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Editorial

Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles

Note: The following text was prepared in response to the present discussion regarding the European Commission's recommendations on the so-called "endocrine disrupting chemicals" and is supported by the Editor of Regulatory Toxicology and Pharmacology. It also refers to a letter sent in response to these recommendations and that was undersigned by a group of toxicologists. This or a similar editorial will appear in other toxicology and pharmacology journals.

We, the undersigned editors of prominent journals of pharmacology and toxicology, are drawing your attention to the imminent decisions by the European Commission to enforce a regulatory framework for so-called endocrine disrupting chemicals (EDCs). The currently drafted framework is based on virtually complete ignorance of all well-established and taught principles of pharmacology and toxicology, of opinions raised by the European Commission's own competent expert authority (European Food Safety Authority (EFSA, 2013), and of critical statements made by member countries, while avoiding asking for support from the European Commission's own scientific expert committees.

As a statement, and as emphasized by others before, "endocrine disruption" is not a toxicologically defined endpoint but a mode-of-action that may or may not result in adverse effects. In itself, the mode-of-action concept implies the necessary existence of a threshold as experimentally proven for numerous other non-genotoxic agents including EDC's. Moreover, endocrine systems play a fundamental role in the physiological response to changes in the environment with the aim of keeping an organism's biology within the homeostatic space. It is the task of toxicologists to make the distinction between those effects that are within this adaptive range and effects that go beyond the boundaries of this space and thus can be called adverse. Such adverse effects can be observed in adequately designed and performed toxicity studies.

While we agree that a concern for possible EDCs is sensible and important, we also think that the identification and regulation of such substances should depend on a) the definition of adverse effects that are relevant to whole human or animal organisms and not to isolated test systems of unknown homeostatic significance, and b) on a characterization of real-life potency and therefore of thresholds of concern.

In contrast, the currently drafted EU framework for EDCs foresees *a priori* regulation of agents that may show presumably endocrine-mediated effects in some experimental system (*in vitro, in silico, in vivo…*), and under the *a priori* default assumption of no thresholds. This approach is based on a very small number of publications (Sheehan, 2006;Vandenberg et al., 2012; Zoeller et al., 2012; Birnbaum, 2013) that lack the required scientific robustness needed for such an important piece of legislation that is sweeping in nature, will set an unforeseen precedence, and finally will have profound ramifications for everyone's livelihood. Furthermore, the regulatory draft specifically states that the identification of an endocrine disruptor relies "*on the*" *demonstration of an* ***adverse effect*** *for which there is convincing evidence of a biologically plausible causal link to an endocrine disrupting mode of action and for which disruption of the endocrine system is not a secondary consequence of other non endocrine-mediated systemic toxicity.* ***Relevance of the data to humans should be assumed in the absence of appropriate data demonstrating non-relevance***".

As all scientists should know, it is biologically and statistically impossible to demonstrate "*absence of effect*" and thus "*absence of relevance*". The mere statement demonstrates the lack of attention paid by the European Commission to the weight of scientific evidence that clearly demonstrates the presence of a threshold for non-genotoxic compounds including EDCs (Rhomberg et al., 2011; Rhomberg and Goodman, 2012; Borgert et al., 2012; Piersma et al., 2011; Boobis et al., 2009), as well as to the scientific detail with regard to the physiological and statistical implausibility of the approach taken. In fact, any scientist familiar with the overwhelming biochemical complexity of life understands that the healthy homeostasis of an organism results from an orchestrated network of myriad thresholds for every component substance.

On this account, a nucleus of scientists sent an open letter on June 18, 2013[1] to Prof. Anne Glover, Chief Scientific Advisor to the President of the European Commission Manuel Barroso[2], pointing out the major deficiencies of the drafted EU framework, and the worrisome ramifications this draft could have for science, the economy, and human welfare the world over.

Although some readers may shrug and think this is not important and not their problem, it soon could be. Regulations that profoundly affect human activities, that legally impose significant fines and even detention, should not be based on irrelevant tests forced to be regarded as relevant by administrative dictates, and on arbitrary default assumptions of no thresholds. Such standards would be contrary not only to science, but to the very principles of

[1] Open Letter to Prof. Anne Glover (to be included in each Journals own format) of June 18, 2013

[2] http://ec.europa.eu/commission_2010–2014/president/chief-scientific-adviser/

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an enlightened governance and social contract. Not only scientists but society itself would pay dearly if unscientific approaches were to undermine our everyday practice of science, and the stringency of data analysis and evaluation developed by scientific thinking over the past centuries. In the present instance, the very credibility of thorough and robust teaching, research, and scientific analysis is questioned. This calls for action, and as beneficiaries of public support it is the utmost responsibility of us scientists to resist and counteract any efforts that undermine the core of science and its continuing promise for the betterment of the human condition and of the planet.

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RE: Draft regulation on endocrine active chemicals June 18, 2013

Dear Prof. Glover.

We, the undersigned are writing to draw your attention to imminent decisions by the European Commission to set a regulatory framework for so-called endocrine disrupting chemicals. We are concerned that the approach proposed could rewrite well-accepted scientific and regulatory principles in the areas of toxicology and ecotoxicology without adequate scientific evidence justifying such a departure from existing practices.

First of all, we want to emphasize that "endocrine disruption" is not a toxicological endpoint, but one of many mechanisms which may cause adverse effects. In addition, we recognise that such a policy initiative is highly technical and complex and requires an understanding of the modes of action for endocrine disruption and their significance. It also implies the in-depth involvement not only of toxicological disciplines but also of environmental