Crystallographic Analysis and Mimicking of Estradiol Binding: Interpretation and Speculation

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1289/ehp.1307987</td>
</tr>
<tr>
<td>Accessed</td>
<td>June 19, 2017 7:18:26 PM EDT</td>
</tr>
<tr>
<td>Citable Link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:12185816">http://nrs.harvard.edu/urn-3:HUL.InstRepos:12185816</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>

(Article begins on next page)
Crystallographic Analysis and Mimicking of Estradiol Binding: Interpretation and Speculation

http://dx.doi.org/10.1289/ehp.1307987

In their recent article, Gosavi et al. (2013) presented the results of a crystallographic analysis of the binding of tetrabromobisphenol A (TBBPA) and 3-hydroxy-2,2’,4,4’-tetrabromodiphenyl ether (3-OH-BDE-47) to estrogen sulfotransferase (SULT1E1). The authors demonstrated that the tested molecules fit into the same binding pocket as estradiol. However, although the study’s methodology and interpretation of the crystallographic analysis provide insight into how binding might occur in isolated and in vitro systems, they did not provide evidence that the tested molecules would initiate any biological activity with the relevant estrogen receptors (ERs) or proteins in a human body. For example, the ability of TBBPA to interact with the ER and estrogen-related receptors has been evaluated in recombinant yeast strains, mammalian cell–based assays, and tests developed by the Organisation for Economic Co-operation and Development (Lee et al. 2012; Nakagawa et al. 2007; Ogunbayo et al. 2007, 2008; Reistad et al. 2005, 2007; Strack et al. 2007). Those studies found that TBBPA either did not interact with ERs or that it acted as a weak ER agonist/antagonist with a potency orders of magnitude below that of natural ER ligands. In addition, the data presented by Gosavi et al. (2013) did not include the use of controls to validate the methods. The use of both positive controls (such as diethylstilbestrol and ethinyl estradiol) and a negative control (such as testosterone) would provide validation of the analysis and allow for the quantification and comparison of the two test substances in relation to the binding potentials of the controls.

The authors also speculated about the possible additivity of the various brominated flame retardants and their metabolites and suggested that low-dose exposure to multiple low-affinity binding compounds may result in endocrine disruption. However, none of the data presented directly addressed this point.

It is highly complex, not well understood, and speculative to extrapolate data on inhibition of enzymes such as SULT1E1 in in vitro assay systems to endocrine-system modulation of selective gene expression, receptor binding, and activation and the production of adverse effects that would characterize endocrine disruption in vivo by additivity of different chemicals competing on the same receptors. Only through a more complete understanding of target tissue dosimetry, potency of interaction of the chemical of interest with the macromolecule of interest (e.g., SULT1E1), and subsequent events can one address the likelihood of in vivo additivity.

This work was supported by the North American Flame Retardant Alliance (NAFRA) Panel of the American Chemistry Council, which previously provided funding for travel expenses and honoraria to the authors as members of NAFRA’s Science Advisory Council. The researchers’ scientific conclusions and professional judgments were not subject to the funder’s control.

Thomas G. Osimitz,1 Michael L. Dourson,2 A. Wallace Hayes,3 and Sam Kacew4

1Science Strategies, Charlottesville, Virginia, USA; 2Toxicology Excellence for Risk Assessment (TERA), Cincinnati, Ohio, USA; 3Harvard School of Public Health, Boston, Massachusetts, USA; 4Cauthlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

E-mail: tom@sciencestrategies.com

REFERENCES


REFERENCES


Correspondence
