THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

AUG 27 2014

David Allen, Ph.D.
Chairman
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-4164

Dear Dr. Allen:

Thank you for your May 22, 2014, letter and for the report, "SAB Advice on Advancing the Application of CompTox Research for EPA Chemical Assessments."

As you indicated in your letter, there are thousands of chemicals found in products we use every day, and hundreds more are introduced each year. Due to the time- and resource-intensive nature of the current animal-based tests, many of the chemicals in these products have not been completely evaluated for their potential toxicity. To address this challenge, the EPA in 2005 launched the Computational Toxicology research effort to study how to change the current chemical-testing paradigm. The EPA's CompTox program is part of the broader Chemical Safety for Sustainability National Research Program.

A central component of the EPA's CompTox research is ToxCast, and it presents a potential solution to fill the gap in chemical toxicity data for new and legacy chemicals. To date, ToxCast has evaluated nearly 2,000 chemicals across more than 500 assays that cover a broad range of potential biological effects. We released the ToxCast chemical data publicly in December 2013 through user-friendly Web applications, called the interactive Chemical Safety for Sustainability (CSS) Dashboard.

As you know, science is the backbone of the EPA's decision making. To ensure we use the best possible science, we depend on rigorous, independent peer reviews from advisory groups such as the Science Advisory Board. I am grateful to the SAB and its Exposure and Human Health Committee for their review of how the EPA is using products from the CompTox research activities, whether the program outputs align with the needs of the EPA's programs and whether limitations or challenges to using CompTox hazard and exposure data for risk assessment and decision making can be identified and addressed.

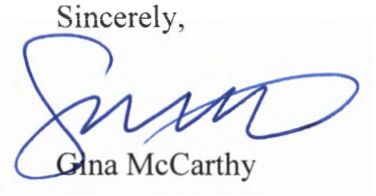
As you read our response, please be aware that much of the report was based on a review of the program in early 2012. Considerable progress has been made since then, but we expect that your clear and insightful recommendations will help to ensure we continue to build confidence in and support for this innovative and impactful research area and enhance its relevance and tailored application to meet the agency's highest-priority needs. Your recommendations are particularly timely as the Office of Research and Development is now developing its FY 2016-19 Strategic Research Action Plans, including one for CSS.

Enclosed are our responses to your recommendations. Our responses are organized based on the areas of ToxCast data applications as listed in your letter. These areas are followed by our responses to additional recommendations in your accompanying report but not present in your letter.

We are proud of the significant progress made in the CompTox research program and the promise it shows for revolutionizing how chemicals are evaluated. However, we recognize that there are still a number of steps we can take to further this progress.

I wish to thank you and the Exposure and Human Health Committee once more for the thoughtful consideration underlying your recommendations and for your service to the EPA.

Sincerely,



Gina McCarthy

Enclosure

THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

AUG 27 2014

Thomas Zoeller, Ph.D.
Chairman
Exposure and Human Health Committee
Science Advisory Board
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-4164

Dear Dr. Zoeller:

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As you indicated in your letter, there are thousands of chemicals found in products we use every day, and hundreds more are introduced each year. Due to the time- and resource-intensive nature of the current animal-based tests, many of the chemicals in these products have not been completely evaluated for their potential toxicity. To address this challenge, the EPA in 2005 launched the Computational Toxicology research effort to study how to change the current chemical-testing paradigm. The EPA's CompTox program is part of the broader Chemical Safety for Sustainability National Research Program.

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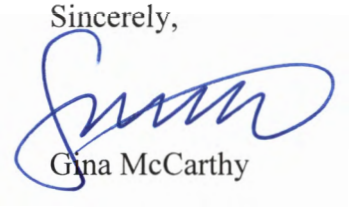

Gina McCarthy

Enclosure

EPA Responses to Recommendations

EPA's responses to the SAB EHHC committee's recommendations are organized by the recommendations for the areas of applications for ToxCast data listed in the SAB's cover letter, followed by responses to the recommendations in the accompanying report that were not already addressed.

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Areas of applications for ToxCast data

Using ToxCast data to develop Adverse Outcome Pathways

The SAB recommends that the agency look not only at whether the ToxCast dataset is predictive of in vivo toxicity, but also whether the endpoints from in vivo studies have associated molecular endpoints in ToxCast. The SAB recommends that the agency explore partnerships with professional societies and institutions devoted to the development of new information and therapeutic approaches for specific diseases.

As highlighted in the SAB report, the CompTox program has already assessed the predictivity of the ToxCast data for a variety of *in vivo* endpoints. A recent example of progress in this area is our evaluation of a subset of the ToxCast assays measuring estrogen receptor function to predict the *in vivo* rodent uterotrophic assay. The *in vivo* uterotrophic assay is part of the Tier 1 battery of assays used to assess estrogenic activity in the Endocrine Disruptor Screening Program (EDSP). The predictivity and overall utility of the ToxCast assays for this *in vivo* endpoint was first reviewed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel in January 2013, and will be further evaluated in additional meetings in 2014. Importantly, the SAB also recommends incorporating the reverse paradigm where an *in vivo* endpoint of interest is first identified and the biological targets, cellular pathways, and feedback processes involved in the endpoint are mapped back to the ToxCast assays to identify potential information gaps. The first part of this process (i.e., identification of the key events involved in an adverse response and their associated interrelationships) is a critical part of developing an adverse outcome pathway (AOP). An example of this reverse paradigm is currently occurring for thyroid toxicity and disease. Over the past decade, the identification of information gaps in relevant pathways has been led by EPA scientists in coordination with international expert groups (e.g., OECD). Just this year an internal *ad hoc* EPA working group conducted comprehensive state-of-the-science review of AOPs relevant to the thyroid. This began with known adverse outcomes of thyroid disruption in human and ecological species, and identified gap in *in vitro* predictive testing methods. To fill these gaps, fit-for-purpose *in vitro* assays are being developed in CSS. As other *in vivo* endpoints of interest are identified, we anticipate additional engagement with our academic partners as well as professional societies and institutions devoted to the development of new information and therapeutic approaches for the associated human diseases. Many of these endpoints are currently being identified in the planning process for the FY16-19 CSS StRAPs.

Using ToxCast data in a consistent manner

The SAB recommends that the agency develop a Data Use Guide or other structured approach to the use of ToxCast data in various applications, including the interpretation of the resulting information.

The SAB's recommendation on the development of a ToxCast Data Use Guide is a very timely suggestion. Over the last year, NCCT has begun implementing a multi-step process for increasing and documenting the quality, transparency, and usability of the ToxCast data. The first step in the process has been to revamp the data analysis software "pipeline". We are condensing multiple statistical and graphical programs into a single software application that is more statistically rigorous, more accurate, and less prone to outliers. Quality control flags are being added to the data files to indicate which data points may be subject to certain systematic errors and require additional caution during interpretation. This step in the process is nearly complete and the new data should be released at the end of the summer. The second step in the process will be a formal external audit of the ToxCast data. This step will be performed following the release of the new data and is intended to reassure the stakeholder community that the data is of high quality. The third step in the process is the development of a ToxCast "Owner's Manual." The manual will detail all the processes involved in ToxCast, beginning with

chemical procurement and quality control. The manual will also include a guide to the various chemical libraries, how chemicals are selected, a detailed description of the data analysis pipeline, how the data fit with the appropriate models, how the potency and efficacy values are calculated, and how "hits" are determined (i.e., which chemicals are positive in a particular assay). The software code underlying the new data analysis pipeline will also be released to allow others to independently reproduce the analysis performed on the data. Finally, the manual will provide detailed information about the ToxCast assays in a standardized ontology consistent with the open-source BioAssay Ontology effort including the specific endpoint measured, the intended biological target, assay technology, and other informative features of the assay. The ToxCast Owner's Manual, data analysis software, and the results from the external audit will be posted to EPA's Chemical Safety Research webpage.

The usability of the ToxCast data for different applications, such as prioritization or screening-level chemical assessments, is currently at different stages of development. The application of the ToxCast data for prioritization of chemicals for additional testing in the context of the EDSP has been outlined in the EDSP21 Work Plan and will be reviewed at upcoming FIFRA Science Advisory Panel meetings. The structured approach for this application will be outlined in the background documents being prepared for the panel review process. The application of the ToxCast data for screening-level assessments is currently part of the FY16-19 StRAPs with integrations across the CSS and Human Health Risk Assessment (HHRA) National Programs. If successful, the structured approach for this application will be documented in a series of publications that will undergo peer review. The usability of the ToxCast data for emergency situations through a retrospective analysis of the Deepwater Horizon accident is currently not underway or being planned. However, there were valuable lessons learned. One of the most important lessons is that ORD can develop new scientific information within a rapid time frame in response to environmental disasters. It is anticipated that the use of ToxCast data for endocrine-related prioritization being reviewed by the FIFRA Science Advisory Panel would also be applicable for prioritization purposes in emergency situations.

Using ToxCast data for evaluating the toxicity of mixtures

The SAB recommends that the agency begin a formal approach to addressing these challenges in the field of mixture research using ToxCast and other CompTox technologies.

The primary focus of ToxCast and CompTox is currently on single chemicals. This focus is a response to in-depth discussions with EPA Program Offices that articulate this a critical data gap. In addition, this focus is also a practical, near-term necessity as the utility of these new approaches are still being evaluated. Being able to assess the potential toxicity of single chemicals using high-throughput screening is a building block to being able to screen chemical mixtures or predict their toxicity through the combination of the results from the single chemical screens. We appreciate that the same advantages derived for the study of single chemicals can also be gained in the study of mixtures. CompTox is conducting a pilot exercise in mixtures-related research by screening a series of surface water samples in the ToxCast assays. In addition, NCCT is collaborating with NIH, NIEHS/NTP and FDA, via the Tox21 MOU, in a pilot project to evaluate a large number of chemical mixtures in a subset of high-throughput screening assays. The analyses of data from these projects are currently underway.

Developing an advisory committee to promote engagement

The SAB recommends that the agency use an advisory committee to promote engagement with external scientists. The goal of this advisory group would be to ensure that the Agency continues to generate tools that are useful not only within EPA but also to a broad array of extramural stakeholders.

The EPA recognized early in the ToxCast program that a parallel effort in stakeholder engagement and

outreach was required to aid in the development, acceptance, and application of these new data sources. As such, it has set up a proactive stakeholder outreach strategy that includes a combination of broad (public workshops) and targeted (focused collaboration with a state agency) engagement. For example, with the release of new ToxCast data, the CompTox program held two stakeholder engagement workshops in 2014. A total of 85 stakeholders participated in the January 2014 workshop in Research Triangle Park, NC with approximately 20% from industry, and approximately 5% each from academia and NGO communities. In a second workshop held in collaboration with the Food and Drug Administration in April 2014, 277 stakeholders participated with 24% from industry, 23% from non-EPA federal government agencies, 18% from EPA's Program or Regional Offices, 7% from non-governmental organizations, 5% from state governments, 4% from academia, and 1% from international governments. The rest of the attendees were from ORD. Both workshops included presentations about the coverage of the ToxCast data, early interpretation of these data, and demonstrations about how to access the ToxCast data through the iCSS dashboard. Workshop participants provided advice to EPA about how ToxCast data and the associated tools could be improved to meet the needs of stakeholders. This feedback is being used in ongoing development of a new version of the iCSS dashboard.

EPA also employs numerous other communication and outreach activities including the Computational Toxicology Communities of Practice monthly meeting; a series of materials describing this research (webpages, fact sheets, videos); proactive scientific media outreach; scientific presentations to various societies and conferences; establishing hundreds of research collaborations worldwide with a wide variety of groups interested in using this data; and actively requesting feedback from stakeholders about ideas for enhancing and using this data. The Computational Toxicology Communities of Practice was specifically highlighted in the SAB report as a successful demonstration of this outreach.

Finally, beginning in calendar year 2014, the EPA will be engaging in and seeking advice from working groups of its SAB and Board of Scientific Counselors focused on the CSS program and its CompTox areas.

Integrating CompTox data with other hazard and exposure information essential to assessing risk
The SAB recommends that the program seek input on the integration of ToxCast products with other data essential to assessing risk.

EPA agrees with this SAB recommendation. Indeed, over the past year, the CSS program has made substantial progress in developing cost-efficient high-throughput exposure models that are capable of providing human exposure estimates for thousands of chemicals. This initiative is called ExpoCast and was developed to complement the hazard-oriented ToxCast program. In a recent publication, EPA researchers have developed high-throughput exposure models to estimate exposures for 1,763 chemicals using production volume, environmental fate and transport models, and a simple indicator of consumer product use (as described in Wambaugh et al, Environ Sci Tech. 2013, *High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project)*. A second generation of the high-throughput exposure model has been developed using more refined indoor and consumer use information, which has resulted in substantial improvement in model performance and decreased uncertainty in exposure estimates. On July 31-August 1, 2014, a FIFRA Science Advisory Panel will hear presentations on the ExpoCast research effort in order to provide recommendations on its application to EDSP. Consistent with SAB recommendations, this input will be valuable as we integrate ToxCast data with other data in a risk-based context.

Additional recommendations provided in the SAB report

The SAB recommends that performance characteristics of assays that relate to specificity, sensitivity and reliability be made available on the EPA website. The SAB understands that the suitability of in vitro data for regulatory decisions depends on the type and level of decisions to be made.

As part of the effort to increase the quality, transparency, and usability of the ToxCast data, the performance characteristics of the individual assays will be released on the EPA's CompTox webpage. This will occur following completion of the new data analysis pipeline and together with the release of the ToxCast "Owner's Manual."

The SAB recommends that the EPA explore AOPs not only based upon how a chemical can perturb biological systems but also from the perspective of how aging and disease processes have underlying AOPs which may be sensitive to chemical effect.

Ongoing planning for FY16-19 research, as outlined in the CSS StRAP, include some AOPs associated with human diseases. For example, one proposed research project aims to integrate ongoing research and knowledge of the role of airborne pollutants and cardiovascular disease into AOPs and then using the AOP development process as a mean to identify key biological targets for which high-throughput *in vitro* methods could be developed. Strategic prioritization of research activities conducted in partnership with EPA Offices and Regions, has resulted in a higher priority focus on chemical exposures during early life stages. In this area, ORD is has developed a Children's Environmental Health (CEH) Research Roadmap to designed integrate and synergize CEH research efforts across ORD. This includes research to develop AOPs specific to developmental life-stages. The EPA agrees that an important goal in the CompTox projects in CSS is to evaluate factors that contribute to susceptibility and variability in response, including aging and underlying disease.

The SAB also recommends that the agency work toward developing a clear rationale describing the different uses of the data depending upon specific effects.

The CompTox program is still in the research and development phase. As noted in previous responses above, the application of ToxCast data and its interpretation with CompTox tools for specific Agency-related decisions on chemicals is just beginning to unfold. The application of the ToxCast data for prioritization decisions in the context of EDSP will be reviewed by FIFRA Science Advisory Panels in 2014 and 2015. The application of the ToxCast data for lower tier assessments is part of the FY16-19 CSS StRAP, where emphasis is being placed on evaluation of whether computational data and models use successfully solves critical Agency assessment and management needs. For each type of application and decision context, a clear and transparent rationale for use will be developed, reviewed by the appropriate advisory bodies, and presented to stakeholders for feedback.

The SAB recommends that the Agency clarify the goals and objectives for ToxCast with respect to chemical screening, prioritization and risk assessment.

All of EPA's CompTox research falls under the cross-cutting CSS National Research Program. As outlined above, CSS is currently going through development and review of the FY16-19 StRAP documents. These documents include the strategic direction of ToxCast and provide the requested clarification on the goals and objectives for its application with respect to prioritization and risk

assessment. Input on the Strategic Research Action Plan documents has been received from the Program Offices and Regions and the documents were reviewed at the joint SAB/Board of Scientific Councilors meeting in July 2014.