***Toxics Use Reduction Institute Science Advisory Board Meeting Minutes***

***June 29, 2022***

***Virtual Zoom Meeting***

***1:00 PM***

***Members Present:*** Robin Dodson (Chair), Christine Rioux (Vice Chair), Helen Poynton, Heather Lynch, Wendy Heiger-Bernays, Dave Williams

***Members not present:*** Amy Cannon, Rich Gurney, Lisa Cashins, Denise Kmetzo, Christy Foran

***Program staff present:*** Liz Harriman (TURI), Heather Tenney (TURI), Hayley Hudson (TURI), Tiffany Skogstrom (OTA), Caredwen Foley (OTA), Sandra Baird (MassDEP), Michael Ellenbecker (TURI), Gregory Cooper (MassDEP)

***Others present:*** Carol Holahan (Foley Hoag ACC), Christina Bramante (Nano-C), Raza Ali (ACC), Tom Lada (Nano-C), David Jones (Arxada LLC), Katherine Robertson (MCTA), Jerome Lang (Nano-C)

***Welcome & Introductions***

The chair noted that this meeting is being conducted remotely, consistent with [An Act Extending Certain COVID-19 Measures Adopted during the State of Emergency](https://www.mass.gov/service-details/updated-guidance-on-holding-meetings-pursuant-to-the-act-extending-certain-covid-19-measures). This Act includes an extension, until July 15, 2022, of the remote meeting provisions of Governor Baker's March 12, 2020, Executive Order resulting from the outbreak of the 2019 novel coronavirus, known as “COVID-19."

Board members introduced themselves, program staff were announced, and attendees were asked to put their name and affiliation in the chat.

***Approve April Meeting Minutes***

A motion was made to approve the April meeting minutes as amended, and there was a second. A roll call vote was conducted and unanimously approved by the six members present.

***Approve May Meeting Minutes***

A motion was made to approve the May meeting minutes with board member’s edits noted. A roll call vote was conducted and unanimously approved by the six members present.

***Remote Meeting Update***

A motion was made to allow for remote participation in accordance with the open meeting law. It was noted that members will state the need for remote participation at the time of RSVP. A roll call vote was conducted, and the motion was unanimously approved by the six members present.

***Single Walled Carbon Nanotubes***

At the March meeting the board made a recommendation **to list MWCNTs based on the evidence of pulmonary toxicity, lung cancer, mesothelioma, and environmental persistence. There are additional concerns for genotoxicity and toxic environmental degradation product**s.

The nano petition also asked us to consider carbon nanofibers (CNF) and single walled carbon nanotubes (SWCNT). The board discussed CNF at the April meeting but did not come to a conclusion. Discussion of SWCNT began at the May meeting. Since then we received a second round of comments from Nano-C and Hayley put together a matrix of physiochemical properties for each of the studies on the LibGuide.

***Pulmonary toxicity***

Board members summarized studies they reviewed and found to be helpful in understanding the pulmonary endpoint. There was further discussion of relevant details.

* Ema 2016 was noted to be a good review paper. Markers of pulmonary toxicity were shown in aspiration and installation studies over a wide range of concentrations (some very high).
* Honda 2017 looked at both long and short SWCNT– shorter SWCNT made it further down in the lungs.
* Oberdorster 2015 conclusions and particle density were discussed. Density is a complex parameter, and overall was not noted as a major driver of toxicity of SWCNT.
* Multiple Shvedova papers summarized continuing research of SWCNT. Shvedova 2005 and Shvedova 2014 were single dose. Inhalation and showed the same effects but more severe than installation. Shvedova 2008 was noted as a repeat dose study and was not on the LibGuide – it will be added for the next meeting.
* Shvedova 2005 found more pulmonary effects from SWCNT than carbon black and silica, which were used as positive controls and are known to be fibrogenic.
* Park 2016 and Pacurari 2011 studies showed strong mechanistic evidence of a pro inflammatory response and fibrotic activity.
* Teeguarden 2011 did comparative proteomics and showed that SWCNT pulmonary effects observed in previous papers at high doses were consistent w/ the changes in proteomics.
* There was extensive discussion on the abundance of single dose studies, potential particle overload, the doses used, and whether they are relevant to humans.
* There was additional discussion on data gaps and uncertainty concerns among the board.
* **Summary Statement:** There is evidence that SWCNT cause pulmonary toxicity in animals, including inflammation, fibrosis, and granulomas. There is a lack of understanding, however, whether the high doses used in the animal studies exceed particle overload conditions, which are common with poorly soluble particles administered via inhalation. Particle overload overwhelms particle clearance mechanisms, resulting in tissue irritation, release of inflammatory cells, and generation of reactive oxygen species (ROS). Persistent lung inflammation can cause cell proliferation and tissue remodeling, which when insufficiently repaired can lead to non-neoplastic effects such as fibrosis, DNA damage, and possibly, tumor formation. Particle overload conditions are not a response to the agent but rather to the overload conditions.

***Environmental effects***

Board members summarized the key studies they reviewed for the environmental endpoint. The major concern is the very high persistence with no degradation. They also may accumulate in the gut of aquatic species and be transferred up the food chain.

***Cancer & Reproductive/Developmental effects***

Board members reviewed previous discussions on the cancer and reproductive/developmental endpoints. Overall, the summary from last month’s meeting remains the same. Both endpoints suffer from lack of studies and/or well-done studies. There were not any new studies since the last meeting.

***Genotoxicity***

For the genotoxicity endpoint board members had nothing to add at this meeting to their summary from the previous meeting (restated here for completeness):

* SWCNTs have been shown to generate reactive oxygen species (ROS) in a dose-response manner. The generation of ROS is considered a major factor in the genotoxicity. ROS are able to cause the oxidation of DNA, DNA strand breaks or lipid peroxidation-mediated DNA adducts.
* Evidence for genotoxicity is not well supported, but there is evidence for ROS and DNA damage.
* Evidence for mutagenicity is not well supported by the evidence, which includes studies that lack adequate chemical and physical characterization of materials.
* Jiang (2020) was noted as a well done study and helpful for this endpoint. Molecular toxicity of SWCNTs is characterized well and is concentration and structure dependent. The materials in this study were well characterized with varying lengths and functionalization, and all except a semiconducting SWCNT exhibited positive genotoxicity.

***Visitor Questions/Comments***

There was an opportunity for visitor comments at this time and there were none.

***Next Meeting***

The SAB will break for the summer and look to have a meeting at the end of September.

***Visitor Comments (inserted verbatim from zoom chat)***

From Christina Bramante to Everyone 01:45 PM

Regarding Shvedova inhalation study dose of 5 mg/m3, Oberdorster, et al., provided the following comment, "It should be noted that most of these SWCNT studies involved bolus exposure, resulting in high lung burdens at a very high dose rate. The single inhalation study with SWCNT involved a relatively high aerosol concentration (5 mg/m3) and 5-d exposure duration (Shvedova et al. 2008). Therefore, dose rate was still relatively high. Thus, there is the need for 13-wk inhalation studies in rodents."Mike, would just like to correct your statement about the NIOSH REL which is 1 µg/m3 (8-hr. TWA), not 10 ug/m3 as stated.

From Tom L to Everyone 02:02 PM

Thank you all for this great discussion. Chris and all, I found the abstract for Maynard et al (2004), which concludes that airborne concentrations generated during handling suggest that concentrations were lower than 53μg/m3. I'm not sure if 53 is the number that Shvedova used in 2008 to determine the length of time for human equivalent exposure, but if it was, then it's 53x larger than what Nano-C used (NIOSH REL of 1 μg/m3) for our estimation of human exposure timeframes in our more recent submission. On Shvedova's low side estimate of 5 μg total dose per mouse in the 2008 work, the human equivalent we calculate at 1 μg/m3 airborne concentration would be 16 years of 40 hour/week work.

From Heather Lynch to Everyone 02:13 PM

There is evidence that SWCNT cause pulmonary toxicity in animals, including inflammation, fibrosis, and granulomas. There is a lack of understanding, however, whether the high doses used in the animal studies exceed the high-end likely human exposure levels. Further, the effects seen at the highest doses in animal studies may be associated with particle overload conditions, which are common with poorly soluble particles administered via inhalation. Particle overload overwhelms particle clearance mechanisms, resulting in tissue irritation, release of inflammatory cells, and generation of reactive oxygen species (ROS). Persistent lung inflammation can cause cell proliferation and tissue remodeling, which when insufficiently repaired can lead to non-neoplastic effects such as fibrosis, DNA damage, and possibly, tumor formation.

From Christina Bramante to Everyone 02:22 PM

Please note the Shvedova inhalation dose is associated with 730 years of worker exposure at the NIOSH REL for 8 hrs/day

The Shvedova inhalation dose is high.

From Heather Lynch to Everyone 02:25 PM

There is evidence that SWCNT cause pulmonary toxicity in animals, including inflammation, fibrosis, and granulomas. There is a lack of understanding, however, whether the high doses used in the animal studies exceed particle overload conditions, which are common with poorly soluble particles administered via inhalation. Particle overload overwhelms particle clearance mechanisms, resulting in tissue irritation, release of inflammatory cells, and generation of reactive oxygen species (ROS). Persistent lung inflammation can cause cell proliferation and tissue remodeling, which when insufficiently repaired can lead to non-neoplastic effects such as fibrosis, DNA damage, and possibly, tumor formation. Particle overload conditions are not a response to the agent but rather to the overload conditions.

From Heather Tenney to Everyone 02:26 PM

I am afraid to leave and come back but I'll try...

From Christina Bramante to Everyone 02:34 PM

Thank you all