



EDF comments on the EPA Science Advisory Board's Exposure and Human Health Committee's 9-7-12 draft report on EPA's CompTox Program

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General Remarks

Environmental Defense Fund (EDF) supports the EPA Scientific Advisory Board (SAB) Exposure and Human Health Committee (EHHC) project to provide advice to the agency as it develops and explores applications of the Computational Toxicology (CompTox) research program to meet agency programmatic needs. EDF recognizes and appreciates the need to develop new approaches for better understanding and predicting chemical hazard, exposure, and ultimately risk. As EPA continues to explore, develop, and implement new chemical assessment technologies, we urge EHHC to encourage the agency to continuously seek input from a broad range of outside experts and stakeholders.

Toward this end, EDF submits the following comments on the SAB EHHC draft report on "The Use of CompTox to Advance Risk Assessment" ("draft report").

Use of ToxCast assays to evaluate dispersants used during Deepwater Horizon oil spill

In crisis situations where there is limited time to evaluate a chemical or mixture before its use, the ability to rely on batteries of rapid high-throughput tests to make a more informed decision is attractive. The EHHC draft report (in both the letter to the Administrator and on page 7 of the draft report) cites EPA's use of a subset of ToxCast assays to [evaluate endocrine activity of dispersants](#) used in the BP oil disaster in 2010 as a positive example of the assays' application. However, the EHHC draft report fails to adequately discuss either: (1) the limitations of the assays themselves, or (2) the failure of EPA to adequately and transparently communicate the major limitations of the assays, including with respect to their current limited ability to capture the full range of endocrine-related activity. This is a serious omission in the EHHC draft report, especially given the attention paid elsewhere in the report to the critical need to clearly explain limitations and uncertainties associated with the assays – something EPA failed to do in this case: In its [dispersant report](#), EPA stated without qualification that "integrating over all of the ER and AR results these data do not indicate that any of the eight dispersants display biologically significant endocrine activity via the androgen or estrogen signaling pathways." And in [associated press and other materials](#), EPA asserted without qualification that "EPA's results indicated that none of the eight dispersants tested, including the product in use in the Gulf, displayed biologically significant endocrine disrupting activity."

As one of the few examples to date of “real-world application” of ToxCast, EHC’s discussion of it needs to acknowledge these shortcomings as well as benefits. EPA’s poor communication of the results of such assays in a manner that can be interpreted as effectively exonerating (in this case example) or, conversely, implicating chemicals vis-à-vis whether they possess or do not possess a specific biological activity, should be seen as a cautionary tale. It warrants more nuanced consideration by EHC in its draft report.

This example, also suggests the need for EPA and the associated research and regulatory communities to develop criteria or decision rules governing appropriate use of ToxCast data for different contexts (including use in crisis situations) and appropriate communication of related limitations and uncertainties.

Data Use Guidance

EDF strongly supports the SAB EHC recommendation that EPA develop a Data Use Guidance (DUG) document for every endpoint examined in the Tox21 and ToxCast batteries of assays (draft report, pages 11-12). Providing information on each of the suggested 12 data elements for each endpoint, in a standardized and readily accessible form as proposed in the draft report, would greatly assist and enhance the ability of both EPA staff and external stakeholders to interpret and constructively engage with the agency regarding the quality, reliability, and appropriate application of the data generated from CompTox high-throughput (HT) *in vitro* assays.

Much of the suggested information to be provided through a DUG document is currently not available to the public and impairs the ability of outside groups and individuals—whether in academia, public interest groups, or industry—to effectively provide feedback to the agency on the potential uses, strengths and limitations, etc., of the various assays.

While perhaps obvious, it is important to note that there may be more than one assay associated with a particular endpoint, and potentially more than one endpoint associated with a given assay. As the EHC draft report is currently drafted, this possibility isn’t made clear. In addition to the 12 data elements listed, we recommend adding:

- as a corollary to the rate of false positives/false negatives, some measure of the relative reliability of an assay in comparison to other assays measuring the same endpoint;
- a description of the assay design;
- the company name and contact information of the assay developer; and
- an indication as to the nature and extent of proprietary constraints associated with the assay.

We are aware of and appreciate the efforts already undertaken by the CompTox program to create databases such as ToxCastDB, which includes a *list* of assay developers (see: <http://1.usa.gov/SIQwvF>) and annotates the gene targets included in the HT *in vitro* assays (see <http://1.usa.gov/QUxVUK>). But we recommend the agency go further and develop online interfaces along the lines of what is recommended in the EHC draft report’s discussion of DUG. We would also encourage that EPA work with outside stakeholders in determining the data elements and design of such an interface.

Coverage of the “Biological Response Landscape”

EDF shares the EHHC’s view stated in the draft report that, “Given that pathways of toxicity are poorly understood, current *in vitro* assays cannot be seen as comprehensive in their scope.” This is not to imply that the CompTox assays are not useful or relevant, but that this limitation needs to be made especially clear in all agency communications regarding the limitations of CompTox assays, including to the broader public. Both qualitative and quantitative means of assessing and communicating the extent to which available assays cover what has been called the “biological response landscape” would appear to be needed, and EHHC should flag this as a priority warranting EPA’s attention.

Equally important, the current limited understanding of toxicity pathways underscores the need for constant communication and engagement between the agency and outside researchers whose work involves identifying and characterizing adverse outcome pathways, so that the battery of CompTox assays continuously improves and reflects and keeps pace with evolving scientific understandings of toxicity.

EHHC should encourage EPA to do as much outreach as possible to solicit advice from outside experts regarding the important targets and endpoints that should be represented in the CompTox assays. EDF appreciates efforts that have been made by the Tox21 program in this regard (see “Collaborate with Tox21” section here <http://1.usa.gov/O1qQ4l>), but we believe efforts in this arena need to be a priority and broadened wherever possible.

Effective Communication to Stakeholders (JM)

EDF acknowledges and appreciates efforts EPA has put into developing the CompTox website, which provides descriptions and factsheets regarding research occurring within the individual CompTox projects (e.g., ToxCast, v-liver, ExpoCast, etc.). The posted information is valuable and informative and we encourage EPA to continue to provide lay-friendly materials that explain research within the CompTox program as well as descriptions of current agency thinking on how new data will be integrated into chemical risk assessments and used to meet programmatic needs (e.g., prioritization, improving chemical categories, etc.). We also support EPA’s Communities of Practice webinar series and see it as an effective means of presenting—internally and externally—agency research and CompTox partners’ research.

Despite these dissemination efforts, EDF respectfully disagrees with the EHHC report’s characterization of EPA “doing a very thorough job of communicating to stakeholders” (Draft Report, page 16). Both the website and the Communities of Practice webinar series are one-way communication vehicles. Neither of these are appropriate forums for constructive dialogue with the range of interested or affected communities, notably the public interest community, which encompasses a wide spectrum of individual from scientists to chemicals policy and regulatory advocates to environmental justice communities. These individuals will certainly have varying levels of technical expertise, but many have considerable experience with and a valuable perspective on the practice of risk assessment at EPA, and certainly have an important perspective to share with regard to appropriateness and sufficiency of data for use in different decision-making contexts, as well as associated communications needs.

EHC should urge EPA to expand its stakeholder engagement efforts so as to provide opportunities for meaningful and sustained two-way exchange of information and perspective.

Avoiding False Negatives

EDF strongly supports the EHC draft report's discussion (page 8) of precautions needed even in applying ToxCast data to the task of chemical prioritization. It appropriately flags the relatively high rate of false negatives for certain categories of assays, and the need to avoid overconfidence leading to premature setting-aside of chemicals in a screening exercise. Another critical need flagged by EHC is to develop a much better understanding of the extent to which a set of assays that might be employed for screening purposes adequately cover the "biological response landscape" that we discussed above. Without sufficient coverage, it may well be that more confidence can be placed in positive "hits" identified in a screening than in negative "misses," especially because such "hits" are likely to undergo more extensive investigation while the tendency may be to indefinitely set aside the "misses."

We agree with the EHC's recommendations that addressing these concerns will require that, for the foreseeable future, ToxCast data will need to be integrated with other available information, including other toxicity information as well as exposure information (the poor quality of which is a critical need to be addressed as well, including through regulatory and legislative reforms). EPA efforts to link and map individual assay outputs to adverse outcome pathways (AOPs) will also be critical if ToxCast data are to be viewed with confidence as truly predictive of either presence or absence of an adverse effect.

Respectfully,



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