

Preliminary Comments from Members of the Chartered SAB and SAB Liaisons on the SAB Draft Report *SAB Advice (1/29/13 Draft) on Advancing the Application of Computational Toxicology Research for Human Health Risk Assessment*

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Comments from lead reviewers

Comments from Dr. George Daston

My overall impression of this report is that, while it does bring up some important concerns about the application of computational toxicology for risk assessment, it is incomplete in its review of EPA's Computational Toxicology Program. The report almost exclusively restricts itself to a review of ToxCast, the Computational Toxicology Program's high-throughput screening effort. While ToxCast is currently the Program's most visible program, the Program also has activities in cheminformatics (DSSTox, ACToR), systems biology (virtual liver and virtual embryo (vLiver and vEmbryo, respectively)) and exposure science (ExpoCast). Only this last project is specifically mentioned in the report, although it is probably the least developed project in the Program.

Many of the ad hoc review group's observations and criticisms of ToxCast are well founded, but some of the comments and recommendations suggest an incomplete understanding of the intention of ToxCast. One that particularly concerns me is the recommendation that the CompTox Program create a Data Use Guidance document that is ostensibly for risk assessors but whose details are unlikely to help a risk assessor make sense of ToxCast data or integrate the results of multiple test systems. Furthermore, some of the recommendations and comments have already been addressed in publications from the Computational Toxicology Program and its collaborators.

We were asked to address four specific questions as part of the quality review.

1. whether the original charge questions to SAB Standing or Ad Hoc Committees were adequately addressed;
2. whether there are any technical errors or omissions in the report or issues that are inadequately dealt with in the Committee's report;
3. whether the Committee's report is clear and logical; and
4. whether the conclusions drawn or recommendations provided are supported by the body of the Committee's report.

Question 1: For the most part the charge questions have been adequately addressed by the committee. However, the responses to questions 2 and 3 have considerable overlap. Charge question 2 is "What issues are there in using CompTox in decision making for risk assessment and risk characterization as opposed to chemical screening, prioritization and green chemistry?" and question 3 is "What are the barriers and limitations that prevent the EPA from using CompTox outputs and how might they be overcome?" I had interpreted the former to be a question about the technical challenges in applying the program's results in risk assessment, and the latter question to be about barriers in changing people's habits so that they use the program's outputs. Instead, the report answers both questions as though they were the same, making the two sections redundant.

Question 2: There are technical errors and omissions in the report that make it less effective than it could have been. Chief among these is the failure to describe the CompTox program in its

totality, and in addressing the charge questions as though the program were exclusively about ToxCast.

EPA's Computational Toxicology Program consists of a number of research areas that leverage chemistry, biotechnology, exposure science, and systems biology together with advanced computational methods to address questions in toxicology and risk assessment in novel ways. ToxCast is an important component of the program, but so are cheminformatics components such as DSSTox and ACToR, ExpoCast, and systems biology (virtual liver and virtual embryo projects). The intention of the overall program is to provide tools that can be used either in isolation or in an integrated fashion. There was no overall description of the Computational Toxicology Program, and no effort made in the report to assess how the other projects and tools complement ToxCast. Only a few are explicitly mentioned in the report, and only ToxCast is explained. Importantly, many of the questions posed in the report, such as the development of adverse outcome pathways and the linkage of molecular-level events with adverse outcome and human morbidity, are being addressed by other components of the CompTox program. I recommend that the report start with a full description of the CompTox program, and the rest of the report either be redrafted to consider other aspects of the program, or that it acknowledge that it is only a critique of ToxCast and that other aspects of the program may in fact be addressing the concerns brought up in the report.

The first paragraph of the Introduction implies that ToxCast (and perhaps the entire CompTox program) was launched in response to the NRC report on Toxicity Testing in the 21st Century. This is inaccurate. The design of the program started in 2003 and started work in 2005. ToxCast itself was designed in 2006 and launched in 2007. (The CompTox website has a presentation on ToxCast dated June 2006). As noted above, it would be helpful for the report to begin with a history and description of the program.

There are a number of instances in the report in which questions are raised as to how the CompTox program will develop knowledge about the connection between molecular-level events and adverse outcomes (AOPs). This includes the first paragraph on p. 4, and the end of page 12. The report should acknowledge that this question is being addressed by the systems biology programs within CompTox (virtual liver and virtual embryo).

The report opines in several places that the CompTox program should compare results from ToxCast with human exposure levels (p. 5, first paragraph, p.7, last paragraph, p. 9, last paragraph). I agree that this is important, but the results should acknowledge that the program has done this, with external collaborators. In fact, one of the citations at the end of the report (Rotroff et al) addresses this very question for ToxCast phase 1. Two other publications from the group and its collaborators also address this question and should be cited (Wetmore et al., 2012, *Tox Sci* 125: 157-74; and Gangwal et al 2012, *Sci Total Environ* 435-436: 316-25).

There are a number of rhetorical questions posed on p. 8 of the report about the interpretation and application of CompTox output. I agree that these are important questions, but some are difficult to interpret, and others are being addressed already, albeit by other projects in the program besides ToxCast. The first question asks "have the most sensitive endpoints been identified in the CompTox assays?". It is not clear to this reader how "sensitive" is being

defined here. Earlier in the report, sensitivity is discussed as a measure of concordance with in vivo data. Is that what is meant here, too? The second question asks how uncertainty factors would be applied to in vitro data, but this question presupposes that there would be some sort of one-to-one replacement of in vivo assays with in vitro, which is clearly not what ToxCast is about. A little more clarity about what is being asked would help the reader understand the nature of the question. As to the fifth and six questions on this list, the report should acknowledge that the CompTox programs and/or its external collaborators are addressing these questions (see for example the Wetmore et al paper cited above, and Lock et al 2012, Tox Sci 126: 578-88).

Question 3: I was able to follow the logic of the report and found it to be reasonable. As noted above, there is considerable redundancy in the responses to charge questions 2 and 3. I recommend that the committee rethink whether these questions are, in fact, different. If so, they should endeavor to answer each question separately. If not, then the responses can be combined.

Question 4: As noted above, one of my principal concerns with the report is that it is not really a review of the entire CompTox program, and because of that many of the conclusions and recommendations make sense only for ToxCast, but not the program as a whole. There are two ways to deal with this. One is to redraft the report considering the other components of the program, the second is to acknowledge that it is only a critique of ToxCast. My opinion is that the former course of action is the one that provides the most value to the Agency.

One specific recommendation that I take issue with is the development of Data Use Guidelines (pp. 10-11). As drafted the recommended guidelines are a strange conflation of assay performance criteria (e.g., dynamic range, positive controls used) and data interpretation. Both of these information streams are useful, but for very different purposes. The performance criteria have already been collected and are available. The interpretation criteria are valuable and should be developed. However, the intention of ToxCast is that a large number of assays are intended to provide information about the potential to produce a given biological response, so it would seem that data use guidelines would only be useful if they describe the use of families of assays, not individual assays. This is why the CompTox program designed tools such as ToxPI and dynamic spider plots, for example, to aid in the visualization of effects in suites of assays covering a wide range of responses.

Comments from Dr. Michael Dourson

Were the charge questions adequately addressed?

I believe that the following questions constituted the charge of the committee

- Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA's programmatic needs?
- What issues are there in using CompTox in decision making for risk assessment and risk characterization as opposed to chemical screening, prioritization and green chemistry?
- What are the barriers and limitations that prevent the EPA from using CompTox outputs and how might they be overcome? and
- How should the use of the CompTox program be effectively communicated to stakeholders? How can the communication be enhanced?

The committee has done a good job in answering these questions and is overall encouraging EPA to continue its work. The committee also does a nice job at laying out the numerous problems associated with this kind of activity. In fact, the problems, taken together, can generate a sense of hopelessness, at least from a toxicology-risk assessor's point of view. This is because the disparities between *in vitro* and *in vivo* systems are so vast that confidence in the prediction of "safe" dose (or any other dose response assessment activity) from *in vitro* findings is low now, and likely to be low for a very long time.

I would encourage the committee to make two points strongly. First, is that this program is research, and as research it is going to lead to some, perhaps many, areas that are not useful. "Blind alleys" is the phrase the committee uses, but the committee needs to put this right up front. Especially since many EPA managers have never done this kind of research and are not aware of the numerous and expected pitfalls in any area of new science. Also, research is a long-range activity that will bear fruit, but not necessarily on the time frame of political activity. EPA, or some group, needs to be in this for the long haul, and protected from the usual ravages of short-term budget considerations.

Second, and perhaps even more important, CompTox can do something that the *in vivo* bioassays cannot. It can readily test mixtures of chemicals. The committee also mentions this, but it is by far the most relevant aspect of the program from a toxicology-risk assessor's point of view. The few *in vivo* mixtures studies done by EPA (specifically, Dr. Jane Ellen Simmons of the RTP labs) and others should be procured and analyzed in by CompTox program, if they have not been done already. Risk assessment scientists from EPA's NCEA and program offices, specifically OSWER and OW, need to then get involved to make sense of the results.

Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

I have numerous comments on the text that might enhance the report. Some of the more significant ones might be:

PDF page 12, definitions: Is this a standard definition of AOP? A receptor interaction, for example, might indicate an exposure, or a biological effect and yet not be an adverse effect.

How then can it be considered as part of the AOP? If such events are considered part of the AOP, but not adverse, what is to prevent absorption being labeled as part of the AOP?

On the definition of CompTox: If the results of CompTox are not useful for the clinical outcome of diseases caused by chemical exposures, then it they not efficient. This defiinition of CompTox should not presume it relevance. This relevance needs to be demonstrated

PDF Page 18, line 12: Please amend this sentence to read: means of enhancing its traditional, but more limited, focus on multiple stressors, endpoints, sources, pathways, and environmental media in the OSWER program, and to a more limited extend in the OPP, to other agency programs.

PDF Page 19, line 19: Of course, this is not an insignificant task. For some chemicals, the MOA, key event, critical effect and adverse effect sequences are well understood. But for many chemicals, and many toxicities, such sequences are not understood.

PDF Page 19, line 28: Hazard identification and green chemistry are two different concepts. Or do the authors mean hazard identification and alternatives assessment? I would agree that these two are similar.

PDF Page 19, line 30: This should go without saying, but no chemical or chemical product is free of toxic properties. It is all a matter of the dose. Please amend this sentence.

PDF Page 20, line 17 and on: I am reminded by the text in this section that Health Canada did a review of 23,000 chemicals in their country by focusing first on exposure parameters and only then considering the hazards (e.g., its Domestic Substances List). Perhaps EPA can lean on the Canadians for guidance in this area, since it may reduce the need for chemical testing.

PDF Page 21, line 18: The current uncertainty factor construct uses mg/kg bw-day data from in vivo comparisons among studies. A similar effort would likely be needed with the in vitro screening data. At this point, I am not sure how to tie the two areas together, but focusing on the critical effect would be a good place to start.

PDF Page 22, line 1: This is also a good concern but it raises a related thought. Variation in assay outcome among individuals is only tangentially related to the use of a 10-fold default uncertainty factor for within human variability. This is because this factor is applied to the NOAEL or BMDL10 (usually), which is in the low part of the population response range. Thus, its use is consistent with likely larger variation amongst folks.

PDF Page 22, line 13: I do not think that this will be a problem. For example, EPA Region 5 has file drawers full of fish tissue data with defined chemical mixtures of concern.

PDF Page 23, line 27: Please add the hormetic and essential to the list of dose response curves.

PDF Page 25, line 8: Please amend this text to include the thought that the current guideline bioassays are general in nature, and together with specialized studies are intended to predict the

full range of endpoints of concern. Such specialized testing is added routinely for chemicals when the general tests indicate a concern.

Page 33, line 22: Again, all chemicals have risk at some dose. So the question here should focus on the likely exposures to the chemicals of interest.

Is the draft report clear and logical?

The draft was clear for the most part and the panel was diverse and likely enthusiastic. I bet the discussions were fun. I have a few minor comments on an attached annotated text.

Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The five concluding statements in the Administrator's letter are spot on. As EPA pursues this work, I would strongly encourage a mix of disciplines in the outreach activity. This mix needs to include clinicians, researchers, and risk assessment scientists in the areas of epidemiology, toxicology and exposure assessment.

I have two further thoughts. In the Administrators Letter, PDF page 1, line 33, this sentence reads as if the authors were not aware of the extensive theoretical EPA work on chemical mixtures, guideline development, and daily risk assessment activity in OSWER and all 10 regions on chemical mixtures. Indeed, EPA is the lead federal agency in these endeavors. Please amend this thought to be complementary to EPA in both the letter and the text.

PDF page 2, lines 36 to 42: The slant of this paragraph is off. First, CompTox will be replacing *in vivo* data, not risk assessment methods. This is because the existing risk assessment methods are general and can be, and have been, used with *in vitro* data to generate risk assessment positions (if needed, examples will be readily given at the public meeting). Second, CompTox's most compelling use is in the testing of chemical mixtures. The committee needs to further emphasize this point in the letter.

Comments from Dr. Nancy Kim

General comment

The panel is to be commended for its draft report. It provided thoughtful comments that should help EPA and other researchers improve the science and usefulness of the results from computational toxicology.

1. Were the charge questions to the committee adequately addressed?

Yes. The charge questions are given on page 2 of the report. The letter to the Administrator (see lines 36-40 on first page) rephrases those questions, generally making them broader and less specific than those in the report. The first part of the first charge question (e.g. Are the outputs of CompTox currently being used by EPA is answered directly in the letter to the Administrator and in the report. The second part, for example, (How well do the outputs align with EPA's programmatic needs?) is answered directly in the report (p.4, line 16) but does not appear to be answered directly in the letter to the Administrator. The other three questions are answered in the body of the report, although more indirectly in the letter to the Administrator.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

The report focuses mainly on the use of CompTox for hazard assessment, risk assessment, and to a more limited extent risk characterization. The report mentions risk management less frequently. Risk management (either by an individual, government agency in the form of regulatory actions or advice, or by the public sector) is the ultimate reason for risk assessment. For example, question 2 on page 2 does not mention risk management although the report does mention it (although less frequently than hazard assessment and risk assessment). For CompTox outputs to be used confidently for risk management, additional understanding of the quality of the outputs in relation to hazard and risk assessment will be valuable. However, if the ultimate use (e.g. risk management) is considered in the evaluation of CompTox outputs, some of the suggestions might be revised. Another example is on page 6, line 5. Risk managers and the regulated community could be added to risk assessors (The next sentence mentions statutory requirements and regulatory action; however, I would still add risk managers and regulated community to the previous sentence since not all risk management that EPA does results in a regulation and getting widespread support for the data from the regulated community would be very useful to the CompTox program.) The panel should consider reviewing the report to include risk management in appropriate statements that mention hazard or risk assessment and to determine if the report's comments/recommendations need to be revised.

The last paragraph on page 4 discusses the Deepwater Horizon accident effort carried out by the CompTox program. In the letter to the Administrator, the panel asks specific questions about the results (second page, lines 8-9). The panel should consider adding

those or additional questions to the body of the report (page 4 or 5) and recommending that EPA validate the original evaluation.

3. Is the draft report clear and logical?

In general, the report is clear and logical.

Letter to the Administrator

The last page of the letter lists 5 bullets as its summary. None of those bullets seem to address the issues raised in the paragraphs starting on line 15 and line 36 of the second page of the letter to the Administrator and discussed in greater detail in the body of the report. The panel should probably add another summary bullet that raises the technical issues facing EPA in developing, using and gaining acceptance of CompTox data and ExpoCast data even though they are discussed in the body of the letter. They are important issues and may be overlooked if the reader focuses on the list at the end of the letter.

Body of report

One area that could be revised to improve clarity is how the report makes recommendations or suggestions. The report does not use the usual phrase included in SAB reports, “the SAB recommends that EPA...” Instead it uses words like, “EPA should explore...” (page 4, line 2), “In principle, weight-of-evidence approaches would be developed... (page 4, line 10), “it would be useful if the agency considered developing the theoretical framework... (page 6, line 17-18), “Thus, to build a credible system, the EPA needs to focus on making the case...” (page 6, line 24-25), “the path to studying and estimating risk from mixtures should be outlined (page 9, line 12), “it may also be helpful to develop... (page 11, line 9), etc.. Similar language is used frequently in the report.

Other areas discuss an issue in some detail, but it isn't clear if any specific recommendations are being made. For example, does the panel have any specific recommendations to include in the discussion in the paragraph starting on page 6, line 28? Similarly, should any specific recommendations be made in the paragraphs starting on page 6, line 28 and page 7, line 17, and page 28, line 4. Does the statement beginning on page 9, line 30, lead to a recommendation? Other similar examples occur in the document.

The report makes numerous suggestions/recommendations to EPA and they likely differ in their level of importance. The panel should consider providing additional assistance to EPA by indicating which of the suggestions it considers should be done first or which are most important.

On page 21, line 11, the report recommends that EPA consider establishing an ongoing external advisory process... and that process should be free of members with financial ties to the program. I am not sure what the phrase “free of members with financial ties to

the program means.” It could mean scientists from industry that may be regulated or scientists who developed computer programs that EPA is using in its CompTox program or have some other meaning. I suspect that EPA has procedures which include disclosure of any particular interest at the start of an advisory process and that might be sufficient. Excluding any particular sector might eliminate some valuable advice and reduce the acceptance of the CompTox and ExpoCast results. If the language remains, additional explanatory wording might help.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
Yes.

Minor comment.

Page 21, line 9. Suggested rewrite. A community of scientists should be developed to provide feedback on ExpoCast in a parallel fashion to ToxCast.

Comments from Dr. Eileen Murphy

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes and no.

Overall, the report identifies some interesting and significant issues with the CompTox program. Much of the narrative in the sections is devoted to presenting additional questions. Answering charge questions with additional questions is tricky. Does it mean more information is needed in order to make recommendations? Are you actually making recommendations in the form of questions? It is not clear how these additional questions will enable use of the data. But, perhaps that is the point – that the program is still in its development and the data is not quite ready for use? That is the impression that I got from the report – that there are still numerous questions about the program itself and that incorporation of the data generated into risk assessments may actually be premature.

Section 2.1. The narrative seems to indicate that the results of CompTox are not really being used by other programs at EPA, although the tools were very useful during the DeepWater Horizon crisis. The SAB report should be more clear and direct in addressing this first charge question – if the program is not being used, then this should be stated directly. The report does provide suggestions as to how the results from CompTox can be used by programs.

Section 2.2. The charge questions are adequately addressed. The development of data use guidelines (DUGs) is doable and would add benefit. However, some of the topics described in this section are very broad and may not be within the purview of the program. For instance, the CompTox program is not equipped to conduct epidemiological studies. While it would be useful if the data generated from the program were used in such studies, the program itself is not staffed for this type of work. The recommendations should focus on how the program can ensure that the data generated are of a quality that can be later used by epidemiologists in population-based studies.

Section 2.3. Most of this section is well focused and provide meaningful advice to EPA. However, the number of additional questions posed here to EPA indicate that the program may not be fully developed enough to provide recommendations on building scientific acceptance of the program throughout the rest of the agency.

In Section 2.4. It is useful to include epidemiologists in this section. Communication with epidemiologist is critical. The CompTox program itself can't do the epidemiology, but the data generated can be used to epidemiologists, so communication is important.

Section 2.5. While the topics listed in this section are interesting, it is the very last recommendation – that EPA consider establishing an ongoing external advisory process, that is probably the most important, and should be highlighted in the letter to the administrator. Given the general tone of the report – which is primarily more questions about the program – perhaps the program is not ready for evaluation. Perhaps what is needed is an advisory group assisting EPA in addressing the questions posted by the authors of the report.

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

No

3. Is the Committee's report clear and logical?

In the letter to the Administrator, the group highlights the development of Data Use Guides (DUGs). The letter is the first time I have seen this term, and I found it unclear, particularly when it appeared as a highlighted component of the letter. It is not clear how the development of DUGs relates to the application of computational toxicology data in the letter. In the report, these are described, but I wonder if they are significant enough to be so prominently featured in the letter. It is a good practice to develop these. However, the appearance of DUGs in the letter make it seem more significant than the other recommendations. I don't think that was the intent.

Further, there is a lot of descriptive information about CompTox and exposure science in the letter to the Administrator. It is not until the third and last page that we see specific recommendations, and these are just listed. I think some of the narrative describing the program could be moved to the body of the report thereby making the letter more consider and focused.

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

The recommendations bulleted on page 3 of the letter to the Administrator are summarized nicely. However, my read of the report left me with the feeling that the program is not ready for full utilization by the agency. The very last recommendation - that EPA consider establishing an ongoing external advisory process - is not mentioned in the letter to the administrator. However, the take-away message to me, as a reader, is that the program needs an advisory group to assist in closing the scientific gaps of the program and address any potential concerns that risk assessment programs may have with the data generated by this program.

Editing:

- p. 1, line 34, remove "also" as this is redundant
- p. 2, line 5, change "obtaining" to "obtain"
- p. 3, lines 5-6, I don't think this sentence provides any value to the letter: "In fact, these data will likely be the source of numerous Ph.D. dissertations in the near future."
- p. 15, line 13, why are there double parenthesis here?
- p. 15, line 17, need to provide the date

Comments from other SAB Members and SAB Liaisons

Comments from Dr. Joseph Arvai

General comments:

I appreciate that a great deal of work went into this report. Even though this is not my area, I found the report to be well written and quite easy to follow.

1) Were the charge questions to the committee adequately addressed?

Yes.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

To the best of my knowledge, no.

3) Is the draft report clear and logical?

The draft report is very clearly written, and it is quite methodically argued. However, I think it would benefit from an executive summary.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

As far as I can tell, yes.

Comments from Dr. Ingrid Burke

1. *Were the charge questions to the committee adequately addressed?*

Yes, and I very much like the Letter to the Administrator, and the report itself. The whole thing is written very well.

2) *Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?*

Not that I could see. I was wondering a bit about whether two things could be added:

- application of the system to public concern/regulation of hydraulic fracturing;, and related,
- publication of the web site on state Departments of Environmental Quality web pages.

3) *Is the draft report clear and logical?*

Yes, it's really well written. It needs an executive summary.

4) *Are the conclusions drawn or recommendations provided supported by the body of the draft report?*

Yes.

Some line by line edits:

Line 24, page 3: "First, data from ToxCast is 24 being compared to data from ToxRef, a database of toxicity studies conducted with guideline, *in vivo*". This should read "data ARE being compared".

Comments from Dr. Edward Carney

1. Were the charge questions adequately addressed?

Clearly, this is a complex area and it would be impossible to cover every possible nuance in the draft report. However, I believe that all of the major issues were addressed. In particular, it was good to see a thorough discussion of exposure in the report.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

P. 7, lines 7-11. This section states “CompTox models developed to screen for chronic, developmental and reproductive toxicity endpoints display high specificity (few false positives) but only moderate sensitivity (multiple false negatives). [Sensitivity relates to the assay’s ability to identify positive results. Specificity relates to the ability of the assay to identify negative results.] Therefore, the rate of false negatives is expected to be high at this stage of the program.”

The basis for a low false positive rate with CompTox is unclear. In fact, there are several reasons why these assays could have relatively high false positive rates. For example, the test concentrations in vitro could be much higher than the concentrations in blood or tissues which could ever be reached in vivo. Often in vitro assays achieve extremely high levels of cell killing or excessive stress and these could create false positive results. In addition, in vivo many compounds are detoxified via metabolism, whereas these metabolic pathways are usually lacking in vitro. In reality, both false positives and false negatives both will need to be dealt with in CompTox assays.

3. Is the draft report clear and logical?

Yes

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. David Dzombak

The SAB Exposure and Human Health Committee, supplemented with two members of the EPA FIFRA Scientific Advisory Panel, has done a very nice job in responding to the charge from the Chartered SAB 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 only major comment that I have is that the report needs an Executive Summary.

1. Were the original charge questions adequately addressed?

Yes, the original charge questions are addressed adequately.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Panel's report?

I found no technical errors or omissions.

3. Is the Panel's draft report clear and logical?

The body of the draft report is well organized and well written. It responds to the charge questions systematically.

The Letter to the Administrator is concise, clear, and well written. On page 2, line 5, there is a typo: "obtaining" should be "obtain"

The report needs an Executive Summary. I realize that this will be somewhat redundant with the Letter to the Administrator for such a concise report, but some readers will only be interested in reading the Executive Summary, a mini-version of the entire report. Moreover, inclusion of an Executive Summary is standard in SAB reports.

4. Are the conclusions drawn or recommendations provided supported by the body of the Panel's report?

The conclusions and recommendations are adequately supported in the body of the report, but the report does not have an Executive Summary and needs one.

Comments from Dr. Robert Johnston

1) Were the charge questions to the committee adequately addressed?

Yes, the charge questions were adequately addressed. However, there is an equivocal and inconclusive tone to the responses which makes it difficult to discern the true prospects for the Comptox program. For example, the report appears to strongly support the program. Yet, when responding to the first charge question, the committee notes that: (i) the program is largely “proof of concept,” (ii) there have been limited uses of Comptox outputs to date, and (iii) EPA faces significant challenges understanding how the resulting information can be used. It is difficult to reconcile the report’s underlying enthusiasm and support for the program with repeated statements highlighting the limitations of the resulting information. At the same time, the report does a good job of highlighting the current limitations of Comptox, and specific steps that will be required to move the program beyond its current status as “proof of concept.”

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

To my knowledge, there are no technical errors or major omissions in the report. One issue that could be better clarified, however, is the disconnect between the shortcomings in EPA’s current hazard assessment (i.e., focus on single stressors, endpoints, sources, pathways and environmental media rather than on multiple interacting factors) and the capacities of Comptox. Currently, the “solution” does not seem to fit the “problem,” leaving Comptox as research program still in search of an application. As noted by the report, Comptox “is still in the development stage,” and “its use is still very limited.” However, the report is not particularly clear on whether Comptox will ever have an extensive, applied use. This ambiguity seems to belie the strong support for the program within the report. The report would be improved if this seeming disconnect could be addressed more clearly.

3) Is the draft report clear and logical?

I found the draft report somewhat difficult to follow. Part of the lack of clarity was due to the inconclusive tone noted above. In addition, the report’s discussion of technical issues (e.g., divergences between *in vivo* and *in vitro* assays) and heavy use of acronyms and jargon made the narrative somewhat difficult to follow in places.

Another area in which greater organization would be useful is under the response to study question 3, addressing “barriers and limitations that prevent EPA from using CompTox outputs.” Here, the report alternates between discussions of data/output reliability and discussions of scientific use/acceptance. There are two different, if related issues here: (1) how to demonstrate reliability and (2) once this is done, how to generate scientific use/acceptance. The discussion would be clarified if these two issues were treated separately, rather than combined in a single section. A related concern is that the report seems to proceed from a position that barriers to acceptance *should* be overcome. However, this is only true if Comptox provides reliable information. Currently, the scientific community maintains a healthy skepticism, which is appropriate given the current limitations of the program. By combining discussions of reliability

and scientific acceptance in a single section, the report confounds this two separate but related issues.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

In general, the recommendations are well supported. However, the report could better justify the primary recommendation that “The SAB applauds the work of the CompTox research program, and recommends the continued development of CompTox outputs...” particularly with regard to statements later in the report which imply that the program may have few direct applications into the foreseeable future.

Comments from Dr. Terry Daniel

General comments

This is a well-conceived and well-presented SAB advisory report that should be of considerable utility to the EPA. The technical and policy issues addressed seem (to a non-expert) to be important and the recommendations for further development and implementation of the CompTox program seem clear and useful.

The panel and the SAB should consider whether it might be useful from a public policy (rather than science/technology) viewpoint to spend an extra paragraph or two in the introduction establishing the larger context for the CompTox program. Aside from the short statement at the beginning of the Letter to the Administrator (“Tens of thousands of chemicals are currently in commerce and hundreds more introduced every year ...”), the report seems for the most part to assume that the reader accepts that the technical advances offered by the CompTox program are needed and then proceeds to focus on how best to accomplish the technical and scientific objectives of the program. The SAB report offers an opportunity to speak more directly to the public/political audience about why (viz. the EPA’s mandate to protect human health and the environment, and the challenges thereto) the technical advantages of CompTox are needed and what benefits the program could provide for public health and safety and for affected industries and commerce.

Specific Quality Review questions

1. *Were the original charge questions to the SAB panel adequately addressed?*

Yes

2. *Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee’s report?*

This reviewer does not have the expertise to comment on the technical issues that were the primary focus of the report.

3. *Is the Committee’s report clear and logical?*

Yes, the report is very well written and seems to identify and thoroughly address a number of important issues related to the CompTox and associated programs.

4. *Are the conclusions drawn or recommendations provided supported by the body of the Committee’s report?*

Yes. The recommendations regarding increasing the emphasis on integrating human exposure pathways and parameters and on forging stronger links to risk assessment were well founded and seem especially important.

Comments from Dr. Bernd Kahn

The draft Review is very clear and well written; my specific responses to the 4 questions are, respectively yes, no, yes, and yes. My specific responses are:

p. ix: The acronym DUG, Data use guidance, is missing.

p.2, 1.17: Replace DATE with March 8, 2013.

p.3, 1.3: The answer to this first question is not sufficiently clear. What structure and activity are available and in use at the time of the review? What is the anticipated time line for the various activities that are 'just beginning' and when will the research that is expected to 'produce' a program do so? In other words, what aspects, if any, of this program are producing outputs at this time, and when, in turn, will the developed continuation and expansion of the program be ready to respond to inquiries concerning certain chemicals?

Comments from Dr. Catherine Karr

- 1) Were the charge questions to the committee adequately addressed? YES
- 2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report? NO
- 3) Is the draft report clear and logical? YES
- 4) Are the conclusions drawn or recommendations provided supported by the body of the draft report? YES

Comments from Dr. Francine Laden

1) Were the charge questions to the committee adequately addressed?

Yes – the charge questions are adequately addressed.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

The report is very thorough and appears to adequately deal with all important issues. The importance of considering chemical mixtures is mentioned a number of times; however, no clear solutions for how to deal with them are presented.

3) Is the draft report clear and logical?

Yes – the draft report is clear and logical

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are supported by the body of the draft report

Comments from Dr. Elizabeth Matsui

I reviewed the three SAB reports and assessed whether the charge questions were adequately addressed, whether there were any technical errors or omissions, whether the draft reports were clear and logical, and whether the conclusions/recommendations were supported by the body of the draft report.

Comments from Dr. Surabi Menon

The report on the CompTox program included response to a few study questions. The suggestions under Study Questions 1 and 2 are well laid out and especially comprehensive for Study Question 2. The specific recommendations for stakeholder engagement detailed under Study Question 4 is especially important for situations when new studies that evolve may or may not contradict the CompTox results. This makes it important that the communication protocol launched and in action stays alert to these types of situations as well.

Comments from Dr. James Mihelcic

- 1) Were the study questions to the committee adequately addressed?

There are four study questions in the report. I believe all were addressed well except the report could be more definite on the outcome of study question (Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA's programmatic needs?). The middle paragraph on page 3 states the "primary use of CompTox outputs has been to determine the reliability of the data" (lines 18-19) and also states "is limited use of CompTox outputs to date" (line 21) yet this section is written as items that are being used. The feel of the report is that EPA is making progress towards eventual use of the outputs, but at this point (5-6 years after start) there is limited use of outputs. We should be clearer about the fact that there is limited use of the outputs.

- 2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not observe any major errors or omissions. However, related to study question 2 (What issues are there in using CompTox in decision making for risk assessment and risk characterization as opposed to chemical screening, prioritization and green chemistry?), the report demonstrates a narrow understanding of what green chemistry is, and presents it as being based on reducing the endpoint of toxicity of the chemical/substance. In reality, **green chemistry** focuses on addressing hazard throughout molecular design and the processes used to synthesize those molecules. It is thus a field devoted to the design and production of chemical products and processes that reduce or eliminate the use and generation of hazardous materials (Anastas, P.T., and J. C. Warner, 1998. *Green Chemistry: Theory and Practice*. Oxford: Oxford University Press). The report does a disservice to the field of green chemistry with this narrow view. Therefore, I recommend the report provide a broader review that addresses the use of CompTox outputs in the design and synthesizing stages. If the committee believes CompTox is only useful to provide information on determining the toxicity expressed by the produced chemical, it should be clear in its text what the broader use of the term green chemistry is.

- 3) Is the draft report clear and logical?

Yes

- 4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. H. Keith Moo-Young

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes. The original charge questions were adequately addressed.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

I found no technical errors or omissions in the report.

3. Is the Committee's report clear and logical?

The report is clear and logical.

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report? Yes. The conclusions are supported by the body of the report.

Comments from Dr. Stephen Roberts

1) Were the charge questions to the committee adequately addressed?

All of the charge questions were adequately addressed and the challenges associated with making computational toxicology achieve its hoped-for capabilities are well cataloged.

2) Are there any technical errors or omissions or issues that are not adequately dealt within the draft report?

I didn't see anything that is patently wrong, although clarity could be increased in a number of sections (see below).

3) Is the draft report clear and logical?

There is room for improvement. For example, the answers to the first questions ("Are the outputs of CompTox currently being used by the EPA? How well do the outputs align with EPA's programmatic needs?") seem to be "not much yet" and "it's too early to tell", respectively. What not state these more clearly? The example cited for use of CompTox is testing of dispersants after the Deepwater Horizon spill. So how did it do? Were the results useful? Did it allow decisions to be made better or more quickly? None of this is covered, leaving the reader to guess whether CompTox was really an asset or not. The alignment question appears to be addressed in lines 16-24 on page 4, yet I can't find a straight answer except text suggesting that the *intent* is to have output align with needs.

For the response to question 2, it would help to start by explaining the different information needs of risk assessment versus chemical screening, prioritization, and green chemistry. Since question 2 focuses on the use of CompTox to support risk assessment, I think that clarity could be enhanced by organizing this section along the lines of basic components of a risk assessment (hazard identification, exposure assessment, dose response assessment, and risk characterization). This would allow a cleaner separation of discussion of issues associated with exposure and dose-response, which are currently muddled together.

Some of the response to question 3 is redundant with the response to question 2, but this is a consequence of overlap in the questions (pointing out "issues" versus "barriers and limitations"). Repeating these points is probably unavoidable.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations are supported by the body of the report.

Picky points:

Letter to the Administrator, first page, lines 31-32: "... in combination with exposure and dose-response data, risk assessment."

Letter to the Administrator, third page, lines 17-20: Suggest revising to make it clearer how this pertains to CompTox.

Page 10, line 27: In the context of CompTox, this should probably be "concentration-response" instead of "dose-response".

Comments from Dr. Amanda Rodewald

1. Were the charge questions adequately addressed?

Yes

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

No.

3. Is the draft report clear and logical?

Yes.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes.

Comments from Dr. Pamela Shubat

Both the letter and report are well written and easy to follow and understand. The report will be an excellent resource for both EPA and those who are tracking the development of the CompTox program.

Consistency between the cover letter and body of the report:

The cover letter is an appropriately abbreviated description of the report. See item 4, below, for a comment on the summary of the letter.

1) Were the charge questions to the committee adequately addressed?

Each question was addressed. Study question 1 is especially important to address at this stage in order to ensure that work products are truly useful to EPA and are used to improve/safeguard public and ecosystem health. I have one comment concerning study question 1 (below).

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

Study question 1 (how outputs are currently used by and align with EPA programs): The report describes meeting with EPA programs and learning how coordination is occurring (page 4, line 22). However, no examples other developing EDC data for releases related to the Deepwater Horizon accident were described. The report describes “the limited use of Comptox outputs to date” (Page 23, line 21). The study question would be more fully answered with a description of EPA program’s anticipated uses of the outputs (or even a clear statement that there were anticipated uses). Perhaps these conversations are implicit in the description of examining the reliability of the ToxCast data (ToxRef comparison, AOP development). However, it was not clear in this section that programs outside of ORD are intimately involved in this work (it sounds as if the data reliability work is all done through ORD). More indications that conversations with programs did not yield a sense of demand for this information from EPA programs is found in other sections (e.g., page 16, lines 21-27).

3) Is the draft report clear and logical?

Yes.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

I was not able to find, in the body of the report, the same succinct summary (five bullet points) that are listed in the letter. While each of these five items are fully discussed in the body of the report, it would not be clear to the reader of the report that these were the key recommendations from the report.

Comments from Dr. Daniel Stram

1) Were the charge questions to the committee adequately addressed?

As an outsider to this general problem I found the report overall a bit hard to read, it seemed like overly specialized terminology was being used in many places, and at times I felt that more specifics would have helped.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I don't have specific comments here

3) Is the draft report clear and logical?;

Again I think that there are places throughout the report where unfamiliar (and in some cases overly general) terminology should have been replaced with simpler language and if possible more specifics. The use of the Deepwater Horizon accident as an example was helpful. Even there, some more specifics about the responses to the disaster (what tests were performed why they were chosen, did the data used already exist, or were new data generated?) could have been illuminating.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report

No specific comments

Comments from Dr. Jeanne VanBriesen

1. Were the charge questions to the committee adequately addressed?
 - a. Yes. The four charge questions were adequately addressed by the report.
2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?
 - a. The content is adequately dealt with in the draft report.
3. Is the draft report clear and logical?
 - a. Yes, the report is clear and logical; however, the technical background required to read and understand the report is quite high. Since the main audience is EPA technical staff with extensive experience in toxicology and human health risk, this is likely fine. However, a few edits to improve understanding for a broader technical audience would be relatively easy to implement.
 - b. In section 2.2, a brief preamble, perhaps a paragraph, regarding risk assessment and risk characterization would be helpful. While the technical reader is aware of why the sub topics of specificity and sensitivity and then exposure assessment are critical for incorporating information into risk assessment and risk characterization, the general reader would benefit by an introduction here of the components that affect our ability to use data in risk assessment and characterization.
 - c. In section 2.2.2 on exposure assessment, the sub-sections of this are not clear. The section begins with exposure potential, segues to hazard identification and mixture issues, and then returns to exposure. The overall objective of this section is not clear from the introductory paragraph. It would benefit from tighter alignment of the sections. Expocast could perhaps be introduced here first before its discussion on page 15. The need for exposure assessment to be incorporated into risk assessment is important, and it represents a current challenge relevant for study question 2 as well as 3.
 - d. The analogy in the middle of page 9 is not helpful to the reader. The balance of the paragraph adequately makes the intended point clear.
 - e. On page 13, the term “read-across approach” has not been previously introduced, nor does it appear in the glossary. It is well known to toxicological researchers, but its introduction here as an alternative to AOP may confuse the less expert reader.
 - f. I particularly appreciated the discussion under charge question 4 about how EPA is currently communicating with stakeholders. Although not specifically part of the charge question, this was helpful and important information.
 - g. Point 8 on page 21 could benefit from a revision for clarity.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?
 - a. Yes. The report provides support for the conclusions and recommendations.

Comments from Dr. John Vena

I was on the report panel and therefore do not have any additional comments.

- 1) Were the charge questions to the committee adequately addressed? Yes
- 2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report? No
- 3) Is the draft report clear and logical? Yes
- 4) Are the conclusions drawn or recommendations provided supported by the body of the draft report? Yes