



July 24, 2014

Comments to the EPA SAB and BOSC

Public Statement from Richard Becker Ph.D. of the American Chemistry Council to EPA's Chartered Scientific Advisory Board and Board of Scientific Counselors for the Discussion of ORD Strategic Research Directions

I am Richard Becker of the American Chemistry Council and wish to provide comments today on EPA's for Chemical Safety for Sustainability Strategic Action Plan (2016-2019)<sup>1</sup>

1. ACC supports EPA's research focus on developing advanced approaches for highthroughput screening, computational profiling and high throughput exposure estimation. Such methods hold great promise to improve the efficiency and effectiveness of chemical evaluations. In the shorter term, exposure activity profiling using HTE estimates and HTS data as indicators of activity likely have greatest applicability in priority setting. As scientific confidence in these methods increase, then as appropriate, uses could potentially expand to screening level regulatory evaluations. There are still a number of significantly hurdles to overcome, including the need to incorporate both metabolic activation and detoxification into these systems as wells as the challenge of covering sufficient biological space.

(One correction for the record, on page 20, it's incorrect to assert that there over 80,000 legacy chemicals are in commerce. Of the 70-80,000 chemical substances on the TSCA Inventory, EPA<sup>2</sup> itself indicated that only approximately 15,000 are actually in commerce. This is still a large number, but it's 5-6 times lower than what's asserted. Of these, the 2000+ high production volume chemicals account for approximately 90% by volume of chemical use, and for most if not all of these HPV substances, EPA and OECD have at health and safety information on file.)

2. We note that the initial efforts focusing on trying to predict complex biological toxicity endpoints such as developmental toxicity, reproductive toxicity, and cancer using HTS tools such as ToxCast have not proven to be as fruitful as was originally anticipated by EPA. In fact, many of these approaches were shown to have limited applicability for predicting in vivo chemical hazards using statistical classification methods. The transformation underway to now more fully explore opportunities to use ToxCast and computational profiling methods to obtain measurements of activity in assays tied to key events in adverse outcome pathways and to evaluate results using high throughput exposure modeling to generate exposure : activity profiles should have more direct application to priority setting as part of improved tiered testing and assessment procedures.

3. I want to bring to the SAB's attention our recent publication entitled "Developing Scientific Confidence in HTS prediction models: Lessons learned from an endocrine case study."<sup>3</sup> I won't go into all the details here, the paper is open

<sup>1</sup> [http://yosemite.epa.gov/sab/sabproduct.nsf/0/337ECE7064DEE1F185257CF3005F5367/\\$File/CSS%20Prelim%20Draft%202016-2019%20StRAP\\_2014\\_07\\_02.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/0/337ECE7064DEE1F185257CF3005F5367/$File/CSS%20Prelim%20Draft%202016-2019%20StRAP_2014_07_02.pdf)

<sup>2</sup> <http://web.archive.org/web/20100808123242/http://www.epa.gov/oppt/newchems/pubs/newvexist.htm>

<sup>3</sup> <http://www.sciencedirect.com/science/article/pii/S0273230014000920>





access and I have copies that can be distributed. I want to get across several points that the SAB and BOSC may wish to reflect on in developing recommendations to EPA.

First – significant research and development has focused on generating data and prediction models, but only limited attention has been paid to systematic approaches for developing and documenting scientific confidence in the assays & prediction models derived therefrom. Based on our experience, where we were unable to ascertain documentation of assay performance or to readily access the prediction model itself, and instead had to invest resources in independently replicating the model, we put forward a straightforward scientific confidence framework for HTS assays and prediction models.

In brief, this Framework is comprised of three elements:

1. Analytical validation: which entails assessment and documentation of the biological basis and performance of assays
2. Qualification: which entails documenting the performance of the prediction model derived from HTS assays
3. Utilization: which entails documenting, by virtue of a weight of the evidence evaluation, the scientific support underpinning application prediction model for a specific purpose.

While I am encouraged to see that EPA's CSS plan has included "validation" in a few places, I urge members of the SAB & BOSC to consider recommending to EPA the need to incorporate such a scientific confidence framework in CSS research strategy to ensure transparency, enable reliability and improve scientific credibility. Stakeholders should not have to reconstruct EPA's prediction models – these should be readily available, in the same manner that EPA has made available ToxCast data.

We have also shown that this scientific confidence framework is applicable also to AOPs, so as the Agency moves ahead with developing and test driving AOPs, again, such a framework needs to be actualized.

4. My 4<sup>th</sup> and final point. EPA is to be commended for its stakeholder outreach and engagement efforts organized by the NCCT and CSS leadership and staff. As EPA proceeds with implementing its CSS plan, this approach should continue and even be expanded. We encourage EPA to develop further opportunities to transparently and openly collaborate with stakeholders and experts outside the agency. Engagement needs to occur at the design stages for each of the main projects illustrated on page 24 of the CSS plan. And importantly, methods, prediction models and results shouldn't be launched over the transom and presented as completed work products or final published manuscripts, but rather disseminated as a series of draft white papers or draft proof of concept papers in a manner that encourages and values stakeholder involvement.

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