Comment

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

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, 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.

[1] Open Letter to Prof. Anne Glover, see below.

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

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 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 sciences and thus requires scientific input from experts in this area. The undersigned are concerned that the Commission's scientific committees have so far not been consulted by the Commission when drafting such regulations. What is even more disturbing is that, where a scientific advisory body such as EFSA has been consulted, critical elements of this body's opinion are ignored. For example, in assessment of chemicals with endocrine activity, EFSA supported a substance specific risk assessment approach integrating exposure and adverse effects instead of developing horizontal criteria for defining whether a substance is an "endocrine disruptor". Development of horizontal lists ignores the long-standing principle that an assessment of a substance should be based on data obtained from toxicity testing on this specific substance and derived information on potency.

If the Commission will adopt a policy stating that it is impossible to define a safe limit or threshold for a substance with classified as endocrine disruptor, this would reverse current scientific and regulatory practices and, more importantly, ignore broadly developed and accepted scientific development and accepted knowledge regarding thresholds of adversity. Moreover, the latter approach may not only apply to potential EDCs but rather would apply to all chemical substances and thus nullify decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and well-established and widely proven procedures in hazard and risk assessment.

It also appears that the Commission will propose that identification of an *in vitro* effect without a causal relationship to adversity in an intact organism may be sufficient to classify a substance as an "endocrine disruptor". This would not only represent a rewriting of the rules and accepted practices of toxicology, which rely on well-defined adverse effects observed in adequately performed studies, but also would be contrary to all accumulated physiological understanding.

This leaves us concerned that there is neither a scientific basis nor broad support by scientists established in risk assessment behind the approach of setting horizontal criteria and the lists of confirmed and suspected "endocrine disruptors".

We have noted your important interventions on the need for scientific evidence to be at the heart of EU policy and are therefore writing to urge your review of the emerging policy to ensure that the opinion of relevant scientific committees and member states authorities are taken into account.

The following individuals are supporting this initiative:

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