Toxics Use Reduction Institute Science Advisory Board Meeting Minutes
December 16, 2024
Virtual Zoom Meeting
9:30 AM

Members Present: Robin Dodson (Chair), Christy Foran, Rich Gurney, Denise Kmetzo, Heather Lynch, Alicia Timme-Laragy, Helen Poynton

Members not present: Ryan Bouldin

Program staff present: Heather Tenney (TURI), Karen Thomas (TURI), Hayley Hudson (TURI), Colin Hannahan (TURI), John Raschko (OTA), Sandra Baird (DEP), Tiffany Skogstrom (OTA), Kari Sasportas (OTA)

Others present: Liz Harriman (LCSP), Owen Jappen (ACC NAFRA), Carol Holahan (Foley Hoag LLP), Katherine Robertson (MCTA), Jacob Lison (ICL), Dr. Christopher Simpson (Lanxess), Liliana Wilson (ICL), Steve Scherrer (Lanxess), Anthony Laber (DLS), Robert Rio (RAR Strategies), Raza Ali (ACC), Lila Hensley (UVM student)

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.

Vote for Vice Chair

The chair summarized the nominating/voting process, asked if there were any questions and then called for nominations for Vice Chair. A member nominated Richard Gurney and there was a second. The nominations were closed and there was a roll call vote. The six members that were in attendance at that time were in favor, a unanimous vote.

Approval of October Meeting Minutes

There was a motion to discuss the October Meeting Minutes. There were no amendments, and a roll call vote was conducted. There were five members in favor and one abstention.

Board member Heather Lynch disclosed previous work on flame retardants, one of which is named in this matter. There is no current work on this flame retardant, but there could be in the future and she wanted to note the appearance of conflict for clear transparency.

Aryl Phosphate Esters

TURI reviewed the difference between today's topic and the previous Flame Retardant (FR) Law work. TURI learned about the aryl phosphate esters while doing the FR Law work, but today's topic is consideration for TURA listing. TURI reviewed the process for a TURA listing consideration and possible adoption by the TURA Administrative Council.

Organophosphates are a group of phosphate-containing chemicals also known as organophosphate esters (OPEs) because they are esters of phosphoric acid. They are best known for their use as pesticides; the second largest use is FRs followed by plasticizers. Toxic properties of OPE FRs are wide-ranging; much attention has been focused on neurotoxicity due to their similar structure to the organophosphorus pesticides.

TURI reviewed the different structures of the OPEs; there are many derivatives among the broad group but the aryl phosphate esters are the current topic. Aryl phosphate esters can be broken into four subgroups that stem from triphenyl phosphate (and derivatives):

- Cresyl, or Xylenyl
- Isopropyl phenyl
- Tert or tris butyl phenyl
- Diphosphate phenyl derivates

Typically, studies will discuss a member or two from more than one subgroup in the research. TURI has summarized about 60 studies. Triphenyl Phosphate (TPP) and its derivates are the most studied of the aryl phosphate esters, followed by the cresyl subgroup then isopropyl, di-, and butyl subgroups.

TURI reviewed the regulatory history of TPP and outlined the regulations and assessments done by several authoritative bodies including the data that lead to a final designation. The most recent being:

- EPA 2019 - designated a High Priority Substance undergoing TSCA Risk Evaluation
- ECHA 2021 – TPP and 16 derivatives – Assessment of Regulatory Needs
- Health Canada 2021 – recommends TPP and 4 derivatives for Toxic Substances List
- 2023 EPA Proposed a SNUR
- ECHA 2024 - SVHC endocrine disrupting (environmental)

Prior to the meeting TURI provided twelve research articles, "Batch 1," that focused on TPP:

- published 2020 or later,
- in vivo/in vitro, mammalian/fish/human,
- specific to the developmental, neuro, reproductive or endocrine disrupting endpoints.

This was intended to be a broad sampling of the available information.

A member noted that the Hu (2023) article was helpful as a review. Numerous effects were reported: reproductive, endocrine, adrenal, thyroid. The summarized results were mostly in vitro. From the epidemiological side (rat and human), they reported disruption in the animal as a whole, changes in cholesterol and LDL. TPP affects lipid metabolism and the reproductive system at current exposure levels.

Many of the available studies are small cross-sectional studies and some are measuring up or down regulation of genes related to developmental neurotoxicity. A member noted that these are not guideline studies and neurotoxicity outcomes are hard to study.

The Witchey (2022) and Newell studies are looking for neuronal effects. Details were light and the methods were not well-reported. It is very important to know what conditions and stress the animals were under in studies like this where they are measuring many things but not adverse outcomes.

Another Board member noted that Hawkey (2023) was an actual in vivo developmental test. Kreutz (2023) had NIEH authors and referenced an OECD document on evaluating data in vitro. The researchers were trying to integrate data from a variety of sources, in vitro, in vivo, and PBK modeling to relevant exposures to see if there was an overlap. Figure 2 was a good summary of results and a summary of what each in vitro test was indicating. PBK was seeing effects in the behavioral areas. Researchers used background exposure modeling and they were showing some overlap in some of the estimated exposures in breastmilk and child exposure levels. This study shows a way to systematically use in vitro data, something the SAB will need to do more as in vitro becomes more predominant.

Newell (2024) used a mixture- one that is commercially relevant- and two dosings to try to understand some of these effects. At the end of the study it was suggested to repeat the tests with the singular chemicals.

Both the Kreutz and Newell papers suggest concerns around developmental neurotoxicity and both emphasize that some of these effects may be rooted in the endocrine system, particularly estrogen activity. Both acknowledge the estrogen and testosterone cycling in developmental neurotoxicity.

A Board member stated interest in how some researchers are effectively relating exposure to experimental studies. Figure 4 in the Kreutz study is very interesting to see how they compare

the different tests. These are looking at home environment and children's exposure, not occupational exposure.

Witchey was a rat study while Kreutz had many assays represented, including rat; Klose (2022) was a neurotoxicity study using a human DNT in vitro testing battery. Klose Table 1 was very interesting as to comparing the various flame retardants.

A Board member summarized Zhang (2024a) which studied zebrafish and several different endpoints. Results show that embryonic exposure to TPP may affect neurogenesis by killing off neurons through this ferroptosis pathway. The authors put this in terms of water exposure, strictly environmental exposure. The concentrations were higher than actual environmental exposure, but when trying to understand the mechanism it was helpful. The clearest result was that TPP was causing this increase in iron from the ferroptosis pathways. The researchers went on to use Astaxanthin (AST), an inhibitor of ROS, and were able to decrease the levels of intracellular iron and ROS to the point where some gross endpoints were recovered (e.g., swimming).

A Board member asked, "Is it the same developmental effect as the other study - affecting neurogenesis during development? Is it right to say that early exposure may affect neurogenesis or neuroproliferation?" A member responded in the affirmative. It seems that early exposure is killing off neurons through this ferroptosis pathway.

Another Board member summarized the Witchey (2023) study which was a basic rat study; authors found a decrease in weight gain in pregnancy, food consumption, and number of pups to survival. Also, both chemicals (TPP and isopropyl triphenyl phosphate) lead to delays in puberty. There are questions here about dose response and environmentally relevant exposures.

A member noted that Jin (2023) was a good overview and noted many different effects to consider (e.g., lipid, liver, intestinal damage); see Figure 2. The Gao (2022) study shows some epidemiological evidence of disrupting hormone homeostasis and potential effects on female reproduction (913 women), measuring urinary metabolites. This is supporting evidence but not primary evidence.

Visitor Comments

There was one visitor comment, "Can you review the process by which these substances will be listed? Asking to distinguish the process from the Flame Retardant statute."

TURI responded that the Board is no longer working on the FR Law and is back to TURA work. The Board is currently reviewing TPP and the aryl phosphate esters as a potential category listing under TURA (not under the FR Law). If the Science Advisory Board decides to make a

recommendation to list an aryl phosphate ester category then the program will prepare a policy analysis, get input from the TURA Advisory Board, then be reviewed by the TURA Administrative Council, which will decide how to proceed. If it goes forward it will go out for public comment. This is the same as any other TURA listing.

Aryl Phosphate Ester Discussion

A Board member asked if the aryl phosphate esters have similar or the same metabolites as the pesticide metabolites. Are the aryl phosphate esters structurally different such that they will not be acetylcholinesterase inhibitors like the pesticides? A member responded that one source-the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment looked specifically into this (whether they'd expect the mechanism to be like the pesticides) and the answer was no. TURI staff will follow up on this.

There was further discussion on acetylcholine inhibition and the methods/doses used in the studies that did show it. This is something that the Board would like more information on.

There was discussion on lipophilicity and whether or not TPP is going to bioaccumulate in the membrane or fat tissue. These are urinary metabolites that are typically measured, so they go through at least phase one oxidation and are not in the body for too long.

Several regulatory agencies cited environmental effects and there was further discussion around the ECHA document and the SVHC designation. ECHA noted TPP has a pH dependent degradation pattern, and it's readily degraded in WWTP and will compartmentalize in soils and sediments. TPP has been detected in mussels, fish, marine animals, so it is pretty ubiquitous. It has a moderate bioaccumulation factor of 110-140. Toxicity values for fish, aquatic plants, etc. are in the 0.1-1 mg/L range which is close to environmentally relevant concentrations.

From the ECHA report, developmental effects are being seen at environmentally relevant exposures and all embryos survived so it is not an acute effect.

There was logistical discussion about what type and how the Board would like to see information. A Board member would like to follow up on how to relate some of the studies, especially those related to stereogenesis, or lipid metabolism effects, with Japanese Medaka and zebrafish to the epidemiology studies. It may be important to tease out these mechanisms in case they apply to other chemicals in the potential category. Members discussed the various endpoints from all the studies and how it may be difficult to narrow the search or direction. There was discussion around the structural similarity of the aryl phosphate esters and there were differing opinions among the Board members. Discussion continued on the plausibility of categorizing them. It was suggested that the aryl phosphate esters with alkyl chains may be

different. Some of these substances may degrade into one substance so that is something to consider as well.

A Board member mentioned TURI's potential category document was helpful. A member mentioned they would be able to handle more than two or three studies once they get a better handle of the material. The Board would like to look at the review articles first to see a larger picture.

TURI will look for and organize the review articles and the remaining 20 or so studies on TPP and consider the potential category members based on the number of carbons. The Board members were encouraged to volunteer for an endpoint of interest.

Visitor Comments

There were no visitor comments.

Adjourn

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

Handouts

Draft October Meeting Minutes for Board Review
Potential Category Aryl Phosphate Esters - overview
Short Summary of the Broad Topic of Organophosphates
APE Batch 1 Spreadsheet

Zoom Chat *(*Lightly edited for clarity)
Owen Jappen 9:34 AM
Owen Jappen, American Chemistry Council

Raza Ali to Everyone 9:34 AM
Raza Ali, American Chemistry Council

Dr Christopher Simpson to Everyone 9:34 AM
Dr. Christopher Simpson (LANXESS CORPORATION)

Jakub Lison - ICL to Everyone 9:34 AM
Jakub Lison, ICL Industrial Products

Anthony.Laber to Everyone 9:34 AM
Anthony Laber, MA OSHA Consultation Program-DLS

Steve Scherrer, LANXESS to Everyone 9:34 AM
Steve Scherrer, LANXESS

Tiffany Skogstrom, OTA (she / her) to Everyone 9:35 AM
Tiffany Skogstrom, Direct of MA Office of Technical Assistance (OTA) & Executive Director of the TURA Administrative Council

Katherine Robertson to Everyone 9:35 AM
Katherine Robertson Massachusetts Chemistry & Technology Alliance

Carol Holahan to Everyone 9:35 AM
Carol Holahan, Foley Hoag, LLP

Kari Sasportas (MA OTA) to Everyone 9:35 AM
Kari Sasportas, MA OTA

Liliana Wilson-ICL to Everyone 9:36 AM
Liliana Wilson-Sr Regulatory Affairs Specialist at ICL

Carol Holahan to Everyone 10:56 AM
Can you review the process by which these substances will be listed?
Asking to distinguish the process form the Flame Retardant statute.

Colin Hannahan - Toxics Use Reduction Institute to Everyone 10:58 AM
https://www.turi.org/publications/decision-making-under-tura-resources-for-the-tura-administrative-council-and-advisory-bodies/#:~:text=It%20generally%20includes%20the%20following,process%20through%20the%20appropriate%20agency.
TURA decision making process document

Carol Holahan 10:58 AM
Thank you. Just wanted to confirm the typical TURA process applies and not the FR statute