Toxics Use Reduction Institute Science Advisory Board Meeting Minutes
November 6, 2023
Virtual Zoom Meeting
9:30 AM

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

Members Not Present: Alicia Timme-Laragy

Program staff present: Liz Harriman (TURI), Heather Tenney (TURI), Karen Thomas (TURI), Hayley Hudson (TURI), Nicole Moody (DEP), Kari Sasportas (OTA), Caredwen Foley (OTA)

Others present: Carol Holahan (Foley Hoag for ACC), Katherine Robertson (MCTA), Owen Jappen (ACC)

Welcome & Introductions
The chair noted that this meeting is being conducted remotely, due to an extension of the temporary provisions of the open meeting law signed March 29th, 2023, by Governor Healey. This allows the extension of the remote meetings under the Open Meeting Law until March 31, 2025**.** Board members introduced themselves, program staff were announced, and attendees were asked to put their name and affiliation in the chat.

Approve September Meeting Minutes
The September meeting minutes were discussed and the following changes were suggested:

1. Change "data is" to "data are"
2. In the sixth paragraph on page four refer to EPA Comptox as "useful screening tool" rather than a "good screening tool" when other data are scarce.
3. Add the documents used at the meeting

There was a motion to approve the amended minutes and there was a second. A roll call vote was conducted, and the minutes were unanimously approved by the ten members present.

Flame Retardant Law
TURI presented information on the MA Flame Retardant Law, highlighting the differences between it and TURA. The Board was reminded of their summary statement for PBDEs:

"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."

Antimony Compounds
Antimony trioxide is the chemical covered under the FR law in this subclass and the question posed to the Board is:
Is each proposed Antimony Compound analogue (specifically antimony pentoxide and sodium antimonate) sufficiently similar to (the included FR antimony trioxide) that it would be reasonably anticipated to have similar concerns re toxic hazard, persistence, bioaccumulation?

Antimony (+3) trioxide is very insoluble, and some studies note that. Data for antimony (+5), the more common form found in the environment, are more limited. One member had researched the ecotoxicity data and noted that it is complicated by the existence of both valence states in the natural environment, suggesting that there is not enough information on specific compounds to say they are similar. Many studies lump them together as "antimony compounds" and don't measure the two oxidation states, so we don't know whether they are staying in +3 or moving to +5. It would depend on the kinetics, ultimately in a natural system you would have about 90% +5 and 10% +3, but because the studies don't distinguish they just refer to antimony compounds. We are being asked to distinguish, but the data may not be there to do that.

Toxicity data are lacking. A Board member mentioned an ECHA profile for sodium hexahydroxoantimonate (+5) that lists a 90-day developmental repeat dose study that showed no adverse effects even at high oral dose. A member noted they would like to see worker studies since workers tend to be exposed to both oxidation states.

The EPA Cheminformatics table lists chronic aquatic toxicity as very high (VH). There are two studies for antimony pentoxide on Cheminformatics with high (H) and VH rating. From Cheminformatics, LeBlanc et al. (1984) found a Fish ChV of 7.5 ug/l, but the study didn't find effects at that concentration, so it's actually a NOEC not a LOEC.

The Board discussed why a "precipitate" is different than something that is dissolved. Traditionally a precipitate is not hazardous. Nanoparticles have changed this way of thinking. Precipitates end up out of the water column depending on their physical or chemical characteristics. It is very chemical specific.

There was discussion around the breakdown of antimony compounds in the body. The transfer from mother to fetus is quite high and there is evidence of conversion in organisms of +5 to +3. Various routes of exposure were discussed and whether existing study results would reflect conversion of +5 to +3. A member stated that if exposure to +5 ends up as exposure to +3 which is listed, that should be considered. There are only certain products in the law and through each of the uses it could end up in various media and there are a variety of exposures that could result. It has low dermal bioavailability, as it is a metal. For absorption, we are looking at the ATSDR profile and the studies they cite for absorption following inhalation.

Visitor Comments
There was an opportunity for visitor comments and there were none.

Summary Statement
There was extensive discussion around constructing a summary statement for antimony compounds.

The +3 and +5 compounds can convert under various conditions. The absence of data doesn't mean absence of effect. These compounds are persistent at least for the antimony itself. Not necessarily in the form that is used in a product, but the antimony itself isn't going away. Bioaccumulation doesn't seem to be a concern, but there is a lack of toxicity data for specific valence state forms.

- A Board member mentioned pg. 85 of the ATSDR Toxicological Profile for Antimony states that +5 and +3 travel to different places in the body. Ribeiro et al. (2010) found these compounds accumulating in the thyroid of dogs, indicating a lot of distribution. Another Board member mentioned another study that found accumulation in the bones.

- There was discussion around distinguishing between environmental conversion and biological conversion. Lopez (2015) was mentioned as a useful paper and others were shared in the chat.
- In oxidative states, as typical in the environment, +5 is predominate; in reductive environment, +3 predominates. Researchers are seeing aquatic toxicity, but they just can't confirm what species or mixture it would be for.
- Both forms are often found together in occupational settings, and lung effects are attributed to antimony trioxide.
- There is exposure information on antimony pentoxide from furniture, etc., in a National Research Council publication; EPA focused on hand to mouth of dust for the pentoxide form.
- Part of the reason we are concerned is carcinogenicity. Antimony trioxide (ATO) has toxicity data and there is concern about conversion between the two valence states. The +5 hasn't been identified as a carcinogen, but all these reasons are why agencies are grouping them all together.
- Route dependent absorption is important. ATO can get into lungs, but it is unclear how it distributes versus injection.
- It should be clarified that antimony pentoxide is not classified as a carcinogen but there are concerns about the conversion of +5 to +3 and that pentoxide is lacking data.
- The kinetics of conversion are unclear. Generally, we see that pentoxide is not as toxic as trioxide in humans for ingestion. The inhalation piece is important and how it gets into your system and then how it is absorbed. There was lengthy discussion about conversion in the body.
- A Board member mentioned that there are health effects and to make sure the summary statement doesn't ignore other health effects. There was further discussion around adding concerns about toxicity to the statement.

There were slight grammatical changes made. The Board was reminded of the question again:
-Is each proposed Antimony Compound analogue (specifically antimony pentoxide and sodium antimonate) sufficiently similar to (the included FR antimony trioxide) that it would be reasonably anticipated to have similar concerns re toxic hazard, persistence, bioaccumulation?

Summary Statement from the Board:
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.

Phthalates/Benzoates
TURI presented information for Subclass 4: Polyhalogenated Phthalates/Benzoates/Imides, and also some related overview for Subclass 5: Polyhalogenated Bisphenol Aliphatics. Similarities in both subclasses were noted. The backbones of each have their own toxicities; there are limited data on

analogues, considerably more data on primary chemicals. For subclass 4, the chemical in the law is Tetrabromophthalate (TBPH) and for subclass 5 it is Tetrabromobisphenol A (TBBPA). They were both originally offered as less hazardous alternatives to PBDEs.

Four analogues of TBPH have been suggested for inclusion in the law. There was discussion on the general toxicity for phthalate esters (not halogenated) and mention of previous work by SAB on phthalate esters.

The challenges of this subclass include lack of data for individual chemicals (Firemaster 550 has four ingredients). Original persistence and bioaccumulation data showed these properties not to be a concern but subsequent experience has shown otherwise (they are now ubiquitous in the environment)

Of note for TBPH:

1. Very persistent and very bioacummulative (vPvB in ECHA)
2. EPA 2015 Hazard Study

There was discussion around the developmental and aquatic toxicity endpoints.

- Aquatic toxicity – exceeds solubility and there are thirty-seven studies that have data points for pure TBPH.

There was discussion on whether the commercial mixtures will contain the analogues.

- Analogues 1,2, and 4 would be reactive, but TBPH is not reactive.
- It is reasonable to say they are analogues of each other, but surprising that some of the chemical properties were so different.

There was a discussion on chemical structure. The backbone is a phthalate and then the phenyl group with bromine - this is a problematic class of chemicals. One member suggested that the Board take exactly what we do have data for, and what we can predict, to say something meaningful. There is concern about the presence of phthalates as a problematic class.

There was discussion about how to look at the developmental and aquatic toxicity endpoints. Persistence information didn't jump out. One member asked if there are toxicity data on the phthalic acid hydrolysis product. Members asked about metabolites and whether there are common metabolites. The mono esters or mono acid would be much closer analogues.

A Board member asked if there are other data or information sources that people would like for the next meeting.

Next Meeting

Heather will send out a When2Meeting for the first two weeks of January.

There was a motion to adjourn, and there was a second.

Handouts

SAB Presentation November 2023
Updated Proposed FR CAS Numbers, Isomers, and Analogues for SAB
FR Questions and Definitions
ACC-NAFRA Comments MA TURA SAB
MA Flame Retardants Law Presentation

September Minutes for Board Review
Antimony Compounds EHS Summary
Cheminformatics Antimony Compounds
ECOTOX Aquatic and Terrestrial Data Antimony Compounds
ATSDR Toxicological Profile for Antimony Compounds
Bisphenols EHS Summary
Cheminformatics data for Bisphenols
Physical and Bioactivity data for Bisphenols
Phthalates EHS Summary
Cheminformatics for Phthalates/Benzoates
Physical and Bioactivity Data for Phthalates/Benzoates

Chat Inserted Verbatim from Zoom Chat

Owen Jappen to Everyone 9:37 AM
Owen Jappen - American Chemistry Council (DC)

Carol Holahan to Everyone 9:37 AM
Carol Holahan, Foley Hoag LLP

Katherine Robertson to Everyone 9:38 AM
Katherine Robertson, MCTA

Heather Lynch to Everyone 10:02 AM
https://echa.europa.eu/registration-dossier/-/registered-dossier/16264/6/1
That is the ECHA profile
for antimony pentoxide
"no potential for bioaccumulation"

Rich Gurney (Simmons U) to Everyone 10:21 AM
In humans administered Ulamina (an experimental drug containing antimony pentachloride and N-methylglucamine) via intramuscular injection, 23% of the pentavalent antimony was converted to trivalent antimony (Vasquez et al. 2006). A study in monkeys administered the pentavalent antimony compound, meglumine antimoniate, reported that the proportion of trivalent antimony in the plasma increased from 5% on exposure day 1 to 50% on exposure day 9; the plasma levels of pentavalent antimony remained constant (11–20%) during this time period (Friedrich et al. 2012). An in vitro study in human blood demonstrated the reduction of pentavalent antimony to trivalent antimony in the presence of glutathione (Lopez et al. 2015). In contrast to these findings in blood, Wyllie and Fairlamb (2006) reported that differences in the toxicity of pentavalent antimony and trivalent antimony to macrophages suggested that pentavalent antimony was not reduced to trivalent antimony in macrophages.
From: ATSDR 2019: Tox Profile for Antimony and Compounds
3.1.1 Absorption Inhaled antimony particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption into blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, liver, kidney).

Rich Gurney (Simmons U) to Everyone 10:32 AM

A study of pentavalent antimony estimated a bioavailability of 10% in dogs administered via gavage a single dose of 100 mg Sb/kg as meglumine antimoniate (Ribeiro et al. 2010); the mean absorption time was 3.1 hours. Gastrointestinal absorption of antimony is likely to be affected by numerous factors, including chemical form and solubility of the ingested antimony, age, and diet. Although quantitative information on the absorption of antimony is not available for all forms, ICRP (1981) has recommended 10% for antimony tartrate and 1% for all other forms of antimony as reference values for gastrointestinal absorption in humans. A dog study (Ribeiro et al. 2010) showed that maximum blood concentration was reached 0.89 hours after gavage administration of 100 mg Sb/kg as meglumine antimoniate.

Lisa Cashins MA Consultation to Everyone 10:35 AM
I am sorry. My computer just restated itself

Caredwen Foley, MA OTA to Everyone 10:42 AM
(Is is correct! It should be agreeing with the word lack, not with the word data! :-))

Rich Gurney (Simmons U) to Everyone 10:48 AM
Vasquez L, Scorza Dagert JV, Scorza JV, et al. 2006. Pharmacokinetics of experimental pentavalent antimony after intramuscular administration in adult volunteers. Curr Ther Res Clin Exp 67(3):193203. http://doi.org/10.1016/j.curtheres.2006.06.005. Friedrich K, Vieira FA, Porrozzi R, et al. 2012. Disposition of antimony in rhesus monkeys infected with Leishmania braziliensis and treated with meglumine antimoniate. J Toxicol Environ Health A 75(2):63-75. http://doi.org/10.1080/15287394.2012.624826.
Felicetti SW, Thomas RG, McClellan RO. 1974b. Metabolism of two valence states of inhaled antimony in hamsters. Am Ind Hyg Assoc J 35:292-300.

Helen Poynton (she/her) to Everyone 10:56 AM
"The Antimony compounds undergo oxidation and reduction under aerobic and anaerobic condition respectively, converting between (+3, +5) oxidation states."

Rich Gurney (Simmons U) to Everyone 10:57 AM
In oxygen rich environmental conditions, the pentoxide form can predominate. In vivo studies have observed pentavalent antimony species converting to antimony trioxide.

christine rioux to Everyone 11:25 AM
Details on exposure characterization https://www.ncbi.nlm.nih.gov/books/NBK225656/

Ryan Bouldin (he/him) - Bentley University to Everyone 11:26 AM
The kinetics of conversion are unclear

Heather Lynch to Everyone 11:30 AM
"There is a concern that antimony pentoxide can convert to the trioxide form in the body, however, there are few studies evaluating this conversion, particularly after inhalation exposure. Moreover, studies on the health effects of antimony pentoxide are lacking."

Rich Gurney (Simmons U) to Everyone 11:43 AM
May we have time for a very short bio break?

Heather Tenney to Everyone 11:47 AM
slight grammatical edit:
see screen share!

Heather Lynch 12:21 PM
https://pubchem.ncbi.nlm.nih.gov/compound/Tetrabromophthalic-acid