



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
**WASHINGTON D.C. 20460**

OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

DATE

EPA-SAB-13-XXX

The Honorable Lisa P. Jackson  
Administrator  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, N.W.  
Washington, D.C. 20460

Subject: SAB advice on advancing the application of Computational Toxicology research for human health risk assessment

Dear Administrator Jackson:

The Science Advisory Board (SAB), as well as the National Academy of Sciences, has encouraged the EPA to improve its risk assessment practices and to modify its single-chemical approach. Tens of thousands of chemicals are currently in commerce and hundreds more introduced every year, yet only a small fraction have been adequately assessed for potential hazard. To meet this challenge, the agency established the Computational Toxicology (CompTox) Research Program to explore ways to exploit modern advances in molecular biology, chemistry, exposure science and computer science to more effectively and efficiently assess chemical hazards and ultimately their risks. The SAB previously has underscored the importance of this research program and has been interested in the successful application of CompTox data to advance the EPA's hazard assessment and, in combination with exposure data, risk assessment.

In addition to permitting more rapid evaluation of individual chemicals, the CompTox research program also has the potential to provide the agency with a means of shifting its traditional focus on single stressors, endpoints, sources, pathways, and environmental media to evaluate, more broadly, multiple factors simultaneously. To assist the EPA in this process, the SAB asked its Exposure and Human Health Committee to evaluate how the products from the CompTox research program are being used by EPA, 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 in decision-making for risk assessment can be identified and addressed. The SAB committee, along with two members of the EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel, received briefings from EPA representatives regarding the use of CompTox research program outputs as one component into EPA risk assessments. In the enclosed report, the SAB provides its analysis and advice regarding the issues that the Agency should consider as they move forward with implementation. This letter highlights the SAB's major recommendations.

The SAB commends the EPA for undertaking the immense effort of establishing the CompTox research program. The program is still in the development stage and the agency has not yet begun to incorporate the information derived from it into various applications (e.g., prioritization, screening, or

1 risk assessment). However, the program already has contributed to the EPA's efforts to conduct a  
2 rapid response evaluation of chemicals. For example, EPA's ability to employ high-throughput  
3 screening (HTS) assays to test for endocrine activity in the eight candidate oil dispersants for use  
4 during the Gulf of Mexico Deepwater Horizon accident was possible, in part, due to the existence of  
5 the CompTox research program. While the agency was able to obtaining such test data in a short  
6 timeframe, the crisis highlights the need to develop a structured approach for utilizing the CompTox  
7 information in emergency situations. Specifically, in the case of the Deepwater Horizon accident, a  
8 very limited subset of assays was used to evaluate the dispersants. Were the data derived from this  
9 limited set of assays the most appropriate? Were they sufficient? The need to obtain data quickly to  
10 inform decisions in a crisis emphasizes the importance of developing a structured approach  
11 beforehand in the form of data use guides (DUGs). These DUGs should be developed after a  
12 thorough characterization of programmatic needs –the intended goals of a prioritization effort,  
13 screening or a risk assessment – together with the identification of examples of where CompTox  
14 information appears to add value.

15 The challenges that the EPA faces regarding the various applications of CompTox data are substantial  
16 and are well known to the agency. These include, but are not limited to, detailed characterization of  
17 each individual assay, determining the accuracy of the assays against traditional *in vivo* studies,  
18 determining how the data generated predict effects on apical endpoints employed in validated  
19 guideline studies, and the ways in which these patterns of data predict the risk of human disease. The  
20 latter issue is the most difficult; as the agency elucidates the Adverse Outcome Pathways (AOPs) that  
21 would link these patterns to human disease, there are new methodologies using new cell and tissue  
22 types that may prove useful to link early gestational exposures or environmental insults to many  
23 common disorders. EPA would be well-served to partner with professional societies and research  
24 institutes whose mission is to understand the diseases under investigation to gain further insight.

25 Exposure science also will be critical to prioritize chemicals for screening and further assessment.  
26 While the CompTox research program is currently focused on understanding AOPs, a similar effort  
27 for incorporating metabolism and other toxicokinetic factors, and understanding exposure through the  
28 ExpoCast effort is needed before these approaches can be fully applied in decision-making. Methods  
29 for incorporating biomonitoring data, exposure pathways, chemical source information, and  
30 information on human activity patterns also need to be developed and incorporated into risk  
31 assessments. A clear explanation of the limitations of the models, the reliability of the assay systems,  
32 the certainty associated with an AOP and knowledge of the metabolism of the chemical being  
33 assessed are only some of the important considerations that should be addressed when screening  
34 untested chemicals or developing the hazard or exposure component of a risk assessment.

35 Demonstrating the predictive value of CompTox data and its utility in the EPA's decisions is needed  
36 to overcome barriers to its acceptance within and outside the agency. This will require a combination  
37 of research to develop reliable methods and experience in using them to predict hazard and risk  
38 relative to more traditional methods. Through incremental change to the current approaches for  
39 assessing risk, first in supplementing and later by replacing existing methodologies, the EPA likely  
40 will be able to demonstrate the value of these new technologies, which will lead to greater confidence  
41 in the use of CompTox and ExpoCast as predictive tools to understand hazard and risk.

42 Outreach, training and communication also are vital to effective implementation of CompTox outputs  
43 and advancing EPA risk assessment. Efforts to reach out to EPA program offices that could benefit  
44 from CompTox data and engaging stakeholders to communicate the value and utility of the research  
45 program are laudable and should continue. We commend EPA for establishing the Computational

1 Toxicology Communities of Practice which is composed of more than 300 people from over 50  
2 public and private sector organizations that are interested in the application of computational  
3 toxicology and exposure science to EPA's risk assessments. We also support the Agency's goal of  
4 transparency, publishing all the data online so that the public can view and interpret these data. In  
5 fact, these data will likely be the source of numerous PhD dissertations in the near future. However,  
6 the website is somewhat difficult to navigate and it would be useful for the Agency to redouble their  
7 efforts to ensure that the public can access the data with relative ease.

8 In summary,

91- The SAB applauds the work of the CompTox research program, and recommends the continued  
10 development of CompTox outputs to lead to a better understanding and expansion of the potential  
11 utility of this technology.

122- EPA should explore partnerships with clinical and research societies whose members represent the  
13 experts in mechanisms of disease to help the Agency develop AOPs.

143- EPA should develop data use guidelines for information generated by CompTox, including ExpoCast,  
15 for the various purposes to which it is intended.

164- EPA should increase its efforts to understand chemical exposure, including determining how and  
17 where the chemicals are used and activity patterns of people that will result in exposure and not just  
18 the chemicals' movement through the environment based on fundamental chemical properties.

195- We encourage the Agency to continue to engage stakeholders and provide easy access to data on the  
20 CompTox website.

21 As the EPA gains more experience and expertise in the use of CompTox outputs in risk assessment,  
22 along with the development of ExpoCast, we look forward to future opportunities for providing  
23 advice to EPA on this important effort.

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27 Sincerely,

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33 Dr. David T. Allen, Chair  
34 EPA Science Advisory Board

Dr. R. Thomas Zoeller, Chair  
SAB Exposure and Human Health Committee

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36

37 Enclosure

NOTICE

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## 1. INTRODUCTION

In 2007, the NRC Committee on Toxicity Testing and Environmental Assessment published a study, “Toxicity Testing in the 21<sup>st</sup> Century: A Vision and a Strategy.” In this report, the NRC Committee recommended developing a program that would incorporate modern tools to provide information about chemical toxicity for use in risk assessments. The overall goal of such a program would be to enhance the efficiency and effectiveness of chemical safety determinations. Guided by the NRC report, the EPA in that same year launched ToxCast<sup>TM</sup>, an initiative to employ rapid automated chemical toxicity tests as part of the computational toxicology (CompTox) research program. The aim of the program was to take advantage of existing technologies to develop ways to predict the toxicity of the thousands of chemicals for which toxicity testing is lacking or absent.

In a recent report on the FY2012 EPA research budget, the SAB noted its concern that , “*there is no proactive budget initiative to develop ways of employing the results of the [Chemical Safety for Sustainability] CSS program, including high throughput data, into hazard or risk assessment*” (EPA SAB 2007). The CSS program, one of six transdisciplinary research programs within the EPA’s Office of Research and Development, is responsible for coordinating the activities of the CompTox research program. In addition to allowing more rapid evaluation of a large number of individual chemicals, CompTox has the potential to provide the Agency with a means of modifying its traditional focus on single stressors, endpoints, sources, pathways, and environmental media to a broader focus on evaluation of these factors in combination to evaluate the potential effects of the co-occurrence of multiple chemicals. For these reasons, the SAB has requested that its Exposure and Human Health Committee (EHHC) develop advice to assist in advancing the application of CompTox research for human health risk assessment to meet EPA’s programmatic needs. In developing its advice to EPA, the EHHC engaged in discussions with ORD and EPA program offices, which currently use or plan to use the CompTox research outputs, in order to address the following questions:

- 1) Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA’s programmatic needs?

1 2) What issues are there in using CompTox in decision making for risk assessment and risk  
2 characterization as opposed to chemical screening, prioritization and green chemistry?

3 3) What are the barriers and limitations that prevent the EPA from using CompTox outputs and  
4 how might they be overcome? and

5 4) How should the use of the CompTox program be effectively communicated to stakeholders?  
6 How can the communication be enhanced?

7 The members of the EHHC were joined for this review by two members of the EPA Federal  
8 Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) who had  
9 reviewed elements of the ToxCast program in 2011. The committee was briefed by representatives  
10 from ORD and program offices regarding the overall scope, structure, and organization of the  
11 program, and the use of ToxCast information within the programs represented. The EHHC met with  
12 representatives of the EPA in a face-to-face meeting on May 30-31, 2012, and discussed the study  
13 questions. A draft committee report was discussed at a teleconference on September 24, 2012, and the  
14 chartered SAB considered the draft report on (DATE). The following report outlines the SAB's  
15 impressions of the work undertaken by the CompTox research program and recommendations on how  
16 to enhance the utility of the program outputs.

17

1                   **2. SAB STUDY FINDINGS AND RECOMMENDATIONS**

2   **2.1.   Applications of CompTox to EPA Programs**

3   *Study Question 1. Are the outputs of CompTox currently being used by EPA? How well do the*  
4   *outputs align with EPA’s programmatic needs?*

5   The ToxCast program currently consists of nearly 700 individual assays provided by nine companies.  
6   A foundational element of ToxCast is a chemical library in which a large number of chemicals are  
7   simultaneously tested to create toxicity profiles in these assays. In Phase I, chemicals for which there  
8   is a substantial amount of toxicity data have been assayed, including 309 pesticide active ingredients  
9   and commercial chemicals. These chemicals will be assayed to provide a “proof of concept”; i.e., the  
10   results will be used to develop toxicity profiles and evaluate the ability of the assays to predict  
11   toxicity. In Phase II, about 2,000 chemicals from a broad range of sources including industrial and  
12   consumer products, food additives, “green” products, nanomaterials and drugs that never made it to  
13   the marketplace are being screened. This information will be used to identify pathways of toxicity –  
14   patterns of responses observed in the CompTox assays that are plausibly and causally related to  
15   observations of apical effects in the *in vivo* assays.

16   At present, the primary use of CompTox outputs has been to determine the reliability of the data for  
17   use in various types of decision-making by EPA programs. There are only a few examples where  
18   information derived from the CompTox research program has been used to inform Agency decisions  
19   (see below), and these were all special cases. Despite the limited use of Comptox outputs to date, the  
20   SAB finds that the program is valuable and has made impressive progress in the five years since the  
21   inception of ToxCast.

22   The reliability of ToxCast data is currently being explored in two ways. First, data from ToxCast is  
23   being compared to data from ToxRef – a database of toxicity studies conducted with guideline, *in*  
24   *vivo* test systems. By comparing the effects of individual chemicals in both ToxCast and ToxRef, the  
25   EPA hopes to identify parallels that will provide confidence that decisions based on ToxCast data will  
26   be predictive of results for endpoints assessed using *in vivo* guideline studies. A second approach is to  
27   develop pathways of toxicity in humans that would lead to the clinical manifestation of disease.

28   These adverse outcome pathways” (AOPs) represent a very important link from *in vitro* high-  
29   throughput assays to human disease, and this effort is just beginning. AOPs should be explored not

**This draft has not been reviewed or approved by the chartered SAB and does not represent EPA policy.**

1 only based upon how a chemical can perturb biological systems but also from the perspective of how  
2 aging and disease processes have underlying AOPs which may be sensitive to chemical effect. By  
3 evaluating upstream events, CompTox has the ability to evaluate how chemical and disease AOPs  
4 may intersect leading to a more complete understanding of chemical action (NAS 2009).

5 The CompTox program is also exploring the possibility that ToxCast data can be combined with large  
6 databases of experimental data at the level of the genome, epigenome, proteome and metabolome to  
7 provide higher resolution data within the context of AOPs. In principle, weight-of-evidence  
8 approaches would be developed to guide the integration of this information into current data and  
9 practices for hazard identification and perhaps risk assessment. If successful, this effort is expected to  
10 shape the future of toxicity testing at EPA in accordance with the recommendations of previous NAS  
11 reports, paying large dividends for the Agency, researchers and the American public that are well  
12 worth the investments currently being made.

13 The outputs of the ToxCast program are being developed to align with the needs of EPA programs  
14 both in the long- and short-term. The EPA faces significant challenges to understanding how  
15 information derived from ToxCast can be employed to inform the various decisions required of the  
16 agency. These efforts will require constant communication between the different programs within the  
17 agency in order to ensure that the outputs meet the needs of the specific programs. At the SAB  
18 committee meeting in May 2012, EPA representatives devoted considerable time to describing how  
19 this coordination is occurring. EPA's expectation is that the current research questions and research  
20 approach, as outlined above, will produce a program that will have broad applicability within the  
21 agency.

22 The high-throughput screening (HTS) assays that form the basis of the CompTox program were used  
23 in a trial approach to supplement the EPA's response to the Deepwater Horizon accident by  
24 calculating toxicity data (endocrine activity screens) on the eight oil dispersants employed by BP in  
25 the Gulf of Mexico. The fact that there was a formal CompTox program in place within EPA at the  
26 time of the Deepwater Horizon accident made it easier to employ these assays. This illustrates an  
27 important issue; namely, that there are a number of ancillary benefits of this program. One benefit is  
28 to have an infrastructure that would allow rapid data generation so that the agency can make better-  
29 informed decisions in a disaster situation. Pairing this data with ExpoCast information to evaluate  
30 potential exposure in response to emergencies can provide a more holistic assessment of the

1 associated risk. Another benefit is that development of the CompTox program has facilitated a great  
2 deal of interaction between various EPA offices. This interaction will foster greater communication  
3 about data needs and data interpretation. This interaction also helps to ensure that the intramural  
4 research program aligns with the routine, and sometimes unanticipated, needs of the agency as well as  
5 to help risk assessors identify early the data gaps that may be filled by the kind of information  
6 produced by CompTox. Additionally, the CompTox program provides an alternative means of  
7 evaluating multiple factors that might influence the risk posed by chemicals. The CompTox program  
8 provides the Agency with a means of shifting its traditional focus on single stressors, endpoints,  
9 sources, pathways, and environmental media to a broader focus on the evaluation of these factors in  
10 combination or the potential co-occurrence among these factors.

11 However, the Deepwater Horizon accident also illustrates that in emergency situations CompTox data  
12 may be generated and used very rapidly without the opportunity to fully screen a chemical's toxic  
13 properties. Strategic planning is needed in advance of such events so the endpoints and assays  
14 available are predictive of adverse effects and relevant to the scenario at hand, and to ensure some  
15 consistency across programs and applications. The limitations of such screening exercises must be  
16 described so as not to imply that the data predict risk (by themselves they do not constitute a risk  
17 assessment) or that the data present a complete toxicological description of effects the chemical can  
18 cause. With such caveats in mind and transparently stated, CompTox can be seen as an aid to risk  
19 management. The Data Use Guide (DUG) proposed later in this document will assist in the design  
20 and interpretation of CompTox screens for different scenarios.

## 21 **2.2. Evaluating CompTox Outputs for Decisionmaking**

22 *Study Question 2. What issues are there in using CompTox in decision making for risk assessment*  
23 *and risk characterization as opposed to chemical screening, prioritization and green chemistry?*

### 24 **2.2.1. Specificity and Sensitivity**

25 A central question at this time is whether the *in vitro* high-throughput assays will produce data that  
26 will be suitable for decision-making such that, eventually, these data could replace *in vivo* testing for  
27 regulatory decisions. The answer to this question will undoubtedly depend on the level of decisions to  
28 be made. Thus, an important – if not essential – goal will be to sufficiently demonstrate and obtain  
29 widespread support for the data generated from ToxCast. This will also need to be consistent with

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1 statutory requirements for the evidence the EPA uses to take regulatory action. Thus, a principal goal  
2 of the research domain of the program is to characterize the data generated from ToxCast assays in  
3 terms of the specificity, sensitivity and reliability of the individual assays, as well as their ability to  
4 predict toxicity either alone or in combination with other findings. The agency appears to be making  
5 good progress toward these goals.

6 The Agency has adopted two general strategies for testing the value of ToxCast data for Agency use.  
7 The first strategy is to identify the patterns of responses for each chemical in the battery of ToxCast  
8 assays and correlate these with the biological activities observed in guideline, *in vivo* studies  
9 associated with the same chemical. This strategy is made possible by considerable amount of *in vivo*  
10 data associated with the Phase I chemicals. Of course, the assays included in ToxCast were pre-  
11 existing HTS assays developed for the pharmaceutical industry; they were not designed for ToxCast  
12 to correlate with endpoints in guideline *in vivo* studies. Therefore, it would be useful if the agency  
13 considered developing the theoretical framework that would support the effectiveness of this strategy.  
14 Essentially, this amounts to developing “AOPs” for the *in vivo* guideline studies.

15 The second strategy is to develop AOPs for human disease that may be reflected in the ToxCast data.  
16 This is an important and valuable strategy and highlights an important weakness in these two  
17 strategies that can be addressed in the commission of building these AOPs. Specifically, the ToxCast  
18 assays were not designed by the agency to inform *in vivo* endpoints, and the guideline *in vivo*  
19 endpoints were not designed overtly to inform human disease. Thus, to build a credible system, the  
20 EPA needs to focus on making the case that there is a relationship between what is observed in the  
21 ToxCast assays, what is observed in the guideline studies, and what is observed (or expected) in the  
22 human population.

23 The data derived from CompTox assays should lend themselves readily to hazard identification and  
24 especially green chemistry. These data may provide insight for the development of chemical products  
25 that have a greater likelihood of being free from toxic properties. Moreover, CompTox data may be  
26 combined with information from structure-activity relationship (SAR) evaluation and any *in vivo* data  
27 that might be available, to facilitate hazard identification and help guide a weight-of-evidence  
28 analysis of hazard. However, there are several cautions that need to be considered when applying the  
29 data for hazard evaluation. First, the strengths and limitations of each assay must be recognized,  
30 including the potential for false negative and false positive results. Given that pathways of toxicity

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1 are poorly understood, current *in vitro* assays cannot be seen as comprehensive in their scope. For  
2 example, according to Judson et al. (2010), CompTox models developed to screen for chronic,  
3 developmental and reproductive toxicity endpoints display high specificity (few false positives) but  
4 only moderate sensitivity (multiple false negatives). [Sensitivity relates to the assay's ability to  
5 identify positive results. Specificity relates to the ability of the assay to identify negative results.]  
6 Therefore, the rate of false negatives is expected to be high at this stage of the program. While some  
7 information is better than none, there is concern that too much confidence will be placed upon the  
8 lack of activity in the available assays. If there is a high degree of reliance on data from these assays,  
9 it may inappropriately give the appearance that a chemical with no activity is safer than other,  
10 alternative chemicals that in fact have more information available.

### 11 **2.2.2. Exposure Considerations**

12 EPA also should consider the potential for exposure to the chemical when determining the degree of  
13 testing required such that even if initial screens of a chemical find little reason for concern, *in vivo*  
14 confirmation may still be desirable if the chemical's exposure potential is high. Conversely, low  
15 exposures may diminish the need for extensive toxicity testing than might be needed for agents whose  
16 exposure is greater. These considerations underscore the need for good exposure/biomonitoring  
17 information which at this point appears to be a limitation of CompTox modeling. Second, there is  
18 uncertainty about the significance of a positive result in any particular assay within ToxCast. A major  
19 effort is apparently underway to link patterns of responses within the battery of ToxCast assays to  
20 AOPs. At present, the ability to link patterns of responses and AOPs is limited since many of the  
21 screening assays are still under development and going through validation exercises on an individual  
22 level. Additionally, there is also a need to better understand the relationships between AOPs and  
23 apical endpoints. The concept is that by evaluating the behavior of known toxicants in the ToxCast  
24 battery, patterns of toxicity linking this HTS behavior to adverse outcomes and thereby enhancing  
25 predictability will become apparent and will serve as validation of the predictive capability of the  
26 assay.

27 Ultimately, the usability of a given result will be dependent upon additional data that is available for  
28 the chemical in question and about the tests and pathways affected by that chemical. The advantage  
29 of CompTox is that thousands of tests can be conducted – these need to be inclusive of as many  
30 potential health effects as possible. The limitations of the information that can be obtained from the

1 breadth of assays should be made clear by the Agency. For example, the testing may be accurate for  
2 cancer, developmental and reproductive endpoints, endocrine and metabolic endpoints, liver and  
3 kidney effects, but not for, say, eye health or neurological health. Positive results on subsets of tests  
4 or tests along certain pathways would suggest further testing and/or *in vivo* studies. Of particular  
5 importance for public health is the accuracy of a negative result in an assay system – which in a  
6 screening step could result in a decision to not proceed with further testing. In other words, for  
7 chemical screening and prioritization, the testing should be sensitive (i.e., detect an effect when there  
8 is one) and specific (i.e., does not detect an effect when there is not one).

9 Regarding more advanced uses of CompTox outputs beyond hazard identification (e.g., use in dose-  
10 response assessment and risk assessment) the following additional concerns should be considered:  
11 (1) have the most sensitive endpoints been identified in the CompTox assays; (2) how well do these  
12 CompTox endpoints relate to apical endpoints such as carcinogenesis, endocrine disruption, organ  
13 toxicity, neurotoxicity and immunotoxicity; (3) how would the uncertainty factors used when starting  
14 with *in vivo* data (e.g., interspecies, intraspecies, acute to subchronic to chronic study duration,  
15 database quality and completeness) be applied and/or modified for *in vitro* screening data; (4) how  
16 would the *in vitro* dose-response relate to *in vivo* behaviour when considering route of entry,  
17 metabolic activation and detoxification systems that may not be present *in vitro*; (5) how would the *in*  
18 *vitro* dose-response relate to *in vivo* behaviour when considering other toxicokinetic factors  
19 governing the external dose associated with a particular concentration at the target cell or receptor,  
20 that may not be taken into account *in vitro*? These factors include metabolic activation and  
21 detoxification, as well as, absorption through relevant route(s) of entry, distribution, and excretion;  
22 and (6) related to #3 above, how well do the *in vitro* test methods capture intra-human variability in  
23 terms of susceptible sub-populations and life stages including genetic polymorphisms and disease  
24 states?

25 To move towards the development of risk assessments that more accurately reflect environmental  
26 conditions, CompTox also needs to develop strategies for studying environmental chemical mixtures  
27 - not just the effects of one chemical at a time. The importance of using CompTox to characterize the  
28 hazard, and ultimately the risk, of environmental chemical mixtures cannot be overstated. Moving in  
29 this direction requires establishing a scientifically defensible foundation—for example, by defining  
30 appropriate AOPs, developing testing methods that address a wide array of AOPs, and evaluating the

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1 accuracy, sensitivity and specificity of the tests. While assessment of mixtures may ultimately be a  
2 long range goal, the path to studying and estimating risk from mixtures should be outlined. Examples  
3 of critical questions include the following: (1) How will relevant mixtures be identified? (2) Can  
4 methods be developed to predict the hazard and/or risk of mixtures of chemicals from CompTox data  
5 on individual chemicals which affect the same AOP(s)? (3) How will risk be quantified for different  
6 types of endpoints based on effects on relevant AOPs? and (4) How much risk is allowable for a  
7 given AOP? As already noted, exposure is a key component of risk assessment and one that needs  
8 greater focus within the CompTox program. A general approach, based solely on chemical properties,  
9 that evaluates transport from large sources and partitioning based on fugacity concepts to predict the  
10 distribution of chemicals from their sources to a population will NOT provide a full exposure  
11 evaluation and will lead to misclassification of exposure. Such an approach is analogous to saying  
12 that nothing needs to be known about metabolism of chemicals when determining toxicity and that  
13 the only information needed is the overall chemical structure and what functional groups are present  
14 to compare with known compounds. Exposure may occur when people come into contact with  
15 chemical agents and often results from being close to the source where the agent is released into the  
16 environment. For example, an agent produced in relatively small quantities but used in personal  
17 products can result in a higher exposure than a high production volume chemical emitted from point  
18 sources located away from populations. The higher exposure potential of a low production chemical  
19 would not be predicted based on an exposure model that does not include information on its use and  
20 potential contact with people. Thus, if these two agents were equally hazardous, the low production  
21 compound would present greater risk, but it is unclear if the current assays used in the CompTox  
22 program would account for this situation. This issue is relevant to all of the EPA applications listed,  
23 i.e., chemical screening, prioritization, risk assessment and green chemistry.

### 24 **2.2.3. Data Use Guidelines**

25 A key issue affecting use of CompTox data is the need for a guide to explain the appropriate use of  
26 data in various applications. Guidance for data needs (and sufficiency or appropriateness of data)  
27 must come from a good characterization of programmatic needs – identification of both the intended  
28 goals of a risk assessment or a prioritization effort – and examples in which CompTox information  
29 appears to add real value. While the data are meant to be used within a weight-of-evidence context  
30 that requires integration across all of the available data (e.g., *in vivo* toxicology data, SAR, read-  
31 across approaches, other supporting *in vitro* data), it may be beneficial to establish general principles

1 for the use and interpretation of the output for any one endpoint or health effect in a Data Use  
2 Guidance (DUG) document. Key aspects to address in such a guidance document include:

- 3 1) name of the assay;
- 4 2) description of assay design;
- 5 3) name of company that developed the assay;
- 6 4) information on any proprietary constraints of the assay;
- 7 5) positive control and other agents used to characterize the assay;
- 8 6) dynamic range of the assay;
- 9 7) where the endpoint fits within one or more AOPs;
- 10 8) related CompTox endpoints (i.e., endpoints likely to be within the same AOP or that are  
11 indicative of similar biological activity but in an independent test system);
- 12 9) interpretative value of the endpoint if altered in isolation;
- 13 10) interpretative value if altered in conjunction with other “aggregated” endpoints;
- 14 11) rate of false positive and negative results if it is to be used for predictive purposes (e.g., to  
15 forecast *in vivo* endocrine activity);
- 16 12) shape of the dose-response curve (e.g., monotonic, non-monotonic, threshold, linear);
- 17 13) potential for the endpoint to be used as a biomarker in toxicity testing or in epidemiology  
18 studies;
- 19 14) whether the endpoint is also affected by disease processes that might potentially lead to a  
20 chemical/disease interaction;
- 21 15) limitations and uncertainties of the endpoint; and
- 22 16) cross reference with other assays that assess the same endpoint(s) and comparison of  
23 reliability of the assay in comparison.

24 It may also be helpful to develop a simple flow chart describing a continuum extending from the least  
25 amount of evidence for a meaningful effect (e.g., perturbation only at high dose) to the greatest  
26 amount of evidence for meaningful effect (e.g., upstream and downstream endpoints affected in a

1 defined AOP with effects occurring on upstream endpoints at low dose and anchored by similar  
2 effects from a known toxicant). The DUG also could provide guidance concerning the different uses  
3 of the data depending upon where on the continuum the evidence for a meaningful effect lies for a  
4 particular chemical. The “ToxPi” pie chart of endocrine-related effects for a chemical appears to be a  
5 useful way to illustrate the types of biological activities of a chemical, but not the meaning and  
6 importance of individual slices relative to other slices. The DUG could also include a section on  
7 aggregated endpoints that describes the implications of a “slice” of the pie for a particular biological  
8 effect and how one determines potency for a slice.

9 The concept of a DUG is not new. For example, the CDC/NHANES biomonitoring data release  
10 provides important information for each exposure including the normative range in the population,  
11 any relevant workplace or environmental standards (e.g., OSHA Biological Exposure Indices), and  
12 limitations of the biomarker itself (e.g., specificity, sensitivity). This information is meant to aid in  
13 the interpretation of the data by various stakeholders and avoid the over-interpretation of the data. As  
14 previously mentioned, the Deepwater Horizon accident revealed a critical programmatic need – the  
15 need for rapid toxicological information in response to emergencies or other sudden demands for  
16 information and recommendations. There is also a need for developing guidance, procedures, and  
17 resources for the use of Comptox outputs in such events.

#### 18 **2.2.4. Relating CompTox Outputs to *in vivo* Assay Results**

19 Finally, for CompTox data to be of sufficient quality for use in risk assessment, it must correspond to  
20 validated endpoints or well-defined AOPs. Importantly, the batteries of CompTox assays were not  
21 specifically designed to inform these endpoints, in contrast to the *in vivo* assays which in some cases  
22 were developed decades ago. Further, the validated *in vivo* guideline assays were not designed to  
23 predict the full range of endpoints that are currently considered to be of public health importance.  
24 Ideally, the results of CompTox assays also should be predictive of additional *in vivo* endpoints of  
25 more recent interest – for example, diseases in adulthood resulting from developmental exposures.  
26 New methodologies, utilizing new cell and tissue types for DNaseI Hypersensitive Site correlation  
27 analysis, have been reported in the scientific literature (e.g., see Maurano et al. 2012). This research  
28 has shown that many common disorders are linked with early gestational exposures or environmental  
29 insults. Incorporation of this methodology into ToxCast and CompTox will enhance the ability to  
30 identify AOPs relevant to a variety of health outcomes. Developing a CompTox research focus on

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1 aging and disease processes common in the U,S, population will allow the exploration of AOPs that  
2 are not concerned with how a chemical is perturbing “normal” and healthy systems but how  
3 chemicals may act in disease pathways to produce health risks in the population. Just as there is an  
4 omics explosion in describing chemical effects, there is also an explosion in our understanding  
5 disease mechanisms/biomarkers and this information should be integrated to give CompTox maximal  
6 relevance to human risk.

7 The data generated by Phase I of the CompTox program should build confidence about the  
8 relationship between patterns of responses in the battery of tests and the effects of the chemicals  
9 being assessed using *in vivo* guideline studies. This empirical analysis will be difficult in part because  
10 of: (1) the inherent uncertainties about how the *in vitro* dose response relates to *in vivo* when  
11 considering route of entry, metabolic activation and detoxification systems that may not be present *in*  
12 *vitro*; (2) the inherent uncertainties about how the *in vitro* dose response relates to *in vivo* when  
13 considering other toxicokinetic factors that govern the external dose associated with a particular  
14 concentration at the target cell or receptor; (3) the possibility that a chemical may have more than one  
15 mode of action; and (4) the possibility that while two “estrogenic” chemicals may overlap in the  
16 patterns of responses observed in the battery of tests, they will likely have large regions of non-  
17 overlap. In the absence of prior knowledge of these characteristics, it will be difficult to find the  
18 common pattern that predicts the responses observed in current guideline *in vivo* studies. Hopefully,  
19 the difficulties in achieving this goal are not insurmountable and over time, through experience with  
20 the rapidly increasing database of information that is being generated, the agency will achieve its  
21 objective of developing this knowledge. Just as important, and probably even more challenging, will  
22 be to understand the relationship between CompTox outputs and the etiology of human disease based  
23 on epidemiological data. The CompTox program should work with epidemiologists within the EPA  
24 and extramurally to design epidemiologic studies that incorporate new and improved biomarkers of  
25 exposure, subclinical effects and disease. The CompTox program is well on its way to addressing  
26 these difficult issues.

### 27 **2.3. Building Scientific Acceptance of CompTox**

28 *Study Question 3. What are the barriers and limitations that prevent EPA from using CompTox*  
29 *outputs and how might they be overcome?*

1 There are a number of challenges facing the CompTox program with respect to preparing outputs for  
2 use in agency decisions and by the broader scientific community. These challenges are specific to the  
3 potential types of applications for these data, including informing decisions when other information is  
4 not available, prioritizing chemicals for further toxicity analysis, and as the basis for risk assessment.  
5 In all cases, a common concern is whether the data generated from high-throughput *in vitro* assays  
6 can be applied reliably, i.e., that the data will have been shown to be sufficiently predictive of toxicity  
7 *in vivo* and ultimately in humans, relative to traditional approaches such that Agency decisions can be  
8 scientifically defensible within an acceptable level of uncertainty.

9 It is worth repeating several points that likely serve as barriers to the use of CompTox data: (1) If an  
10 *in vivo* endpoint is not well anchored in an AOP or read-across approach, then perturbation of that  
11 endpoint may be difficult to detect in CompTox assays and thus difficult to apply in screening or risk  
12 assessment; (2) there must be an understanding of the impact of the route of entry, metabolic  
13 activation and detoxification systems and other toxicokinetic factors that may not be present *in vitro*;  
14 (3) dose-response assessment must take into account *in vitro* to *in vivo* extrapolation including  
15 metabolism and other toxicokinetic factors, application of uncertainty factors and special  
16 consideration of vulnerable sub-groups; (4) there is a likelihood for false negative results at this stage  
17 of testing which requires caution when considering a chemical for increased usage based upon  
18 CompTox results; and (5) exposure information is often limited but is a key part of any screening and  
19 prioritization program, as well as necessary for risk assessment.

20 The CompTox program is in the development stage, as noted in response to Study Question 1, and so  
21 its use is still very limited. The program has not had sufficient time to demonstrate that it can deliver  
22 on its promise. Questions about the reliability of individual assays, the availability of assays  
23 predictive of the full range of relevant endpoints, the power of “pattern recognition” as a predictor of  
24 toxicity, the value of the current design of the system to generate the kind of information needed to be  
25 predictive, all are legitimate questions that require time and experience to answer. Considering the  
26 importance of these goals and the complexity of the issues involved, there will be unavoidable “blind  
27 alleys”. However, the number of these “blind alleys” may be minimized by being more proactive  
28 about building AOPs and pathways of toxicity. In this regard, there are currently no internationally  
29 accepted methods in the scientific literature for performing a weight-of-evidence analysis for such  
30 pathways . While this task is not the purview of the CompTox program *per se*, the ability of the EPA

1 to employ peer-reviewed science in the Tox21 program would be enhanced by developing an  
2 accepted method of analysis for determining the ability of CompTox assays to predict human disease.  
3 In the absence of such an accepted method, the agency will be limited in associating CompTox data  
4 to data generated from guideline assays and this would be a severe limitation.

5 One of the ways to improve acceptance of CompTox and overcome some of the barriers to its use is  
6 to demonstrate that it provides equivalent (or more accurate) answers relative to the currently  
7 accepted methods for characterizing hazard and estimating risk. Moreover, if it does so with fewer  
8 resources (e.g., cost and time), thereby allowing for the characterization of the large number of agents  
9 that the EPA must make decisions about, then it will quickly become the methodology of choice.

10 There also is a need to commit similar resources to develop ExpoCast in parallel to CompTox to more  
11 fully support the needs of EPA programs. This will require not only acceptance by scientists at EPA's  
12 National Exposure Research Laboratory (NERL) but also a recognition by others within the agency  
13 that exposure is a key component of risk assessment, risk characterization and risk management and  
14 that the volume of an emission is not equivalent to exposure and the dose humans receive.

15 According to the EPA's 2009 strategy document on evaluating chemical toxicity (U.S. EPA 2009),  
16 the agency appears to be following the recommendation of the NRC 2007 committee which said,  
17 "...*in vitro* tests would be developed not to predict the results of current [animal] apical toxicity tests  
18 but rather as [human] cell-based assays that are informative about mechanistic responses of human  
19 tissues to toxic chemicals. The NRC committee is aware of the implementation challenges that the  
20 new toxicity-testing paradigm would face." With this in mind, the EPA is currently conducting  
21 research to identify AOPs that can serve as predictors of toxicity; the need to relate these AOPs to  
22 currently understood toxicity endpoints is critical. Once appropriate AOPs are established, the EPA  
23 will be positioned to transition to the methodologies recommended by the NRC. However, as the  
24 agency pursues this path, there are several issues that will need to be addressed. They include:

- 25 (1) How well do the *in vitro* and *in silico* tests translate to human systems?  
26 (2) How predictive of human pathways are the identified AOPs (data on this is important to share and  
27 make public)? and  
28 (3) How do the testing methods account for differences between *in vitro/in vivo* animal testing and  
29 human toxicokinetics, particularly metabolism but also absorption, distribution, and excretion? (for  
30 instance, how are chemicals that are cleared through multiple pathways (renal, GI, etc) treated in the

1 analysis; how do these testing methods account for chemicals that are actively reabsorbed by renal  
2 organic anion transporters (OATs) or those that are strongly bound to plasma proteins, lipids, etc.  
3 And how would the testing methods determine the toxicity of chemicals which are initially  
4 metabolized in one organ and further metabolized to the ultimate toxic metabolite in another organ?.

5 (4) Given that there are multiple methods to estimate pharmacokinetic behavior (as described in  
6 Rotroff et al. 2010) and since the results may differ based on which methods are employed, how will  
7 decisions be made regarding which ones to use, their accuracy and certainty?

8 (5) Are the proposed tests useful for chemicals that are stored in humans (e.g., adipose tissue depot or  
9 other sites)?

10 (6) How are human exposure characterization and biomonitoring data used in the prioritization and  
11 testing of chemicals (although the tests are designed to identify chemical hazards, if exposure is low  
12 or non-existent then how should the chemical be prioritized)?

13 (7) Incorporating human exposure data should be a high priority since it is such an important  
14 component of risk assessment - a description should be provided of where these data will come from,  
15 how they will be used (upper bounds, central tendency, etc.). and

16 (8) How is the existing data from the scientific literature incorporated into these AOPs and how will  
17 the AOPs remain current?

18  
19 The scientific acceptance of these approaches in a weight of evidence for decision-making will  
20 depend on the accuracy, sensitivity, and specificity of the computational toxicity testing for predicting  
21 actual and potential human health effects. To assist in gaining acceptance, a transparent strategy  
22 should be developed for quantifying the endpoints upon which risk assessments will be based. The  
23 agency also should indicate what issues should be considered for EPA applications such as chemical  
24 screening, prioritization, risk assessment, and green chemistry. While relevance to humans is always  
25 important, these applications may be ranked in order from highest to lowest in terms of the scrutiny  
26 with regard to human relevance as follows: risk assessment, prioritization, screening chemicals and  
27 green chemistry.

28 Finally, the interactions between ORD and the various EPA programs (e.g., pesticides, water or  
29 toxics) that will use CompTox data are commendable and should continue in order to understand  
30 what would make such data most useful. Perhaps, in addition to providing opportunities for program  
31 office scientists to spend time in the ORD laboratories to become familiar with the CompTox

1 program, extensive remote learning and training modules could be developed to reduce the cost and  
2 logistic challenges. This may also serve to engage more key EPA scientists outside of the Research  
3 Triangle Park, North Carolina area.

#### 4 **2.4. Communicating CompTox Approaches and Outputs**

5 *Study Question 4. How should the use of the CompTox program be effectively communicated to*  
6 *stakeholders? How can the communication be enhanced?*

7 The EPA appears to be doing a very thorough job of communicating to stakeholders about the  
8 CompTox program. The agency has created multiple web-based learning tools and models—such as  
9 webinars and dashboards— for the public to learn more about the program and to access the data it is  
10 generating. The EPA has actively sought input from stakeholders as it developed the CompTox  
11 program and also has disseminated information to the scientific community through publications and  
12 presentations at scientific conferences. The EPA established the Computational Toxicology  
13 Communities of Practice, which is composed of more than 300 people from over 50 public and  
14 private sector organizations that are interested in the application of computational toxicology and  
15 exposure science to risk assessments. The SAB commends this effort; it is a powerful tool for keeping  
16 up with technical issues that the EPA is confronting and addressing as a part of the CompTox  
17 program.

18 EPA's communication effort has focused on two areas. First is conveying the importance of the  
19 approach and the value of the strategy to stakeholders including the public. Many in the regulated  
20 community have worked at developing computational toxicology models of various kinds, often quite  
21 specific to their products; they are, obviously, convinced of the strength of the approach or they  
22 would not be pursuing it. If stakeholders are included in the process of development, validation, and  
23 application of these methods in a collaborative fashion, they may be more likely to accept the results  
24 and provide constructive feedback. Second is providing the data to all stakeholders, including the  
25 general public. The CompTox website (<http://www.epa.gov/ncct/>) is relatively easy to navigate, but it  
26 would be useful to provide some information about strategies for extracting relevant data.

27 As EPA moves forward with the development of the CompTox program, communication can be  
28 enhanced by being transparent about the limitations and uncertainties in the use of CompTox assays  
29 to predict any particular endpoint in isolation and in combination with data from other CompTox

1 assays, and providing a broader understanding about what is known about a chemical's biological  
2 activity based upon CompTox data in conjunction with SAR, *in vivo* testing, etc. It may also be useful  
3 to provide stakeholders with some summary statistics about the results – perhaps along the lines of  
4 AOPs, with a transparent, easily accessible (e.g., on a website) location for the details of the testing  
5 and the raw data. However, it should be kept in mind that uninitiated evaluators of large datasets are  
6 often daunted by the sheer volume of data and may not consider the quality and limitations of those  
7 data. As ExpoCast develops, the website should incorporate estimates of exposure to chemicals and  
8 mixtures (especially upper bounds if possible) potentially stratified by age, gender, regions of the  
9 country, population density (rural, suburban, urban), ethnicity and so forth

10 Communication with epidemiologists and clinical investigators needs to be part of the process. It may  
11 be difficult for some health scientists to discern the potential relevance of computational toxicology  
12 to human exposure and health effects. Data generated and provided by EPA (and collaborators) can  
13 be used to demonstrate that the tests utilized are relevant to human health effects. In addition, the  
14 agency should clarify in what situations the data may fall short and be inadequate. For instance, there  
15 is a higher level of uncertainty for specific AOPs, outcomes and/or for specific classes of chemicals.  
16 Thus, it is essential to combine CompTox outputs with data on toxicokinetics, particularly  
17 metabolism, of the chemical in humans. Finally, biomonitoring data, exposure pathways, chemical  
18 source information and human activity patterns related to human exposure needs to be included in the  
19 assessment of chemical risk.

20 The EPA should continue to partner with existing academic health science centers to disseminate  
21 information on CompTox. The agency can utilize existing relationships via community outreach and  
22 translation cores. This would allow for the analysis of high-throughput data and development of  
23 predictive modeling using CompTox data sets. As AOPs are developed, it would also be useful for  
24 the agency to develop partnerships with relevant professional societies or institutions. For example, a  
25 group within the EPA developing an AOP on asthma would benefit from a partnership with the  
26 American Lung Association or the National Heart, Lung, and Blood Institute to access physicians and  
27 researchers at the cutting edge in this field. The EPA also may benefit from more collaboration with  
28 international agencies regarding data sources, data access and technology transfer. Another important  
29 group of stakeholders are risk assessors and public health professionals in state and tribal  
30 environmental and health agencies. Outreach to state and tribal public health scientists would be

1 helpful in informing them about the use of CompTox data in hazard identification and risk  
2 assessment.

3 Some additional suggestions for research regarding communication and achieving a broader  
4 understanding of the potential contributions and limitations of these approaches include the  
5 following: (1) an evaluation of the pesticide stakeholder dialog process  
6 (<http://www.epa.gov/oppfead1/cb/ppdc/#about>) by an independent expert (group) in communication  
7 and stakeholder participation to see what can be learned from that experience; and (2) pursue a mental  
8 model study to compare expert and public understandings of how CompTox findings could be  
9 informative (this might identify structural reasons why there might be communication difficulties and  
10 how they could be addressed).

## 11 **2.5. Other Issues**

12 In addition to addressing the study questions, the SAB also identified several additional issues that  
13 should be considered by the agency as it continues to develop the CompTox research program and  
14 apply the program outputs.

15 1) The agency should clarify the goals and objectives for CompTox with respect to chemical  
16 screening, prioritization and risk assessment. How will application of CompTox information improve  
17 current EPA practice? Because risk assessments are conducted for a variety of purposes, demands on  
18 the information base will necessarily differ among situations, but are there context-specific criteria for  
19 when particular types of information are informative enough to be useful? Resolution of some of  
20 these structural issues could be a useful contribution of the CompTox program even before it is  
21 producing actionable information. The Deepwater Horizon provides an example of a programmatic  
22 need – provision of information in emergency or other fast-moving settings – for which guidance is  
23 lacking.

24 2) There is a need to better delineate what CompTox can and cannot contribute, both now and in  
25 the future. Which contributions might be feasible over the next few years versus which ones will take  
26 longer to develop? What is the extent of the universe of chemicals that will be evaluated (e.g.,  
27 soluble? not too volatile)? What sort of health effects can be assessed at the current time and in the  
28 future? The identification of critical pathways is an important step toward clarifying a number of key  
29 risk challenges – mixtures, interactions with background exposures, existing conditions and

1 susceptibilities – and it provides an attractive possible approach for using CompTox data to assess  
2 risk, but are there risks that may be obscured or ignored when an approach based on critical pathways  
3 is used?

4 3) How well developed are EPA’s capabilities for synthesizing and using fragmentary and  
5 incomplete information? For the near term, CompTox results will be quite limited and their best use  
6 likely will be in combination with limited information from other sources. Current EPA practice tends  
7 to be chemical-specific and to focus on particular types of information. How far along is EPA in  
8 developing multi-chemical and multi-factor risk assessments? A future vision for CompTox is that  
9 the data will deliver a complete identification of critical pathways and a measure of the response  
10 along them, but realizing such a vision is still remote. For some period of time, perhaps indefinitely,  
11 the information provided by CompTox will be fragmentary and new methods will be needed for its  
12 interpretation. The primary challenges thus are transitional – how to build analytic structures that can  
13 incorporate new kinds of information in incremental steps.

14 4) Analytic capabilities are a major consideration for the CompTox program, but it is also  
15 important to think about institutional capabilities for developing, organizing, and using the  
16 information. Are data resources constantly updated and expanded and are there ongoing  
17 improvements in accessibility and analytic flexibility? How can staff and scientist training and  
18 development in use of new CompTox data be accomplished? Is there an institutional culture that  
19 identifies opportunities for the use of new information and is vigilant to detect warning signs  
20 concerning new issues and new difficulties? Is there good communication between groups that might  
21 use the same or similar information and methods? Can the institutions develop and support  
22 incremental changes? Can they engage stakeholders and other governmental and non-governmental  
23 organizations as supporters of such change?

24 5) Critical data for steps in the transition from current risk assessment practices will only partly  
25 come from CompTox; those data must be synthesized with other, more familiar, types of information.  
26 Data needs and requirements for data quality must be addressed as well.

27 6) How will EPA handle the inevitable occurrence when future data from *in vivo* or human  
28 studies contradict the ToxCast data? As the science moves forward, there may/will be results  
29 generated from *in vivo* and/or epidemiologic studies that contradict or are not consistent with the

1 CompTox results. This is an inherent characteristic of science and is not unique to the CompTox  
2 program. However, as inconsistencies occur how will EPA respond? What will be EPA's approach  
3 to handling the comments and perceptions that are sure to arise questioning whether the CompTox  
4 data either overestimated the risk of a chemical or did not identify the hazard(s) of a chemical? What  
5 would the implications be for the CompTox program and the use of its outputs? The public is  
6 bombarded with studies that show a risk for chemical X, and then other studies later show no risk,  
7 and then another wave of additional studies again showing a risk. The EPA needs to be prepared for  
8 the shifting playing field since future data from *in vivo* and human studies will not always be  
9 consistent with the CompTox results. The inconsistency that evolves over time as new data are  
10 generated is inevitable in scientific research, but EPA needs to develop a plan to address this as it will  
11 definitely occur and its occurrence will accelerate as more of the results from CompTox testing  
12 become available and begin to be used for prioritization and risk assessment.

13 7) It is clear that effective communication with all stakeholders, both within and outside the  
14 Agency, will be essential to the long term use of CompTox and ExpoCast findings.

15 8) There is a need to develop a community of scientists to provide feedback on ExpoCast in a  
16 parallel fashion to ToxCast is needed.

17 9) Finally, the SAB recommends that the EPA consider establishing an ongoing external  
18 advisory process to institutionalize a long term program built around the idea of incremental  
19 transformation. This process should be free of members with financial ties to the program. An  
20 independent perspective on the current program and prospects for the future can be provided along  
21 with constructive suggestions. The potential for longer term engagement by an external advisory  
22 committee should be considered.

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## REFERENCES

Judson, R., D. J. Dix, K. A. Houck, M. T. Martin, T. B. Knudsen, and R. J. Kavlock. 2010. Predictive Signatures from ToxCast Data for Chronic, Developmental and Reproductive Toxicity Endpoints. Presented at Society of Toxicology Annual Meeting, Salt Lake City, UT, March 07 - 11, 2010.

Maurano et al., 2012. Supplementary Materials for Systematic Localization of Common Disease-Associated Variation in Regulatory DNA. *Science* 337: 1190-1195 (DOI: 10.1126/science.1222794) Published Online September 5 2012.

National Research Council. 2007. *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC: The National Academies Press. ISBN-10: 0-309-15173-2, ISBN-13: 978-0-309-15173-3

National Research Council. 2009. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, "Front Matter." *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press, ISBN-10: 0-309-12046-2, ISBN-13: 978-0-309-12047-0

Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, Lecluyse EL, Andersen ME, Judson RS, Smith CM, Sochaski MA, Kavlock RJ, Boellmann F, Martin MT, Reif DM, Wambaugh JF, Thomas RS. 2010. Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening. *Toxicol Sci.* 117(2):348-58. Epub 2010 Jul 16.

EPA/100/K-09/001 I, 2009. The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals, March 2009, [http://www.epa.gov/osa/spc/toxicitytesting/docs/toxtest\\_strategy\\_032309.pdf](http://www.epa.gov/osa/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf)

EPA-SAB-11-007. 2011. U.S. Environmental Protection Agency (EPA) Science Advisory Board (SAB). Science Advisory Board Comments on the President's Requested FY 2012 Research Budget