereas **TDBPP** caused extensive tubular necrosis accompanied by elevated levels of plasma urea and creatinine" (Søderlund, 1985). **Analogue #3 (BDBPP):** "The mutagenicity of pure synthesized samples of bis(2,3-dibromopropyl)phosphate (bis-BP) and mono(2,3-dibromopropyl)phosphate (mono-BP) against Salmonella typhimurium TA100 was examined in relation to microsomal activation of tris(2,3-dibromopropyl)phosphate (tris-BP). Both mono- and bis-BPs were weak direct mutagens. Their mutagenicities increased with S9 mix, but the rates were much less than that of tris-BP. The magnesium and ammonium salts of mono- and bis-BPs were also prepared and their mutagenicities were examined with S9 mix in relation to 2 commercial flame retardants (our abbreviations: DB-1 and DB-2). In both mono- and bis-BP series, an apparent increase of mutagenicity was observed in the order: ammonium salt greater than magnesium salt greater than free acid. On the other hand, mono-BP and its salts are usually more active than the corresponding bis-BPs independently of the kind of cation. DB-1 (DB-2), however, is more potent than the magnesium (ammonium) salts of mono- and bis-BPs, the constituents in DB-1 (DB-2). No synergistic effect between mono-BP salts and bis-BP salts was observed. The different unknown mutagenic compounds in DB-1 and DB-2 are suggested" (Nakumara, 1983).
Endocrine Disruption	**TDCPP** is listed on the TEDx List of potential endocrine disruptors. "**TDCPP** exerts endocrine disruption activity through multiple mechanisms including steroidogenesis, estrogen metabolism, thyroid hormone (TH) and thyroid receptor (TR) interference, agonistic activity on retinoid X receptor α, or antagonistic activity on the androgen receptor and glucocorticoid receptor in in vivo and in vitro studies (Godfrey et al., 2019; Kojima et al., 2013; Liu et al., 2012; Moser et al., 2014; Ren et al., 2016b)" (Wang, 2020). "**TDCPP** in house dust has been correlated with altered levels of hormones related to fertility and thyroid function in men. TDCPP inhibited the luciferase expression induced by dihydrotestosterone in a reporter-gene assay using cultured cells and induced delays in remethylation of the zygotic genome (mechanism that may be associated with enhanced developmental toxicity) in zebrafish. In addition, TDCPP disrupted steroidogenic pathways and metabolism of estrogen in human cell lines (H2925R and WVLN) and in zebrafish. A 2-year combined chronic toxicity and carcinogenicity assay in rats resulted in changes of the parathyroid, testes, and epididymis; it is unclear if these observed changes may be an indication of endocrine activity" (EPA, 2015).

Thyroid	**TDCPP** produced lymphoid depletion of the thymus and decreases in LPS (B-cell antigen) and Con A (T-cell antigen) in mice following subcutaneous injection for 4 days (EPA, 2015). "**TDCPP** exhibited more potent toxicity to THs and TRs than other OPFRs, such as TMP, TEP, and TCEP (Moser et al., 2014; Ren et al., 2016b). Exposure of zebrafish to TDCPP for 14 d led to a significant reduction in the plasma levels of triiodothyronine (T3) and thyroxine (T4) in males, but an increase in females (Liu et al., 2019). TDCPP altered the transcript levels of regulatory genes and receptors in the fish hypothalamus, pituitary, and thyroid glands in a sex-dependent manner (Liu et al., 2019)" (Wang, 2020). "Parental exposure to **TDCPP** alone or in combination with PS-NPs induces thyroid disruption in adults, and then leads to thyroid endocrine disruption in their larval offspring. Reduced thyroxine (T4) and 3,5,3'-triiodothyronine (T3) levels contributed to the observed transgenerational thyroid dysfunction, which inhibited developmental growth and disturbed the transcription of genes and expression of proteins involved in the hypothalamic-pituitary-thyroid (HPT) axis in the F1 larvae. The increased transfer of TDCIPP to the offspring in the presence of PS-NPs also enhanced transgenerational thyroid endocrine disruption, demonstrated by a further reduction in T4 and the upregulation of thyroglobulin (tg), uridine diphosphate-glucuronosyltransferase (ugt1ab), thyroid-stimulating hormone (tshβ), and thyroid hormone receptor (trα) expression in the F1 larvae compared with the effects of parental **TDCPP** exposure alone." (Zhao, 2021) (Liu, 2022) Reported a significantly high-risk association between exposure of organophosphate esters including, **tris (1,3-dichloro-2-propyl) phosphate** and others and thyroid cancer in both males and females.
Kidney	**Analogue #1 (TDBPP)** and its metabolites **Analogue #3 bis(2,3-dibromopropyl)-phosphate (BDBPP)** and mono(2,3-dibromopropyl phosphate are nephrotoxic in rodents (IARC 1987). Potential **Analogue #1 (TDBPP)** metabolites **Analogue #3** (**BBDPP)** and Mono BP were mutagenic and nephrotoxic in rats, presenting similar hazards to the parent compound TDBPP. **Although Analogue #1 (TDBPP) is more mutagenic than Analogue #3 (BBDPP) and Mono BP, the two potential metabolites were shown to be more nephrotoxic than TDBPP** (Søderlund, 1982). **Analogue #1 (TDBPP)** can penetrate the skin of rabbits and significant quantities to cause serious organ damage. Rabbits exposed to TDBPP resulted in pathologic lesions in kidneys after the skin painted for 90 days and caused benign and malignant tumors of the skin, forestomach, and oral cavity in a statistically significant number of mice when compound was applied to the skin three times a week (Reznik, 1979).

	Analogue #1 (TDBPP) and Analogue #3 (BBDPP): "The mechanism of Tri or Bis-BP (a metabolite of Tris-BP) induced nephrotoxicity was investigated by determining urinary excretion of enzymes and selected metabolites. Rats received single oral doses of 0, 71.7, 143.4 and 286.8 mumol/kg tris (2,3-dibromopropyl) phosphate (Tris-BP) or bis (2,3-dibromopropyl) phosphate (Bis-BP). Urine was collected over a 24 h period and subjected to biochemical examinations. Comparative studies on Tris-BP- and Bis-BP-induced nephrotoxicities were carried out for abnormal patterns of urinary excretion. Histopathologically, the nephrotoxic effect of Tris-BP appeared one day later and was more obvious than that of Bis-BP in rats after single oral administration" (Fukuoka, 1988).
ENVIRONMENTAL & ECO-SYSTEM HAZARDS	
PBT	**TDCPP** is considered a high hazard for persistence based on experimental guideline studies. Evidence of **TDCPP** biodegradation resulting in a half-life of 60 days (EPA, 2015). In an EU risk assessment **TDCPP** was determined to meet the criteria of being persistent or very persistent in the environment, but it does not meet the criteria of being bioaccumulate or toxic in the environment (EU, 2008). "**TDCPP** appears to be a persistent and mobile organic chemical (PMOC), which are highly polar (mobile in water) and can pass through WWTPs, subsurface water, and potentially drinking water treatment processes (Reemtsma et al., 2016). Compared with PBDES, TDCPP is more soluble and can persist in water, which gives it the ability to undergo long-range transport via waterborne routes (Blum et al., 2019)" (Wang, 2020). **Analogue #2 (TTBNP)** has a molecular weight slightly >1,000. It is expected to have negligible water solubility and poor bioavailability to microorganisms indicating that biodegradation is not expected. Estimated hydrolysis half-lives of around 10 years indicate that this will not be an important environmental removal process. TTBNP does not contain functional groups that would be expected to absorb light at environmentally significant wavelengths. **TTBNP is expected to have high potential for environmental persistence** (EPA, 2014).
Bioaccumulation	"Threats of **TDCPP** to ecological systems have been widely reported in the literature, and different degrees of TDCPP have been detected in various biological samples such as mussels (Harino et al., 2014), bivalves (Rebecca et al., 2018), and other tissues of high trophic level species such as the muscles of freshwater fish (Ma et al., 2013, Sundkvist et al., 2010), feathers and plasma of white-tailed eagle nestlings (Eulaers et al., 2014), and blubber of harbor seals (Rebecca et al., 2018) (Fig. 3; Table S8). Ma et al. (2013) showed that TDCPP is prone to bioaccumulate in aquatic organisms, and levels up to 251 μg/kg lw (lipid weight) have been detected in the muscles of freshwater fish. Sundkvist et al. (2010) made a similar conclusion when studying freshwater Swedish

	perch because larger (older) perch had higher levels of TDCPP than smaller perch from the same lake." (Wang, 2020).
Aquatic Toxicity: LC_{50}, EC_{50}, ErC_{50}, NOAEC/NOEC	**TDCPP** is a high hazard for acute and chronic aquatic toxicity based on several studies including a measured 96-hour LC50 of 1.1 mg/L in fish, a 48-hour LC50 of 3.8 mg/L in daphnia, and a 72-hour ErC10 = 2.3 mg/L in green algae. Chronic was based on a measured 21-day NOEC of 0.5 mg/L (LOEC = 1.0 mg/L) in daphnid for reduced reproduction; the NOEC and LOEC for reduced growth was 1.0 mg/L and 2.0 mg/L, respectively (EPA, 2015).

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