



THE HUMANE SOCIETY
OF THE UNITED STATES

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Dear Dr. Nugent:

I appreciate the opportunity to submit comments to the Scientific Advisory Board (SAB) regarding the Draft SAB Report on the Use of CompTox To Advance Risk Assessment (78 FR 9689 Feb 11, 2013) on behalf of The Humane Society of the United States and our more than 11 million members who are concerned about the use of animals and support the incorporation of non-animal approaches in chemical evaluation.

We fully support EPA's activities in the area of Computational Toxicology and its efforts to actualize the vision outlined in the 2007 National Research Council Report "Toxicity Testing for the 21st Century: a vision and a strategy." This Draft SAB Report provides critical advice to EPA for improving this process, and our brief comments are meant to support and augment suggestions made by the SAB.

Study Question 1: Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA's programmatic needs?

Page 10, paragraph 1 (lines 1 – 7): While it is true that the concept and implementation of Adverse Outcome Pathways (AOPs) is in its infancy, it might be appropriate to acknowledge EPA's efforts in development of AOPs, including those for fish reproductive toxicity and thyroid hormone pathways.¹²

¹ Ankley et al. 2010. Adverse Outcome Pathways: A Conceptual Framework to Support Ecotoxicology Research and Risk Assessment. *Environ.Toxicol.Chem.* 29 (3): 730–741.

² Crofton, K. US EPA. 2012. The Role of Thyroid Hormones in Neurodevelopment: Using the Adverse Action Pathway Concept to Focused Research Strategies. Presented at DC area SOT, May 2012.

Thus far the most impressive attempt to incorporate CompTox information has been with regard to the Endocrine Disruptor Screening Program (EDSP).³ While it may be premature to describe in detail, and, depending on the timing of submission of this Report, the summary recommendations of the January SAP may not be available, it is worth mentioning this project and the work leading up to the January meeting, including the Estrogen Receptor expert decision framework.^{4,5} And while this impressive effort has indeed required extensive collaboration between EPA programs, it also highlighted the importance of communication throughout implementation of CompTox methods in program activities: specifically in this case, the high-throughput data would have been more appropriate for comparison with the ER expert system if different dose-ranges and a different spectrum of chemicals had been tested.

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?

Page 6, paragraph 1 and 2 (lines 1 – 19): The suitability of CompTox data for application to hazard or risk assessment or eventual replacement of *in vivo* testing will depend not only on the level of decisions to be made, but also on the quality of the data, the thoroughness of the AOPs, and how well the assays query those pathways. While the Report notes that EPA is making progress in characterizing CompTox assays in terms of specificity, sensitivity and reliability – such characterization should be a precursor to testing, and should in fact be the first step in the strategy to implement *in vitro* assays (high-throughput or not). Testing a large number of uncharacterized and chemically diverse substances with uncharacterized assays will lead to the generation of an enormous amount of data of questionable value. The importance of the recommendation to develop the theoretical framework in the form of pathways cannot be overstated. It is important also to recognize that different uses of AOPs require different levels of completeness (a relatively sparsely described pathway can be useful for prioritization or initial screening, whereas a pathway with more well established, ideally quantities links between key events is more appropriate for hazard and risk assessment).

Page 9, lines 1 – 3: Note that this “additional concern” is actually addressable using human cell and tissue-based assays and appropriate adverse outcome pathways in a way that it is not using traditional animal testing.

Page 10, lines 14 – 27: Completion of the recommended list of key aspects to include in the Data Use Guideline would greatly enhance the utility of CompTox assays; however, caution should be applied to item 11: if comparing to adverse outcomes in standard animal tests the caveat that this may not be appropriate or relevant to human health must be kept in mind. In the case of estrogenic activity, a weight-of-evidence approach has been used to determine the activity a set of standard chemicals for use in characterizing assays that measure estrogenic activity.⁴

³ FIFRA SAP Meeting: Prioritizing the Universe of Endocrine Disruptor Screening Program (EDSP) Chemicals Using Computational Toxicology Tools. January 29 – Feb 1, 2013. Docket ID EPA-HQ-OPP-2012-0818.

⁴ US EPA. 2012. Prioritization of the Endocrine Disruptor Screening Program Universe of Chemicals for an Estrogen Receptor Adverse Outcome Pathway Using Computational Toxicology Tools. Endocrine Disruptor Screening Program. Document Number: EPA-HQ-OPP-2012-0818-0017.

⁵ FIFRA SAP. 2009. An Effects-based Expert System to Predict Estrogen Receptor Binding 2186 Affinity for Food Use Inert Ingredients and Antimicrobial Pesticides: Application in a 2187 Prioritization Scheme for Endocrine Disruptor Screening, Meeting Materials. Document number: EPA-HQ-OPP-2009-0322.

Page 12, line 30: This concept is not limited to “estrogenic” chemicals – was the use of “estrogenic” meant to be an example?

Page 13, lines 7 – 11: Relating CompTox outputs to human biology may be challenging, but is possible, and critical for moving toxicology from an observational to a predictive science (with respect to human health).

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

Page 14, lines 6 – 7: It should be noted that this is not specific to the use of CompTox data but is a general risk assessment issue.

Page 14, lines 16 – 18. The OECD is developing guidance for the development of AOPs.⁶ EPA is participating in these discussions and it would be good to support the implementation of such harmonized guidance here. It is also important to develop guidance for the use of AOPs – including the different levels of confidence and proof necessary for different uses (as mentioned above).

Study Question 4: How should the use of the CompTox program be effectively communicated to stakeholders? How can the communication be enhanced?

Page 17, paragraph 1 (lines 1 – 11): EPA’s Office of Pesticide Programs is also communicating its incorporation of “Tox21” approaches through its Pesticide Program Dialogue Committee, which has organized several FACAs to cover various aspects of Tox21; another covering AOPs is planned for July.⁷

Page 17, lines 19 – 20: The ToxRefDB could be made significantly more user-friendly for non-experts.

Page 17, lines 21 – 24: Completion of the list of key aspects suggested for inclusion in the Data Use Guideline on page 10 would begin to address this communication concern.

Page 18, lines 6 – 7: Demonstration of the relevance of CompTox and the AOP approach to human health effects is a very important point: for example, not only can biomonitoring inform AOPs, but AOPs can inform the identification of relevant biomarkers.

Page 18, lines 14 – 15: EPA could also continue to collaborate with NGOs who are interested in implementation of CompTox and AOP approaches, for example The Humane Society of the United States coordinates the Human Toxicology Project Consortium that sponsors activities that further pathway-based approaches, and the Environmental Defense Fund has recently developed a web-page and held a workshop that explores these issues.

Other Issues:

⁶ OECD. 2012. Proposal for a Template and Guidance on Developing and Assessing the Completeness of Adverse Outcome Pathways. Available at:

⁷ For example, see: <http://www.epa.gov/pesticides/science/testing-assessment.html>

Page 19, line 28 – Page 20 line 8: EPA Office of Pollution Prevention and Toxics has a long history of using incomplete information in risk assessment, including extensive use of QSAR and read-across. The potential use of CompTox information in furthering the accuracy and coverage of chemical class groupings should not be overlooked.

It would be good to include in this list a plan for incorporation of human information in AOP development. Such a plan would include not only collaborations with epidemiologists but with FDA and pharmaceutical companies that hold a wealth of human toxicological information.