

## Open letter to the European commission: scientifically unfounded precaution drives European commission's recommendations on EDC regulation, while defying common sense, well-established science, and risk assessment principles

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Received: 6 August 2013 / Accepted: 6 August 2013 / Published online: 27 August 2013  
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We, the undersigned editors of 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).<sup>1</sup> 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 end point 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 EDCs. Moreover, endocrine systems play a fundamental role in the physiological response to changes in the environment with the aim of keeping an organism's

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<sup>1</sup> This letter was provided by Prof. Daniel R. Dietrich. A similar text has been published in ALTEX. 30, 3/13, 381–385 and in Chemico Biological Interactions.

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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, and 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 (see footnote 1) to Prof. Anne Glover, Chief Scientific Advisor to the President of the European Commission Manuel Barroso, 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 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 our 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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