Toxics Use Reduction Institute Science Advisory Board Meeting Minutes
June 20, 2024
Virtual Zoom Meeting
10 AM

Members Present: Robin Dodson (Chair), Lisa Cashins, Christy Foran, Rich Gurney, Denise Kmetzo, Wendy Heiger-Bernays, Helen Poynton, Heather Lynch

Members not present: Ryan Bouldin, Alicia Timme-Laragy, Christine Rioux

Program staff present: Liz Harriman (TURI), Heather Tenney (TURI), Karen Thomas (TURI), Hayley Hudson (TURI), Gabriel Salierno (TURI), Colin Hannahan (TURI), Caredwen Foley (OTA), Nicole Moody (MassDEP), John Raschko (OTA), Kari Sasportas (OTA)

Others present: Owen Jappen (ACC), Carol Holahan (Foley Hoag LLP), Raza Ali (ACC),

Welcome & Introductions

The chair noted that this meeting is being conducted remotely, consistent with *An Act Relative to Extending Certain State of Emergency Accommodations* signed by Governor Baker on June 16th, 2022. This allows the extension of the remote meetings under the Open Meeting Law until March 31, 2025. Board members and program staff were introduced, and visitors were asked to put their name and affiliation in the chat.

Approve April Meeting Minutes

There was a motion to review the April meeting minutes and there was a second. The minutes were available for review prior to the meeting. There were two edits to the minutes: "with" and "that" were deleted from the sentence that originally said, "Chain length and amount of chlorination affect bioaccumulation, with chlorinated paraffins in each grouping that are bioaccumulative." The sentence now reads, "Chain length and amount of chlorination affect bioaccumulation, chlorinated paraffins in each grouping are bioaccumulative." The minutes were approved with six in favor and one abstaining.

Polyhalogenated Organophosphates

The final of seven subclasses, "polyhalogenated organophosphates" was introduced by looking at the basic organophosphate ester structure, with 3 "R" groups connected through the ester bond to the phosphorous and the double bond with oxygen. This class is best known for its use as pesticides- its second largest industrial use is as flame retardants (FRs). There are four main functional "R" groups for the organophosphate ester flame retardants: 1) phenyl groups, 2) aliphatic chlorinated or brominated groups, 3) a combination of 1 and 2, and 4) aromatic diphosphates. Organophosphate esters (OPEs) are also used as plasticizers.

Toxic properties of OPE flame retardants are wide-ranging. Because of their similarity to OPE pesticides, most attention has been paid to their potential neurotoxicity, ecotoxicity, persistence and bioaccumulative properties.

In August 2023, the Consumer Product Safety Commission (CPSC) issued a report, "Organohalogen Flame Retardant Scope Document: Polyhalogenated Organophosphate Subclass." All 8 organophosphate ester flame retardants being discussed today, 3 named in the MA FR Law and the 5 proposed analogues, are identified in the CPSC subclass. Conclusions of this report include:

> Endpoints specific to this subclass are - systemic repeated dose toxicity, developmental neurotoxicity, carcinogenicity, endocrine disruption.
>
> And
>
> "the subclass has sufficient data to proceed with risk assessment." (i.e., At least one data-rich chemical among the subclass, multiple chemicals with some data, only a minority of the substances in the subclass are "no data" substances.)

The three OPE FRs in the MA FR Law and the five analogues identified are:

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

Tris(2-chloroethyl)phosphate (TCEP) (CAS# 115-96-8) * in the Law
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)

Tris(1-chloro-2-propyl)phosphate (TCPP) (CAS# 13674-84-5) * in the Law

The structures of each were reviewed as well as the information provided by TURI for the meeting. The Board took up question Q3b for TDCPP and Analogues: Are analogues sufficiently similar to the named flame retardant such that they would be reasonably anticipated to have similar concerns re: toxic hazard, persistence, bioaccumulation?

TURI reviewed the health and environmental effects contained in the EHS Summary provided before the meeting.

Discussion of TDCPP and Analogues

One Board member noted that Analogue #3 is a hydrolysis product of Analogue #1, which is the "Brominated tris" of children's pajamas from the 1970's. As a hydrolysis product, it is by nature, similar. It was noted that the body of evidence for mammalian toxicity for TDCPP, Analogue #1 and Analogue #2 is sufficient, specifically for cancer, neurotoxicity and endocrine disruption. Other Board members agreed with the evidence for cancer and neurotoxicity especially, though the evidence for Analogue #2 is weaker and based more on structural similarity. There was agreement that as a breakdown product, Analogue #3 is similar to Analogue #1. One member suggested that the endocrine disruption evidence for these is from their similarity to organophosphate pesticides rather than on their own accord. Analogue #1 is more mutagenic than Analogue #3 and Analogue #3 is more nephrotoxic than Analogue #1.

The persistence data was somewhat conflicting or lacking for the analogues. One member stated that for the following reasons, it can be assumed that they will all be persistent.

- the structural similarity of all
- data for some
- the fact that halogenated substances are much more likely to be persistent
- Analogue #2 has a high log Kow (will adhere to sediments) and a bioconcentration factor of 610
- Not much data for Analogue #3 but it is a metabolite

For aquatic toxicity, TDCPP shows chronic growth and developmental toxicity to aquatic organisms in concentrations seen in natural environments (Liu 2020). The EPA 2015 study rated it a "high risk of aquatic toxicity." It was noted it makes sense to put Analogue #1 and #2 in the same high-risk category based on structural similarity, but data is lacking. It is expected to have similar aquatic toxicity with a simple halogen substitution.

Visitor Comments

There were no visitor comments.

Continued Discussion

There are data for endocrine disruption for TDCPP. There are data for developmental reproductive toxicity for Analogue #2. Analogues #1 and #2 are both nephrotoxic but there is no proof that TDCPP is.

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 – the only data is for TDCPP, however similar impacts are expected across the chemicals, especially in conserved developmental pathways

Discussion of TCEP and Analogues

The Board took up question Q3b for TCEP and Analogues: Are analogues sufficiently similar to the named flame retardant such that they would be reasonably anticipated to have similar concerns re: toxic hazard, persistence, bioaccumulation?

Analogue #1 does not have the third ester bond. The carbon is bonded directly to the phosphorous. There is a significant lack of data for Analogue #1. With the lack of data and the unclear chemical/chemistry similarity, a member noted there was not much to be said about Analogue #1. We can't rely on the EU Classification, Labelling and Packaging (CLP) data for this.

Analogue #2 exists as a mixture (10%) with TCEP. Analogue #2 has some reproductive toxicity and persistence evidence. The structures are obviously very similar. Analogue #2 has low biodegradability (half life >30 days) so it is likely persistent. Bioaccumulation is low for TCEP and Analogue #2. These have lower hydrophobicity than the TDCPP group.

There was a discussion around EPA 2015 (*Flame Retardants for Flexible Foam: Alternatives Assessment*) and the use of an 'analogue of an analogue' and what body of evidence would make that sufficient. One of the reproductive toxin studies uses an analogue of Analogue #2.

Tris(2-chloroethyl) phosphite is a precursor of both TCEP and Analogue #1 (Jansa 2011). TCEP and Analogue #2 likely have common metabolites. There appears to be one Russian article that looks at the toxicity of Analogue #1. TURI ordered it through interlibrary loan, but it has not come in.

In the OECD reproduction study, Analogue #2 did not show treatment-related effects. TCEP and Analogue #2 have differences with regard to developmental and reproductive toxicity.

TCEP and Analogue #2 have persistence data. They hardly break down. Looking at the structures, TCEP and both analogues would be expected to be persistent. Bioaccumulation potential is low for these chemicals. Analogue #2 has higher aquatic toxicity than TCEP but TCEP is not very toxic to aquatic life. EPA labels TCEP a PMOC (persistent mobile organic compound).

Visitor Comments

There were no visitor comments.

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.)

Adjourn

There was a motion to adjourn and there was a second. The meeting was adjourned.

Handouts

TURI Presentation from April Meeting
Draft April Minutes for Board Review
EHS Summary TCEP and Analogues
TCEP and Analogues CompTox Physical and Chemical Properties and Bioassay
TCEP and Analogues NOAEL and LD50 from CompTox
TCEP and Analogues Chemiformatics
EHS Summary TDCPP and AnaloguesEHS Summary TDCPP and Analogues
TDCPP and Analogues CompTox Physical and Chemical Properties and Bioassay
TDCPP and Analogues Cheminformatics

Zoom chat
Owen Jappen to Everyone 10:04 AM

Owen Jappen, American Chemistry Council

Raza Ali to Everyone 10:07 AM
Raza Ali, American Chemistry Council

Carol Holahan to Everyone 10:07 AM
Carol Holahan, Foley Hoag LLP

Gabriel Salierno (TURI) to Everyone 10:21 AM
Gabriel Salierno, Toxics Use Reduction Institute

Helen Poynton (she/her) to Everyone 10:48 AM
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.

Lisa Cashins MA Consultation to Everyone 10:57 AM
I have to step out for a min

Rich Gurney (Simmons U) to Everyone 11:29 AM
TRIS(2-CHLOROETHYL) PHOSPHITE 140-08-9

Rich Gurney (Simmons U) to Everyone 11:31 AM
Citation for that note: Jansa, P., Holý, A., Dračinský, M., Baszczyňski, O., Česnek, M., & Janeba, Z. (2011). Efficient and 'green'microwave-assisted synthesis of haloalkylphosphonates via the Michaelis–Arbuzov reaction. Green chemistry, 13(4), 882-888.

Helen Poynton (she/her) to Everyone 11:35 AM
Environmental: V6 has low biodegradation and likely to be persistent. V6 has higher aquatic toxicity than TCEP, but TCEP is not very toxic to aquatic life.

Rich Gurney (Simmons U) to Everyone 11:48 AM
Acute Tox. 4 (100%)
Repr. 2 (77.08%)
STOT RE 2 (77.08%)
Aquatic Chronic 3 (77.08%
https://pubchem.ncbi.nlm.nih.gov/compound/80518#section=GHS-Classification

Wendy Heiger-Bernays to Everyone 11:49 AM
2 generation OECD guideline study for V 6 does not show treatment related reproductive effects.

Rich Gurney (Simmons U) to Everyone 11:49 AM

Meditsina Truda i Promyshlennaya Ekologiya. Industrial Medicine and Ecology., (2)(21), 1993 [PMID:8061964]

Karen_Thomas1 to Everyone 11:55 AM
The Russian article we are waiting for: Medicina truda i promyšlennaja ėkologija naučno-praktičeskij žurnal = Russian journal of occupational health and industrial ecology: [Toxicological characteristics of bis-(2-chloroethyl)2-chloroethyl phosphonate]

Rich Gurney (Simmons U) to Everyone 11:56 AM
That is the same article mentioned in PubChem
UV light breaks carbon chlorine bonds