EPA's Report to Congress on Endocrine Disruptor Research

Congressional Reporting Requirement Origins

At the request of the FY 2015 House of Representatives Department of the Interior, Environment, and Related Agencies Appropriations Bill, EPA is providing this report on:

Endocrine Disruptor Research.—The Committee has longstanding interest in EPA's effort to determine possible health and environmental effects of chemicals. As part of EPA's overall efforts to modernize risk assessment protocols, the Committee encourages EPA to incorporate the various recommendations of the National Academy of Sciences' reports as well as all other relevant scientific literature and recommendations. Further, the Committee commends EPA for developing new scientific methods, removing barriers, and fostering cooperation in implementing the toxicity testing agenda that the 2007 National Academy of Sciences' (NAS') Report on Toxicity Testing in the 21st Century puts forth. The agency is directed to submit to the Committee a report that outlines: (1) progress to date to research, develop, validate and translate innovative chemical testing methods that characterize toxicity pathways, (2) efforts to coordinate across federal agencies, and (3) future plans to continue to implement the toxicity testing vision and strategy in the NAS report.

Executive Summary

Progress to date and cross-agency collaborations: Since its inception just over a decade ago, the EPA's computational toxicology (CompTox) research area has taken on the challenge of generating toxicity information on data poor chemicals, developing tools to put this information in the context of exposure and risk, and training the community of stakeholders inside and outside the agency in using the data/tools -- all of which EPA has made publicly available. Using traditional animal tests, it costs nearly $1 million and several years to test a single chemical. With CompTox approaches chemicals can be evaluated in high-throughput experiments or assays in a fraction of the time, and at costs as low as $30,000 per chemical, without using animals for testing. These approaches were adapted from advances in biotechnology, robotics, and pharmaceutical research – and now the explosion of new science and engineering applications in these fields, including 3-D printing and modeling of 'human organs on a chip,' which promises new opportunities for EPA to further evolve its Chemical Safety for Sustainability research activities, most recently described in its t Strategic Research Action Plan (StRAP).

The 2007 National Academy of Science (NAS) report *Toxicity Testing in the 21st Century* provided a vision and strategy for transforming toxicity testing and estimated a 15-20 year timeframe for the vision to begin to be realized. Fast paced advancements in biotechnology, computational chemistry, and related fields, as well as the unprecedented collaborations fueled by the Tox21 federal partnership between EPA, NIH, and FDA, are allowing this transformation to unfold much sooner than expected.

To date, EPA's ToxCast has screened nearly 2,000 chemicals across approximately 700 assay human health endpoints, and Tox21 has screened over 8,000 chemicals across approximately 50 human health endpoints. The partnership has worked extremely effectively to enhance the ability to predict the safety of chemicals. Significant improvements also have been made in data access, reliability, and usability for the community of stakeholders inside and outside the agency. In the FY16 – FY19 window, assuming current funding levels, EPA expects to:

- **Accelerate the pace of chemical safety evaluations:** Make the CompTox data and tools more user-friendly and accessible to agency decision-makers and external stakeholders.
- **Enable the agency to use 21st century science to make sustainable and public-health protective decisions:** Work with agency programs and regional partners to develop tailored, relevant, and fit-for-purpose solutions using CompTox data, tools, and models.
- **Promote the concept of "tipping points" as early indicators:** Develop tools to interpret earlier signals of biological harm or damage in order to increase the agency's capacity to predict and

prevent the impact of individual or multiple chemicals. This approach brings focus on what exposures would be safe rather than the traditional approach of what exposures are hazardous.

- **Support sustainable innovation and evaluation of chemicals and nanomaterials:** Application of CompTox models, tools, and data to enable innovative, safer, and more sustainable design, development, and use of manufactured chemicals and materials across the product lifecycle.

So far, EPA has used ToxCast and its computational tools primarily to inform the agency's chemical screening and prioritization needs, most recently, in the Endocrine Disruptor Screening Program (EDSP). Other state (*e.g.* California EPA) and national (*e.g.* Health Canada and Australian) organizations also have been evaluating these data and tools for use in their programs. To further assess and build scientific confidence in the progress and readiness of EPA's computational toxicology (CompTox) data/tools, EPA requested that the NAS conduct a follow-up study, *Incorporating 21st Century Science into Risk-Based Evaluations*, and provide recommendations on next steps in the rapid evolution and applications of these computational data, models, and tools. The new study, estimated to be released in mid-2016, is expected to build on earlier NAS reports, which provided recommendations on 'problem formulation' and more simplified 'fit-for-purpose' risk assessments.

Future plans: Moving forward, the agency fully recognizes the opportunity to further evolve the CompTox area and broaden its application to agency activities potentially across its diverse regulatory frameworks. These novel applications can add significant efficiency and effectiveness to agency operations, enable it to participate in the Big Data revolution, and enhance the agency's visibility as a High Performing organization. In addition to expanding the chemical screening activities beyond the current 8,000 chemicals in Tox21, opportunities to further accelerate the pace of the revolution in toxicity testing include:

- Exploring how the ToxCast/Tox21 data can be used to develop high-throughput risk assessments, in particular for data poor chemicals;
- In concert with growing international efforts such as the European REACH, incorporating advancements in computational chemistry to allow 'read-across' from chemical structures with known bioactivity to other structures with less data;
- Using the high-throughput hazard and exposure information to begin to evaluate cumulative risk of chemical exposures;
- Expanding and extrapolating to novel assays that have relevance to ecological impacts;
- Customizing and uniquely adapting the emerging 'organs-on-a-chip' technologies for specific application to EPA chemical testing and evaluation systems; and
- Integrating computational activities with complementary experimental capacity to enhance synergies, performance, and reliability on the emerging data.

These activities would be a direct extension of and build on existing capacity that is being enriched through continual integration of expertise and resources and cross-agency collaborations. They also are 'implementation-ready' so that if opportunities are presented and additional resources were made available, they could be deployed and some of the outputs from them could be realized beginning in FY 2017. Achieving these ambitious, but reasonable outputs is contingent and dependent on sufficient appropriated resources.

Progress to Date and Cross-Agency Collaborations

Tox21 & ToxCast Background

Tens of thousands of chemicals are currently in use and hundreds more are introduced into commerce every year. Traditional chemical testing is expensive and time consuming; only a small fraction of chemicals have been evaluated fully for potential human health effects. Through its computational toxicology (CompTox) research within its Chemical Safety for Sustainability (CSS) research program, the U.S. Environmental Protection Agency (EPA) is exploring ways to evolve the current approaches used to evaluate the safety of manufactured chemicals. CompTox research integrates advances in biology, biotechnology, chemistry, and computer science to identify important human-relevant biological processes that may be disrupted by the chemicals and traces those biological disruptions to a related exposure and dose levels at which these disruptions occur.

A core component of EPA's CSS CompTox research is the Toxicity Forecaster (ToxCast™). Launched in 2007, ToxCast is a multi-year effort that uses automated chemical screening technologies, called "high-throughput screening assays," to expose living cells or isolated proteins to chemicals. The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects. Using the ToxCast data, thousands of chemicals can be evaluated for potential adverse health effects at a relatively low cost and in a short amount of time. To illustrate, EPA's Endocrine Disruptor Screening Program (EDSP) had evaluated nearly 100 chemicals in a decade and issued test orders for about 52 chemicals. These tests typically cost approximately $1 million per chemical tested. In comparison, ToxCast screened 1,800 chemicals in about three years for an average cost of $30,000 per chemical. It is understood that high-throughput screening is not the same as traditional toxicity testing. However, historically, chemicals were not tested more broadly partly because such testing would be cost prohibitive and require the use of a very large number of animals. Using CompTox tools, EPA now has data on 1,800 chemicals through ToxCast and almost 8,000 more through Tox21. Even if the types of tests and respective data are not identical, the high-throughput approaches have provided an unprecedented volume of data that provide estimates of toxicity and exposures to be used to screen, prioritize, and manage the risk of chemicals. These advances have been made possible because these new, different, and less expensive methods have been developed. Many related scientific activities have germinated (inside and outside EPA, in the U.S., and internationally) that will help build the bridges between traditional testing and these new approaches. Some of these activities and the broader application of CompTox to enhance the EDSP program are described later in this report.

The Tox21 program , first established in 2008, is a federal collaboration involving the EPA, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA). This collaboration, which was guided by the 2007 National Academy of Sciences (NAS) report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*, pools resources and expertise from among these agencies to develop better toxicity assessment methods. Using automated chemical screening technologies together with specialized robotic technology, Tox21 has compiled high-throughput screening data on nearly 10,000 chemicals for nearly 50 biological pathways. Tox21 integrates these results with chemical research, data, and screening tools from the EPA, NIH's National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS), the National Center for Advancing Translational Sciences (NCATS), and the FDA. The resulting data are published in public databases, such as the National Library of Medicine's PubChem, EPA's ToxCast and Aggregated Computational Toxicology Resource (ACToR), and NTP's Chemical Effects in Biological Systems (CEBS).

EPA Tox21 & ToxCast Update

The first phase of ToxCast, which was completed in 2009, was a "proof of concept." 300 well-studied chemicals (primarily pesticides) were evaluated in more than 500 high-throughput screening assays. Because most of these chemicals already had undergone extensive animal-based testing, EPA researchers were able to use these data to evaluate the application of the high-throughput assays.

The second phase of ToxCast was completed in 2013, and evaluated over 1,800 chemicals from a broad range of sources, including industrial and consumer products, food additives, and potentially "green" chemicals that could be safer alternatives to existing chemicals. These chemicals were evaluated in more than 650 high-throughput screening assay endpoints for potential endocrine disruption, reproductive toxicity, developmental toxicity, and carcinogenesis. In December 2013, EPA released these data through the new interactive Chemical Safety for Sustainability (iCSS) dashboard, a customizable and user-friendly web-based application that makes it easier to find and use toxicity data from the high-throughput screening assays. The iCSS dashboard allows users to search for chemical data of interest, filter chemicals based on specific consumer and industrial uses, and identify which biological processes may be impacted by chemical exposure. The resulting information may be used to prioritize chemicals for further testing based on user-specific criteria.

After the new ToxCast data were released, EPA launched an extensive stakeholder engagement effort to familiarize the stakeholder community with the new computational data, to encourage them to explore the data, and develop approaches to use these new data, as appropriate, to inform decisions related to the safety of chemicals. In 2014, EPA hosted multiple stakeholder webinars, two workshops, and a Data Summit. During the workshops, EPA staff provided hands-on demonstrations to stakeholders, showing them how to access and use the new data. Based on feedback from the workshops, EPA released two videos guiding users through the functionalities of the iCSS dashboard. Additional video information about these CompTox tools is available.
Stakeholders also provided EPA feedback about how data access could be improved and suggested ideas for enhancing data visualization and analysis tools. As a result of this feedback, a new version of the iCSS dashboard was released in August 2015.

Also, in 2014, EPA released a series of 'big data' challenges using innovative online crowd sourcing platforms to ask the scientific, technology, and computational community for their ideas about ways to use this new toxicity data to predict the doses of chemicals in humans that may result in adverse health effects. The big data challenges were distributed through the InnoCentive and TopCoder (now Apprio) crowdsourcing platforms. These challenges gave EPA exposure and access to some of the best computer programmers internationally. InnoCentive attracted 153 entries of whom two were selected as winners. The size of the data set and the subject domain of the problem combined to present a very ambitious challenge for a machine learning solution. The challenge successfully produced predictive solutions, as indicated by the statistical significance of the solutions developed across the range of techniques utilized. That these solutions also out-performed the algorithms supplied by the EPA reinforced confidence in the applicability of data science techniques to this problem. The TopCoder phase brought 436 entries from over 32 countries; five were selected as winners. More information about these challenges is available.

Since evaluating the potential risks of chemicals requires an analysis of both hazard and exposure (including dose), EPA's CSS research program also examines human and ecological exposures to thousands of chemicals evaluated through ToxCast. The EPA refers to this research effort as ExpoCast. These exposure estimates complement the high-throughput toxicity data from ToxCast to help better inform potential risks to human health and the environment. Through ExpoCast, information about the use of the chemical in different product types and applications were integrated with other important information such as production volume in order to develop high-throughput predictions of exposure

potential. These exposure estimates were calibrated based on concentrations of approximately 100 chemicals found in the blood and urine of the U.S. public that were measured by the Centers for Disease Control in the National Health and Nutrition Examination Survey. As described in this peer-reviewed journal article, the calibrated computational model was then used to predict exposures for nearly 8,000 chemicals in ToxCast for which no exposure information had been previously available. Data from ExpoCast also were incorporated into the dashboard to allow for integration with bioactivity/hazard information in risk-based decisions.

High-throughput exposure models can be improved and their uncertainties reduced significantly by adding more refined indoor and consumer use information. In 2014, the EPA released the Chemical and Product Categories Database (CPCat). The database catalogs consumer use of over 40,000 chemicals and their presence in different consumer products, compiled from multiple online sources.

To enhance collaborative development and use of these new chemical evaluation tools and data, EPA actively partners with hundreds of different organizations ranging from industry, academia, trade associations, other federal agencies, and state government and non-governmental organizations to explore ways to use these new chemical data in a variety of ways, including prioritizing chemicals for further testing and evaluating safer alternatives. Some examples of active research partnerships include: L'OREAL Cosmetic Company, pharmaceutical companies such as Pfizer and Merck, Health Canada, European Chemicals Agency, DOW Chemical, and Harvard University. A complete list of EPA's computational toxicology research partners is available.

In order to ensure public access to high quality science related to its computational toxicology research, EPA scientists have authored or co-authored hundreds of papers published in peer-reviewed scientific journals. An example includes an article published in the high-profile *Nature Biotechnology* journal that demonstrated that ToxCast data were useful in identifying the biological mechanisms with which chemicals interact and cause toxicity, confirming that ToxCast has the ability to prioritize chemicals for additional testing. EPA published a blog that describes the paper in more detail. In addition, *Environmental Science and Technology* recently published a paper about ExpoCast and the high-throughput exposure predictions described above. A listing of published scientific papers about EPA's CompTox research is available online. Nearly a dozen papers published by non-EPA scientists also have begun to probe the relevance, applicability, and utility of the ToxCast and related CompTox data, including one, for example, on predicting cancer risk using alternative approaches.

EPA continues to take advantage of developments in biomedical research to advance the frontiers of its CSS research program. Building on the 'Human-on-a-Chip' collaboration among Defense Advanced Research Projects Agency (DARPA), NIH, and FDA, in 2014 EPA released a solicitation under its Science to Achieve Results (STAR) grants program to develop three-dimensional organotypic cell culture models (OCMs) that will help accelerate translational research in predictive toxicology. Four Center grants were awarded under this solicitation to develop OCMs for high-priority biological systems such as the brain, liver, kidney, testis, breast tissue, heart and neurovascular, and evaluate them as testing platforms for research into the interactions of chemicals with key biological processes. This research will provide new biological insight as to how tissues and organs function during chemical exposures. The data will then be used to develop advanced computational models of how organs and tissues respond to chemicals, and also to ultimately validate predictive models of human disease or response.

Applications to EPA's Endocrine Disruptor Screening Program

One of the first applications of EPA's CompTox data is to inform policy decisions about the safety of chemicals in EPA's EDSP program. Beginning in 2012, EDSP began a multi-year transition to validate and more efficiently use CompTox data and models to more quickly and cost-effectively assess potential

chemical toxicity. The initiative, referred to as EDSP21 – or EDSP in the 21st century – aims to use ToxCast data and computational models to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen, or thyroid bioactivity. In 2015, EPA announced its plans to adopt in vitro high-throughput assays and computational models for detecting and measuring estrogen receptor (ER) agonist and antagonist bioactivity as an alternative for three current Tier 1 assays.

EPA is accordingly planning to accept existing results for chemicals that have been evaluated using the ToxCast "ER Model" for bioactivity. This approach for application of CompTox to a regulatory and policy context was described in a peer-reviewed journal article. The accompanying database contains the ER agonist bioactivity and ER antagonist bioactivity for over 1,800 chemicals and identifies those chemicals that are pesticide active ingredients, pesticide inert ingredients, and on EDSP Lists 1 or 2. This is a "living" database that will continue to incorporate bioactivity results for chemicals as they become available. It is important, however, not to equate a determination of a chemical's bioactivity from the "ER Model" with a determination that a chemical causes endocrine disruption. The World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) defines endocrine disruption as being caused by "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny, or (sub)populations." Bioactivity is an indicator that a chemical has the potential to alter endocrine function, but (1) whether the chemical actually alters endocrine function and (2) whether that altered function produces an adverse outcome in an intact animal cannot be determined without further testing (i.e., Tier 2 testing).

The EDSP has been developed over the past 19 years and has demonstrated that the current screening process may take upwards of five years before a Tier 1 decision is available or Tier 2 test orders are issued. In light of recent advances in high-throughput assays and computational models, in addition to predicted advances likely to come in the next two years, EPA is moving to consider new, rapid screening methods. The availability of additional alternative high-throughput assays and computational models in the near term will allow EPA to screen more chemicals in less time, involve fewer animals, and cost less for everyone. Furthermore, reconsideration of the EDSP List 2 chemicals may be appropriate since "ER Model" data are available for many List 2 and other chemicals. Ongoing use of high-throughput screening assays and computational models will address thousands of chemicals in the future.

These advancements in the EDSP screening program will not affect the overall framework—i.e., the Tier 1 screening battery and Tier 2 testing approach focused on estrogen, androgen, and thyroid pathways in humans and wildlife remains unaffected. Instead, as discussed above, EPA is planning to adopt sensitive, specific, quantitative, and efficient screening methods that will rapidly screen many chemicals and substantially decrease costs and animal use and may be used as an alternative to some EDSP Tier 1 screening assays. Accordingly, EPA intends a future recipient of an EDSP test order to be able to satisfy the screening requirement for ER, ERTA, and uterotrophic in one of three ways: (1) cite existing ToxCast "ER Model" for bioactivity data as "other scientifically relevant information" (where available); (2) generate new data relying on the high-throughput assays and the ToxCast "ER Model" for bioactivity; or (3) generate their own data using the current Tier 1 ER binding, ERTA, and uterotrophic assays.

With the support of the CSS research program, EPA is expanding the use of CompTox research and data for high-throughput and computational alternatives to the EDSP Tier 1 screening tests across the estrogen, androgen, and thyroid pathways (http://www.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor). EPA researchers are developing assays, models, and tools extrapolating ToxCast data collected using human-related assays to predict effects in a diverse array of species in order to help support EDSP screening decisions about the safety of chemicals and pesticides. Better linking of ToxCast to EPA ecological research provides an opportunity to evaluate the CompTox data as alternatives for current screening and testing of effects in endocrine pathways of rodents and fish in full biological systems.

Building Scientific Confidence: Progress of NAS Report Toxicity Testing in the 21st Century Activities

The 2007 NAS report *Toxicity Testing in the 21st Century* projected a 15-20 year timeframe for the vision of a transformative paradigm in toxicity testing to begin to be realized. FY 2016 provides a pivotal opportunity to evolve the EPA's CSS research program to further realize this vision. This could be achieved by expanding the breadth of the CSS CompTox efforts to include: a) more assays that can represent the biology and health effects of interest, b) stronger emphasis on estimating relevant exposures to individual and multiple chemicals, c) better integration of human and ecological risk evaluations, and d) most importantly, enhancing the predictive capacity of the computational models/data. These enhancements would be highly applicable and relevant both for evaluating the impact of existing chemicals and for selection of safer alternatives. The application of the CompTox research to inform selection of safer alternatives was evaluated and incorporated by the NAS in the framework they developed and described in their 2014 report, *A Framework to Guide Selection of Chemical Alternatives*.

The fast paced advancements in biotechnology, computational chemistry, and related fields have enabled EPA and the broader scientific community to make significant progress in revolutionizing toxicity testing. Thus far, EPA has used its computational tools primarily to inform the agency's chemical screening and prioritization needs. To build scientific confidence in the progress of EPA's CompTox research, its readiness for broader application to decisions, and plans to further develop this research area, EPA requested that the NAS conduct a follow-up study to its *Toxicity Testing in the 21st* Century, and provide recommendations on next steps in the rapid evolution and applications of these computational data, models, and tools. More information about this committee, *Integrating 21st Century Science into Risk-Based Evaluations*, is available. The new study is expected to build on a related 2009 NAS report, *Science and Decisions: Advancing Risk Assessment*, which provides recommendations on 'problem formulation' and more simplified 'fit-for-purpose' risk assessments. It also will integrate recommendations from the NAS 2012 report, *Exposure Science in the 21st Century*, which articulates the role of a modernized exposure science to enable and ensure chemical safety.

Future Plans

EPA plans to continue to pool its investment of resources and scientific expertise with the Tox21 federal partners. The partnership has worked extremely effectively to enhance the ability to predict the safety of chemicals. In addition, these collaborations have resulted in significant improvement in data access, reliability, and usability of the data for the community of stakeholders inside and outside the agency, such as:

- Public release of Tox21 and ToxCast data on PubChem and EPA website (raw and processed data)
- Upgraded ToxCast data analysis pipeline to increase access to and transparency of information about the data quality of assays and models
- Targeted workshops and webinars to educate stakeholders on high-throughput screening data analysis and interpretation

The path forward for the EPA's CSS research, including ToxCast/Tox21 efforts, were recently described in the FY 2016-2019 Strategic Research Action Plan (StRAP) for the Chemical Safety for Sustainability Research Program where the CompTox research is housed. Here, EPA articulated the following anticipated accomplishments:

1. **Accelerate the pace of data-driven chemical safety evaluations:** Make the data and tools more user-friendly and accessible to agency decision-makers and external stakeholders.
2. **Enable the agency to use 21st Century Science to make sustainable and public-health protective decisions:** Work with agency programs and regional partners to develop tailored, relevant, and fit-for-purpose solutions using CompTox data, tools, and models.
3. **Shift the paradigm of toxicity characterization from apical endpoints to "tipping points":** Develop tools to interpret earlier signals of biological harm or damage in order to increase the agency's capacity to predict the impact of individual or multiple chemicals.
4. **Apply CSS tools to support sustainable innovation and evaluation of chemicals and emerging materials:** Application of CompTox models, tools, and data to enable innovation and support safe and sustainable development and use of manufactured chemicals and materials across the product lifecycle.

The agency has built additional experimental and CompTox capacity around ToxCast to enhance the application of its data to the agency's evaluation strategies and to help inform decision-making. Assuming current levels of funding, this focus will be shifted in FY 2016-FY 2019 in a number of ways, to take advantage of the continuing revolution in biomedical research, including:

- Develop a low cost high-throughput global transcriptomic platform to screen across battery of cell types, concentration responses, and times. This will provide the ability to quickly screen a large number of chemicals across a broad array of biological responses (that predict hazards or health effects);
- Build the capability to retrofit current assays to include metabolism. This will allow us to account for how biological systems realistically react to environmental hazards;
- Develop and incorporate novel assays for priority health effect targets and include more complex "organotypic" cultures (sometimes referred to as 'organ-on-a-chip');
- Apply induced pluripotent stem cells (iPSCs) to model inter-individual variability in responses to environmental hazards. This will inform how well the results of toxicity testing represent effects on populations;
- Advance the applications of computational chemistry to further incorporate chemical structure and bioactivity into predictive models; and
- Continue advancing high-throughput exposure modeling.

Through continued engagement with agency and trans-federal partners as well as external stakeholders, including industry, academia, the states, and environmental/public health advocacy groups, the CSS program will explore and probe data-poor contexts that would benefit from tailored application of CompTox data. The report from the newly formed NAS committee, *Integrating 21st Century Science into Risk Based Evaluations* (expected in late 2016) will provide additional guidance on how to incorporate the emerging data for additional 'fit-for-purpose' application to agency decisions.

Potential Opportunities and Synergies

The discussion thus far has been centered on progressive efforts to meet the ambitious goals set out by CSS. The agency fully recognizes the opportunity to evolve the CompTox program in CSS and broaden its application to agency activities and decision contexts, potentially across its diverse regulatory frameworks. These novel applications can add significant efficiency and effectiveness to agency operations, enable it to participate in the Big Data revolution, realize the vision articulated in the National Bioeconomy Blueprint, and enhance the agency's visibility as a High Performing organization. Potential

opportunities exist which may allow EPA to accelerate the pace of the revolution in toxicity testing. It also will significantly advance the translational aspects of its CompTox research. These include:

- Explore how the ToxCast/Tox21 data can be used to develop high-throughput risk assessments, in particular for data poor chemicals;
- In concert with growing international efforts, integrate ToxCast data with chemical structure to enhance 'read-across' of toxicological hazards to other structures;
- Extend the derived hazard and exposure information to begin to evaluate cumulative risk of chemical exposures;
- Expand and extrapolate to novel assays that have relevance to ecological impacts;
- Customize and uniquely adapt the emerging organotypic cell models for specific application to EPA and incorporate into testing and evaluation systems;
- Functionally integrate computational activities with experimental capacity to enhance synergies, performance, and reliability on the emerging data.

These activities would be a direct extension of and build on existing capacity that is being enriched through continual integration of expertise and resources and cross-agency collaborations. They also are 'implementation-ready' so that if opportunities were presented and additional resources were made available, they could be deployed and some of the outputs from them could be realized beginning in FY 2017. Achieving these ambitious, but reasonable outputs is contingent and dependent on sufficient appropriated resources.