Flame Retardants

Advice and Summary Statements provided

by the Science Advisory Board to MassDEP

General questions and answers regarding CAS numbers, isomers and analogues

May 12, 2023 Meeting Minutes

Does the board agree that these **additional CAS numbers** of the original flame retardants in the law should be included in the regulations? The board agreed they should be included, noting that those CAS numbers that are mixtures (e.g., paraffins) also meet the definition of analogue.

Does the board agree that these **isomers** of the original flame retardants in the law should be included in the regulations? The board agreed the isomers presented are all similar enough to be included.

Do these **isomers** also fit the analogue definition? The board agreed they meet the analogue definition.

Do the 24 proposed close **analogues** meet the analogue definition? Each proposed analogue was briefly reviewed, and the board agreed they all fit the definition, while also noting that the definition is quite broad.

Summary Statements for each subclass

Polyhalogenated Diphenyl Ethers Subclass

September 22, 2023 Meeting Minutes

"Deca- to di-bromodiphenyl ether are reasonably anticipated to have similar concerns regarding toxicity hazard, persistence, and bioaccumulation to the original flame retardants (octa- and penta-bromodiphenyl ether) in the Massachusetts Flame Retardant Law. Mono-bromodiphenyl ether shows ecotoxicity concerns but likely has lower persistence and bioaccumulation. Also, mono-bromodiphenyl ether is likely to have higher brominated isomers in the mixture."

Inorganic Subclass

November 6, 2023 Meeting Minutes

As metals, antimony trioxide, antimony pentoxide, and sodium antimonate are persistent. Oxidation states convert from trioxide/pentoxide and back under certain conditions. The antimony compounds undergo oxidation and reduction under aerobic and anaerobic conditions respectively, converting between (+3,+5) oxidation states. In vivo studies have observed pentavalent antimony species converting to antimony trioxide. There is similar (low) bioaccumulation for antimony trioxide, antimony pentoxide, and sodium antimonate. Regarding aquatic toxicity there are studies that show toxicity but there is a lack of data distinguishing the two (+3,+5) valence forms. Because antimony trioxide, but not antimony pentoxide, is reasonably anticipated to be a human carcinogen by NTP, and ATSDR notes other occupational effects for ATO, there is a concern that antimony pentoxide can convert to the trioxide form in the body. There are few studies evaluating this conversion, particularly after inhalation exposure. Moreover, studies on the health effects of antimony pentoxide are lacking.

Polyhalogenated Bisphenol Aliphatics Subclass

January 19, 2024 Meeting Minutes and addition February 29, 2024

- Given the structural homology of “analogue 1, 3 & 4” with TBBPA, and the fact they are precursors to TBBPA via environmental degradation and metabolism, and therefore are likely to exert similar effects as TBBPA including, endocrine, developmental, reproductive effects, and environmental persistence. There is evidence of aquatic toxicity for these analogues in multiple test systems.
- While there is a paucity of data for "Analogue #4", the structural homology and the small difference - introduction of a methyl group - preserves the physical and chemical properties of the original structure and therefore can reasonably be included in this group of similar substances.
- Analogues that have TBBPA as a metabolite are justified to be included in the law.
- Analogue #2 is also structurally homologous and has compelling evidence in multiple species for reproductive toxicity, developmental toxicity, and endocrine disruption.
- Carbon chlorine bonds are more easily broken in the environment (to form BPA). While all four analogues (and TBBPA) have the potential to break down to BPA, analogue #2 may be the most likely to.

All (above) analogues are sufficiently similar to TBBPA that they would be reasonably anticipated to have similar concerns regarding toxic hazard. Analogue 1, 3, and 4 would be reasonably anticipated to have similar concerns regarding persistence.

Polyhalogenated Phthalates Subclass

February 29, 2024 Meeting Minutes

1. The analogues share the same primary degradation product (tetrabromophthalic acid) so toxic effects of that metabolite would be expected to be shared by the proposed analogues.

2. Persistence – TBPH is persistent and the primary degradation product common to all proposed analogues (and TBPH), tetrabromophthalic acid, is also persistent (EPA, 2015).

3. Bioaccumulation was not reviewed, due to a lack of information for the analogues, including a lack of empirically-based bioaccumulation factors.

Toxicity data on analogues are limited, with some evidence of reproductive and developmental toxicity. However, based on the structural homology and that the differences in each structure does not substantially change the degradation processes of these analogues into the common metabolites of TBPH, similar hazard profiles among TBPH and its analogues are anticipated.

At high temperatures, high pH, and highly aqueous environments occurring during use such as in extinguishing fires the rate of conversion of “analogue 1, 2, 3 & 4” into the common metabolites of TBPH is in fact highly accelerated. The common degradation product, tetrabromophthalic acid, is persistent.

Degradation of TBPH and its analogues is likely given that carboxylesterases, which catalyze the ester bond cleavage in a variety of conditions and play an important role in metabolism, are widely distributed in the environment. Polymerized applications on reacted versions of “analogue 4” will likely have much slower rates of degradation due to lower bioavailability and higher steric hindrance and hydrophobicity in polymeric form.

The analogues are sufficiently similar to TBPH that they would be reasonably anticipated to have similar concerns regarding toxic hazard and persistence.

While conclusions are based upon chemical structure, as toxicity data on analogues are limited, the paucity of data for individual analogues 1, 2, 3 & 4 is not a concern as the structural homology is compelling and the change in each structure does not substantially change the degradation processes of these analogues into the common metabolites of TBPH.

Analogues: #1: 2-(2- hydroxyethoxy)ethyl-2- hyroxypropyl-3,4,5,6- tetrabromo phthalate, CAS 20566-35-2 #2: 2-(2- hydroxyethoxy)ethyl-2- hyroxypropyl-3,4,5,6- tetrabromo phthalate mixed esters with diethylene and propylene glycol, CAS 77098-07-8 #3: Tetrabromophthalic acid dimethyl ester, CAS 55481- 60-2 #4: Diallyl tetrabromophthalate, CAS 49693-09-6

Polyhalogenated Alicycles Subclass

February 29, 2024 Meeting Minutes

The strongest empirical evidence regarding the similarity of the analogues to HBCDD pertains to bioaccumulation. Based on hydrophobicity and modeled BCF values, PBCC and HBCyD are expected to be bioaccumulative to highly bioaccumulative. Experimental data also confirm the high bioaccumulation for PBCC.

• It appears that the analogues to HBCDD have similar concerns regarding acute and chronic aquatic toxicity based upon predicted Cheminformatics values. Acute aquatic toxicity for PBCC is greater than HBCD, based upon limited experimental data (Usenko 2016).

• There is a general lack of human toxicity and persistence data for these analogues. There is no empirical - only predicted - information on analogue 1 (HBCyD).

• PBCC has suggestive evidence of carcinogenic potential (based on one study, EPA 1985), an effect that has not been seen in HBCDD. Note PBCC is noted as a "less close" analogue to HBCDD.

Polyhalogenated Aliphatic Chains

April 29, 2024 Meeting Minutes

The Board agreed that MCCPs and LCCPs are analogues of SCCPs according to the DEP definition of analogue.

- There was agreement from the Board that MCCPs and LCCPs are analogues to SCCPs. Short, medium and long chain chlorinated paraffins are anticipated to have identical intermolecular forces irrespective of the length and can be reasonably considered analogues.
- Various paraffin lengths are present in commercial mixtures. Mixtures of chlorinated n-alkanes are produced by reacting normal paraffin fractions obtained from petroleum distillation with gaseous chlorine exothermically at 80–120°C in the liquid phase (Chlorinated Paraffins Industry Association, 1988). Synthesis of pure isomers is not at all typical of manufacturing processes.
- Since the SCCPs were included in the Stockholm Convention in 2017, the production of MCCPs and LCCPs has increased as alternatives (Liao, 2023).
- Persistence is a concern for all three groupings SCCPs, MCCPs, and LCCPs.
- Chain length and amount of chlorination affect bioaccumulation, chlorinated paraffins in each grouping are bioaccumulative.

- While MCCPs have lower predicted ecotoxicity, they have higher predicted persistence in soil (in one meta study Kobeticova, 2018).
- There is a lack of data regarding toxicity on LCCPs.
- Data are lacking to assess whether MCCP and LCCP will have similar carcinogenic effects seen in SCCPs.

Polyhalogenated Organophosphates

June 20, 2024 Meeting Minutes

Summary Statement for TDCPP and Analogues

Tris(1,3-dichloro-2- propyl)phosphate (TDCPP) (CAS#: 13674-87-8)
Analogue #1: Tris(2,3-dibromopropyl) phosphate (TDBPP) (CAS#: 126-72-7)
Analogue #2: Tris(tribromoneopentyl) phosphate (TTBNP) (CAS#: 19186-97-1)
Analogue #3: Bis(2,3-dibromopropyl) phosphate (BDBPP) (CAS#: 5412-25-9)

-Reasonable similarity/good evidence across all three analogues for carcinogenicity and neurotoxicity
-Analogue 3 is a metabolite of analogue 1; similar toxicity effects expected; similar nephrotoxic effects seen for analogue 1and 3 (Fukuoka 1988) (this is not a comparison to the listed FR)
-Persistence: TTBNP> TDCPP =TDBPP > BDBPP. Most of these compounds are persistent, have low water solubility and likely bioaccumulate. Persistence and bioaccumulation are likely less for BDBPP.
-Strong evidence for reproductive and neurodevelopmental toxicity for TDCPP; evidence for analogue 2 (EPA 2014)
-Aquatic toxicity - only data is for TDCPP, however similar impacts are expected across the chemicals, especially in conserved developmental pathways

Summary Statement for TCEP and Analogues

Tris(2-chloroethyl)phosphate (TCEP) (CAS# 115-96-8)
Analogue #1: Bis(2-chloroethyl)2-chloroethylphosphonate (CAS#: 6294-34-4)
Analogue #2: “V6” 2,2-bis(chloromethyl)-propane-1,3- diyltetrakis(2- chloroethyl) bisphosphate (CAS#: 38051-10-4)

Analogues #1 and #2 are chemically related to TCEP and are all* persistent; for other endpoints (bioaccumulation, toxicity) there are not enough data for Analogue #1 and there are dissimilarities for Analogue #2. Analogue #2 can be a mixture with TCEP in production.

Analogue #1 does not have enough data to draw conclusions, except: *expect similar persistence due to structural similarity.

Analogue #2

- Can be a mixture with TCEP in production
- Has low biodegradation and is likely to be persistent.
- Has higher aquatic toxicity than TCEP, but TCEP is not very toxic to aquatic life.
- Not similar to TCEP for the reproductive endpoint (2 generation OECD guideline study for Analogue #2 does not show treatment related reproductive effects.)

Acronyms (not previously defined)

ATO – Antimony trioxide

ATSDR – Agency for Toxic Substances and Disease Registry

BCF – Bioconcentration Factor

CAS – Chemical Abstract Services

DEP – Massachusetts Department of Environmental Protection

EPA – US Environmental Protection Agency

FR – Flame Retardant

HBCDD – Hexabromocyclododecane

HBCyD – Hexabromocyclodecane

LCCP – Long chain chlorinated paraffin

MCCP – Medium chain chlorinated paraffin

NTP – National Toxicology Program

PBCC – 1,2,3,4,5-Pentabromo-6-chlorocyclohexane

SCCP – Short chain chlorinated paraffin

TBBPA – Tetrabromobisphenol A

TBPH – Bis-2(ethylhexyl)-3,4,5,6-tetrabromophthalate

For identification of the specific analogues, see "Proposed FR CAS Numbers, Isomers and Analogues for SAB Consideration"