Erschienen in: Toxicological Sciences ; 149 (2016), 2. - S. 273-274
https://dx.doi.org/10.1093/toxsci/kfv256

Response to "The Path Forward on Endocrine Disruptors Requires Focus"

To the Editor,

Dear Dr Miller, thank you for giving us the opportunity to respond to the letter to the editor by Zoeller *et al.* referring to our publication titled "Principles of pharmacology and toxicol ogy also govern effects of chemicals on the endocrine system," published in *Toxicol Sci.* 2015 Jul;146(1):11 5 as Forum article.

With the Forum contribution, we wanted to start a discus sion in toxicology and pharmacology on issues with chemicals that have the potential to interfere with the endocrine system, often termed "endocrine disruptors" (EDs). A discussion is needed due to several claims made in this area that challenge basic concepts of our field.

Unfortunately, the letter by Zoeller *et al.* provides only gen eral statements on some of the issues raised by us and does not elaborate science based arguments to challenge our conclusions.

We would like to respond to some of the points in the letter that may be interpreted as critical of our conclusions:

- In the EU, proposals made to classify a chemical as ED range from the use of interactions with endocrine pathways to specific adverse endpoints from appropriate animal experiments. Thus, our claim is not "erroneous." If Zoeller *et al.* accept that adverse effects from animal studies supplemented by mode of action data are required as a basis to classify as an ED, this is an impor tant step toward an agreement on some of the issues. However, under these circumstances, a specific classification for "endo crine disruption" is not required. Chemicals that cause adverse effects on reproduction or development, the main areas of con cern in the ED discussion, will be classified regarding these end points and additional classification is unnecessary.
- We were not discussing legal mandates and are aware that, un fortunately, potency is often not considered in hazard based reg ulations. Hazard assessment only addresses the ability of a chemical to induce specific effects regardless of the administered dose. Risk characterization incorporates information on hazard, potency, and human exposures and is one of the main tasks of toxicology. Classification for specific toxicities does not abolish the need for risk characterization. Exposures of humans to clas sified chemicals, whether of natural or synthetic origin, con tinue. Therefore, risk characterization considering potency remains most important even in the context of hazard based classification. Moreover, humans are exposed to EDs from many sources not subjected to classification such as pharmaceuticals and natural chemicals from diet and environmental sources. Therefore, the points raised by Zoeller *et al.* have no validity and do not question our conclusions.
- Many publications in the debate claim that interactions of chemi cals with the endocrine system require special considerations not applicable to other toxicity endpoints. We conclude that interac tions of chemicals with the endocrine system are one of many modes of action that may result in adverse effects. These interac tions follow basic laws of chemistry and physics. Complexities with EDs are not different from those in other areas of toxicology and pharmacology. We welcome the statement that adverse effects are apparently not equivalent to "receptor activation." However, again, our conclusions remain unchallenged.
- Regarding the comments on potency of DES made by Zoeller *et al.*, it is important to recognize that potency and safety are two differ ent issues. We are of the opinion that DES can serve as a basis for conclusions on other chemicals due to its high potency and a large database on adverse effects including human data. Despite high potency, the doses of DES resulting in adverse effects were huge when compared with doses of environmental chemicals that hu mans are potentially exposed to. Moreover, the environmental chemicals discussed are many orders of magnitude less potent than DES. The argument by Zoeller *et al.* that human exposures to environmental chemicals are less well documented as that to DES is neither relevant nor convincing. Exposures of human popula tions to many environmental chemicals of concern, including EDs, are well defined based on exposure modeling and biomonitoring (Calafat, 2012; Karjalainen *et al.*, 2012; Kolossa Gehring *et al.*, 2012; CHAP, 2014; Den Hond *et al.*, 2015; EFSA, 2015). Thus, the statement of inconclusive exposure information on environmental chemi cals is somewhat surprising.
- We are well aware that absence of an effect cannot be experi mentally demonstrated. Therefore, conclusions on the presence or absence of thresholds have to be made based on theoretical considerations integrating basic knowledge of toxicology and pharmacology. Our conclusions regarding thresholds for EDs again are not challenged by Zoeller *et al.*
- Our Forum article does not discuss implications of science. At least, Zoeller *et al.* agree on some basic concepts that are well developed in our field and supported by a vast amount of scien tific information. However, besides the qualitative features ac knowledged, quantitative aspects such as potency are essential for understanding toxicology, pharmacology and risk characteri zation and potency is relevant in several areas of classification such as specific target organ toxicity.
- The issues with the suspected conflict of interest (CoI) raised by Zoeller *et al.* and others in discussions on chemical safety seem to be mainly used in attempts to discredit scientific argumenta tion not in line with certain concepts. This information was in cluded in the CoI forms submitted to the journal. The Forum article represents the scientific view of the authors based on their widely recognized professional experience. In the context of CoI, it is of interest that Zoeller and colleagues received fund ing in the range of millions of Euros for ED related research from the EC (EC Funding, 2015) and NIEHS/NIH (NIEHS/NIH Funding, 2015).

SUPPLEMENTARY DATA

Supplementary data are available online at http://toxsci.oxfordjournals.org/.

REFERENCES

For References, see Supplementary Data.

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There has been considerable debate and disagreement in the field of endocrine disruption, especially as it related to toxicological and regulatory principles. While the journal supports the open exchange of ideas, such as these letters, it is important to emphasize that the debate will not be resolved by words, but rather with data. Both sides are encouraged to conduct studies that lead to the crucial experiment (experimentum crucis a concept first introduced by Francis Bacon in his Novus Organum, and promulgated and expanded by Karl Popper). In the crucial experiment data are generated that definitively refute one of the two rival hypotheses. Both sides must also be cognizant of their own biases and strive to design experiments that minimize their impact, such that the debate can be settled in the laboratory. Moreover, given the confidence of both sides, neither should be afraid to conduct studies that hold the potential to refute their own hypotheses.