

Toxics Use Reduction Institute Science Advisory Board Meeting Minutes
January 14, 2021
Virtual Zoom Meeting
12:30 PM

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

Members not present: Amy Cannon

Program staff present: Liz Harriman (TURI), Heather Tenney (TURI), Hayley Byra (TURI), Pam Eliason (TURI), Christopher Hansen (TURI), Hardiesse Dicka-Bessonneau (MassDEP), Tiffany Skogstrom (OTA), John Raschko (OTA), Caredwen Foley (OTA), Sandy Baird (MassDEP)

Others present: Terry Hrubec (VCOM at Virginia Tech), Katherine Robertson (MCTA), Carol Holahan (Foley Hoag ACC), Trisha McCarthy (Coyne PC for ACC), Margaret Gorman (ACC), Harry Hechehouche (ACC), Keith Hostetler (Toxicology Regulatory Services, ADBAC/DDAC ISC), Dave Jones (ADBAC/DDAC ISC), Robert Holden (Stateside Associates), Ken Littel (Stephan Company), Stephen McInerney (Capaccio Environmental), Hannah Alleman (Household & Commercial Products Association), Judi Anderson (Kroeger Associates), Aron Pollard (Mason Chemical Company), Erin DeSantis (ACC), Casey Crownhart (NYU), Kate Sande (Ecolab), Sean Keefer (Ecolab)

Welcome & Introductions

Please note that this meeting is being conducted remotely, consistent with Governor Baker's Executive Order of March 12, 2020, in response to the current State of Emergency in the Commonwealth due to the outbreak of the 2019 novel coronavirus, known as, "COVID-19".

All attendees were asked to introduce themselves and state their affiliation using the chat function. Visitors were asked to then mute and use the chat function, which TURI monitored, thereafter. Visitors were also invited to ask questions or offer comments periodically during the meeting.

Approve November 14th Meeting Minutes

A motion was made and seconded to approve the November 14th meeting minutes. The minutes were unanimously approved by the 9 members in attendance at that time.

Quaternary Ammonium Compounds

We are reviewing the scientific environmental, health and safety hazard information for certain quaternary ammonium compounds (QACs) as a potential listing under TURA.

Presentation: Quaternary Ammonium Compounds, Dr. Keith Hostetler

Dr. Hostetler is a Senior Managing Toxicologist with Toxicology Regulatory Services and has more than 25 years of experience in the food and specialty chemicals industries. His PhD is in Pharmacology and Toxicology from Virginia Commonwealth University.

Representing the ADBAC/DDAC Issues Steering Committee, Dr. Hostetler presented information on QACs, specifically the substances of interest: ADBAC and DDAC. Dr. Hostetler's presentation is available on the TURI website.

Questions for Dr. Hostetler from SAB Members

A board member asked for clarification on degradability in wastewater treatment plants (WWTPs) and biosolids. How long does it take and where does it end up?

- Not a rapid degradation in soils but it does happen over time.

There was additional discussion regarding fate in WWTPs; there are concerns that when the treatment plant only removes 95% it may be present at low concentrations.

- Dr. Hostetler indicated that there is more work on this on-going, and that we know QAC break down in the environment because we have been using them for 50 years and have not seen them building up.

A board member asked if some more of the data will be made available. Also, is there any data on endocrine disruption, and if so, will that be made available?

- When the manuscript is done it will all be available. The EPA screening work did not flag QAC for endocrine disruption - they didn't see structural reasons for more testing. In the EU there was an endocrine disruption assessment conducted by the Biocidal Products Committee that was inconclusive. Industry has agreed to provide more testing to rule that out.

A board member noted data in EPA's EDSP21 (Endocrine Disruption Screening Program for the 21st Century) and also positive results for estrogen screening assays.

- Dr. Hostetler said they would investigate to see if there is endocrine disruption data available beyond the screening assays.

A board member asked if the Buehler test was the only test used to determine skin sensitization or are there lymph node assays (LNA)?

- Dr. Hostetler was unsure and will check. He would assume that those tests have been done, and that they would have been negative. Dermal sensitization is rare.

A board member noted they had reviewed the data on asthmagen potential, and saw a general recognition that quats are asthmagens in some situations.

- Proving QACs to be asthmagens is difficult. The active ingredients are not volatile. There is evidence showing an association with cleaning products and asthma, but there are other ingredients that could be responsible. Dr. Hostetler agreed that we need more studies of exposure and asthma, although they believe that due to the widespread use over a long period of time, there would be more evidence apparent in the studies that do exist.

A board member asked about Adverse Outcome Pathways (AOPs), and the detailed pathways developed for skin and mucous membranes, e.g., discussion in the literature of mitochondrial function, lipid interaction, etc.

- Others are doing that research and it has been submitted to EPA; Dr. Hostetler would need permission to share that.

Presentation: Quaternary Ammonium Compounds, Dr. Terry Hrubec

Dr. Hrubec is a Professor of Anatomy and Embryology at Edward Via College of Osteopathic Medicine at Virginia Tech. Her PhD is in Veterinary Medical Science from Virginia Polytechnic Institute and she holds a DVM from VA-MD College of Veterinary Medicine.

Dr. Hrubec explained how she accidentally discovered the effects of these substances when the control mice in her original research (testing a pharmaceutical) started to exhibit birth defects (neural tube defects, NTD). She repeated the study and saw the same thing. Her lab spent over a year trying to figure out why and found out that the animal care staff had changed disinfectants that they used to clean the cages to a QAC based cleaner. Dr. Hrubec presented information on her research and findings, and her presentation is posted on the TURI website.

- Notes one exposure caused effects for three generations.
- They measured levels in mouse liver, brain and testes (largest for DDAC) - therefore these substances cross the blood brain barrier and blood testis barrier.
- Increased markers of inflammation, decreased mitochondrial function and altered cholesterol synthesis.
- Noted that there are numerous patents for ADBAC use as contraceptives since the early 1970s and licensed for use as a spermicide in Canada and Europe.

Questions for Dr. Hrubec from SAB Board Members

Could you explain the reason you use mice vs rats and what strain you use?

- CD1 strain of mice (presented here) and black 6 showed NTD effects
- Also did a study with Sprague Dawley rats and observed NTD.
- Mice are easier to work with and we saw higher rates of effects to see a clear exposure rate.
- It's hard to translate one species to another.

Did you measure serum levels of ADBAC or DDAC and how those related to your administered dose?

- Serum levels were not measured in the mouse study; they are shown in a separate human study.
- We are assuming the initial exposure crosses the placenta to stem cells; believe this is an epigenetic effect.

The placenta is increasingly identified as important for reproductive outcome. We are interested in understanding gestational day 17 versus neural tube development. Could you share with us what the relationship is and where the timing is critical?

- Most researchers don't look at day 9 and 10 embryos, unless they are looking for early brain development or NTDs. We just happened to be looking at that stage so happened to notice the

defects right away. At that point the placenta is still a yolk sac placenta, then a definitive placenta takes over for later stages of development. The placenta is also involved in producing growth hormones. The placenta is critical for development by transferring nutrients from the mother, but is also involved in producing growth hormones that direct growth of the fetus. We measured cytokines in the placenta, which were altered with QAC exposure indicating a possible change in placenta function.

When talking about ambient exposure, what was the exposure route and did you ever try to quantify it?

- Some evidence says inhalation, but mice groom themselves constantly so there is so much exposure potential from various routes. They haven't measured what is going on with ambient exposure. The control mice are not given any dose, but are just in the same room as mice that are receiving the substance via saline gavage. There is no open bucket, spraying, or cleaning with the substances.

In OECD two generation studies, wouldn't you expect to see those defects in at-term animals?

- Neural Tube Defects are normally not lethal and you will see them manifest later in development. Anencephaly is not compatible with life, so those affected don't survive. Mouse mothers will eat offspring if defective before the next one is delivered, so they aren't always observed. If they die by day 10, for example, they will count as resorption.

Increased resorptions were not seen in the regulatory studies. Why?

- Not certain, but noted that regulatory studies use rats and they see lower response rate in rats than in mice. In normal pregnancy they will see normal rate of resorptions as background; will only note resorptions if significantly different than background.

Additional Questions for Dr. Hostetler and Dr. Hrubec

A board member asked if Dr. Hostetler could comment on ambient water concentrations, noting the low values for aquatic invertebrate toxicity.

- Dr. Hostetler explained that aquatic toxicity tests are done in pure water systems. Free floating in aquatic system is unlikely because they bind to everything so easily. He will check to see if they have ambient water data, but would expect it to be low.

A TURA Representative asked about issues with maternal toxicity and the possibility that was raised that some of that could be due to the burden of dead fetuses on the mother, would the OECD protocol catch that kind of effect?

- Dr. Hostetler noted that one of the reasons that mice aren't used is that they are difficult to handle and sensitive to stresses.
- Dr. Hrubec explained that they have looked at histopathologic changes and are fairly confident that the effects are due to the exposure. Stomach, esophagus, muscle, pancreas, reproductive organs, just about everything was reviewed, and in both the ways the mice were dosed.

Quaternary Ammonium Compounds Discussion: DDAC, ADBAC

A board member would like to disclose an appearance of conflict form. It has been submitted to the Governor, but not yet confirmed as received. He has a student that is working on a quaternary ammonium compound application for a similar but different substance than the board is considering. His former student has also submitted a patent on this application.

Reproductive/ Developmental Endpoint

- There are guideline studies that show no effects except maternal toxicity, and the other studies are those by Dr. Hrubec, which do show effects.
- There are still some questions but there is compelling data that says more research is warranted. The guideline studies are consistent with each other but not with non-guideline studies. Guideline studies are insufficient to document some effects. There are still a lot of questions and uncertainty.
- Additional research is needed on mixtures; mouse vs rat; measure of serum vs. dose; and still there is sufficient evidence that reproductive toxicity needs to be taken seriously.
- While not dismissing the concerns for repro/developmental effects, is it possible that they are mouse limited - why don't we see NTDs in rats? We look for consistent effects across species, so concerning but not convincing.
- Fetal weight, placental effects, birth defects, endocrine disruption, there are many pieces that are missing. We are just learning about fetal and placental links. However, there are pieces of the puzzle, including endocrine in vitro results, that are partially consistent with Dr. Hrubec's results.
- Dr. Hostetler mentioned that a panel of developmental and reproductive toxicity experts are currently conducting a systematic review of the information.
- A Board member noted that there are likely several mechanisms in play, and that additional information could help understand study results. A board member noted a paper to review: Herron, 2019 in preprint. TURI will post to the LibGuide for next meeting.

Asthma Endpoint

- Sufficient body of evidence for asthma and irritant, and listed various references including Gonzalez and Dumas.
 - A board member asked to look into more Dumas references.
- For concentrated disinfectant what does the warning relate to, corrosivity? Is that warning issued for the diluted product? What is the percentage used in industry? Dilution tasks are often high risk tasks and when effects are seen.
 - TURI will look into safety data sheets and get concentration of industrial products that a formulator would use.
- Is it the irritancy? Did any of the studies state if it was atopic or non-atopic?
 - Phenotype of asthma was broken down in some studies but not all of them. Distinguishing the type of asthma is a difficult area.

Environmental Endpoints

- DeLeo showed very high toxicity to invertebrates and fish, and if we look at ambient water concentrations they may be higher than these toxicity values. Hora paper comes up with a risk

quotient that suggests concentrations in the environment are higher than ones that cause effects. It is true that a lot gets adsorbed, but the 5% left over is enough to cause problems for aquatic life.

- Another board member said they found information on wastewater effluent concentrations, but not ambient water concentrations and shares the concern for surface water. Mentioned Li 2010 that found concentrations in estuary sediments in relatively high concentrations.
- Concern for the potential to change microbial environment in wastewater treatment and the potential for antibiotic resistance.
- Are there studies on exposed sediments and airborne dust from dry soils, for example in estuaries?
- What is the fate when sprayed indoors or outdoors? Aerosolized or adsorbed onto particles?
- This is a conversation to follow up with next meeting as board members expressed additional references they wanted to review and search for information if any on QAC presence in surface water or ambient water concentrations.

Other Endpoints/uses of Interest

- Product summary-concentrations in products
- BACs used in mosquito spraying

Next Meeting

Plan for a meeting in March and a doodle poll will be sent out for that meeting.

Adjourn

Handouts

All handouts were posted on the TURI website prior to the meeting.

- DRAFT November Meeting Minutes
- TURA Program Update
- Screenshot of LibGuide

Quaternary Ammonium Compounds

- EPA 2016: ADBAC Final Work Plan
- EPA 2016: DDAC Final Work Plan
- EPA 1988: Clustering of Quaternary Ammonium Compounds
- Draft DDAC EHS Summary
- Draft ADBAC EHS Summary
- QAC Research Bibliography

Chat Box Conversation (inserted verbatim from zoom chat)

12:27:39 From Pam Eliason, TURI: Pam Eliason, TURI
12:27:48 From Liz Harriman - Toxics Use Reduction Institute: Liz Harriman - TURI
12:27:55 From DAVID JONES: David Jones, ISC Quats, Lonza LLC
12:28:05 From Keith GEO-Bells: Keith Hostetler, PhD. TRS/ADBAC DDAC ISC

12:28:17 From Rich Gurney (he, his): Rich Gurney - TURA SAB Member - Gov Baker Appointee - Simmons University, Co-Chair Chemistry & Physics Department

12:28:23 From Wendy Heiger-Bernays: Wendy Heiger-Bernays, Boston University School of Public Health, SAB

12:28:23 From Robert Holden: Robert Holden, Stateside Associates

12:28:26 From Hayley Byra: Hayley Byra - TURI

12:28:47 From Lisa Cashins: Lisa Cashins - MA Department of Labor

12:29:33 From Tricia McCarthy's iPad: Tricia McCarthy, Coyne PC for American Chemistry Council

12:30:15 From Tiffany Skogstrom: Tiffany Skogstrom, MA Office of Technical Assistance (OTA)

12:30:47 From mgorman: Margaret Gorman, Northeast Region, American Chemistry Council

12:30:48 From Katherine Robertson, MCTA: Katherine Robertson, MCTA

12:30:54 From Harry Hechehouche: Harry Hechehouche, ACC Northeast Region

12:30:59 From Erin DeSantis, ACC: Erin DeSantis, Northeast Region, American Chemistry Council

12:31:19 From Judi Anderson: Hello all

12:31:25 From Christy Foran: Christy Foran, RAND Corporation and SAB member

12:31:40 From Ken Littel: Ken Littel, Stepan Company

12:32:15 From Denise Kmetzo: Denise Kmetzo, Collaborative Risk Solutions, Board Member

12:32:24 From Caredwen Foley: Caredwen Foley, OTA

12:32:27 From Hannah Alleman: Hannah Alleman, Household & Commercial Products Association

12:32:29 From Christopher Hansen: Christopher Hansen, University of Massachusetts Lowell

12:32:30 From Heather Lynch: Heather Lynch, Cardno ChemRisk, Board Member

12:32:37 From Sandy Baird: Sandra Baird, MassDEP, Office of Research and Standards, Toxicologist

12:32:38 From Robin Dodson, SAB, Silent Spring Institute: Robin Dodson, Vice Chair SAB, Silent Spring Institute

12:32:47 From John Raschko: John Raschko, OTA

12:33:07 From Judi Anderson: Affiliation: Kroeger Associates

12:33:35 From Carol Holahan: Carol Holahan on behalf of ACC

12:33:55 From Aron Pollard: Aron Pollard with Mason Chemical Company

12:43:06 From Pam Eliason, TURI: If you have not done so already, please put your name and affiliation in the chat. Thank you

12:43:50 From christine rioux: christine rioux

12:44:03 From christine rioux: environmental health scientist

12:44:04 From Stephen McInerney: Steve McInerney with Capaccio Environmental

12:44:16 From christine rioux: Independent Consultant

12:50:25 From Casey Crownhart: Casey Crownhart, NYU

12:50:41 From Pam Eliason, TURI: If you have not done so already, please put your name and affiliation in the chat. Thank you

12:52:38 From Katherine Robertson, MCTA: Will these slides be made available?

15:36:20 From Ken Littel: K. Littel, these quats are effective against the Covid-19 by impacting the lipid coating.

15:40:22 From Liz Harriman - Toxics Use Reduction Institute: Thanks, Ken, we got around to that!