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Editorial

Low dose effects and non-monotonic dose responses for endocrine active chemicals: Science to practice workshop: Workshop summary ☆

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HIGHLIGHTS

- Report of workshop on low dose and non-monotonic effects of endocrine disruptors.
- Need for research on low dose effects and non-monotonic dose responses to EDCs.
- No consensus on importance of non-monotonic responses to risk assessment.
- Changes needed to risk assessments to accommodate EDC effects.
- More workshops and improved communication between relevant parties.

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ABSTRACT

A workshop was held in Berlin September 12–14th 2012 to assess the state of the science of the data supporting low dose effects and non-monotonic dose responses (“low dose hypothesis”) for chemicals with endocrine activity (endocrine disrupting chemicals or EDCs). This workshop consisted of lectures to present the current state of the science of EDC action and also the risk assessment process. These lectures were followed by breakout sessions to integrate scientists from various backgrounds to discuss in an open and unbiased manner the data supporting the “low dose hypothesis”. While no consensus was reached the robust discussions were helpful to inform both basic scientists and risk assessors on all the issues. There were a number of important ideas developed to help continue the discussion and improve communication over the next few years.

1. Introduction

There are continuing discussions in Europe and the United States to identify and develop the best methods to translate scientific findings to human health risk assessment. Risk assessment processes, used by regulatory agencies around the world, have been developed based on the principles of toxicology where it is generally assumed that the response of an organism to a toxicant increases with increasing level and duration of exposure (known as a monotonic dose response). Moreover for many chemicals a

Abbreviations: ANSES, French Agency for Food, Environmental and Occupational Health & Safety; BfR, Bundesinstitut für Risikobewertung, German Federal Institute for Risk Assessment; BPA, bisphenol A; EAC, endocrine active compound; EDC, endocrine disrupting chemical; EFSA, European Food Safety Authority; EPA, US Environmental Protection Agency; FDA, US Food and Drug Administration; GLP, Good Laboratory Practices; NGO, non-governmental organization; NIEHS, National Institutes of Environmental Health Sciences; NMDR, non-monotonic dose response; NMDRC, non-monotonic dose response curve; NOAEL, no observed adverse effect level; NTP, US National Toxicology Program; OECD, Organization for Economic Cooperation and Development.

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threshold approach is applied which assumes that there is no adverse effect below a certain exposure level. However there is a class of toxicants, endocrine disrupting chemicals (EDCs), for which there is evidence that they do not obey the principles of toxicology. Thus there are data showing effects at doses below apparent no effect levels in toxicity studies conducted according to current standard protocols. In addition, there are data showing that EDCs in some cases show non-monotonic dose responses (NMDRs). In these cases extrapolation from effects observed at high doses to human/environmental exposure levels may not be applicable. This so-called 'low dose hypothesis' challenges the traditional dose–response paradigm in toxicology and has been received with skepticism and caution by some scientists including many risk assessment practitioners. This topic is of special interest now because of the need to develop criteria for the identification and assessment of EDCs for application under various chemical control regulations in the European Union.

Over the past decade there have been several meetings addressing the "low dose" paradigm and its implications for risk assessment. The first formal assessment of the effects of chemicals at doses lower than those traditionally tested was held at the National Institute of Environmental Health Sciences (NIEHS) in collaboration with the US Environmental Protection Agency (EPA) in 2001 (Melnick et al., 2002). This scientific peer review of the data provided a "rigorous, open, transparent, and objective evaluation of the scientific evidence showing the presence or absence of low-dose effects of endocrine disrupting agents. . .". The workshop verified low dose effects for four EDCs (diethylstilbestrol, genistein, methoxyclor, and nonylphenol) and estradiol. The workshop report noted that "the findings of the panel indicate that the current testing paradigm used for assessments of reproductive and developmental toxicity should be revisited to see whether changes are needed regarding dose selection, animal-model selection, age when animals are evaluated, and the end points being measured following exposure to endocrine-active agents." In the following years there were reviews focused on "low dose" effects of bisphenol A (BPA) (vom Saal and Hughes, 2005; vom Saal et al., 2007) but no institutional attempts to analyze or examine the wider low dose literature.

In 2009, the German Federal Institute for Risk Assessment (BfR) held a workshop to establish assessment and decision criteria in human risk assessment for substances with potential endocrine disrupting properties focusing on active substances in plant protection products (Federal Institute for Risk Assessment (BfR), 2009). While this workshop was not focused on low dose effects, one point of discussion was whether effects occur at doses below those normally tested and if NMDRs exist for EDCs. Several recommendations were made:

1. Robust evidence of low dose effects of endocrine disrupting substances was considered to be important to be established before regulatory action might be taken. This evidence should include reproducibility of effects with the same compound in different studies.
2. Funding of international projects for the validation of methods and the development of new methodology to assess low dose effects as well as the development of a literature search on evidence for potential low dose effects of substances with endocrine disrupting properties were recommended.
3. The development of workshops on low dose issues was considered to be of major relevance.

Responding to BfR's meeting conclusions, a group of scientists developed a comprehensive review of the low dose and NMDR literature (Vandenberg et al., 2012). The authors concluded that low dose effects and NMDRs are to be expected for chemicals with endocrine disrupting activity and that these responses may occur frequently enough to be a concern. The review focused in part on the evidence of associations between current human exposures to various chemicals and specific diseases and in part on the data showing that these observations are supported by mechanistic *in vitro* and animal studies.

The Vandenberg et al. review stimulated the development of several workshops on the topic of low dose effects and NMDR. For instance, shortly after its publication The Pew Charitable Trusts held a workshop cosponsored by the journal *Nature* and the Institute of Food Technologists (see discussion of presentation by Tom Neltner, below). This multidisciplinary workshop included more than 60 leading scientists from government, academia, private sector and non-profit organizations from Europe and North America. The take away messages were that the public health implications of not being able to predict adverse health effects at doses relevant to human exposures are significant enough to warrant making the issue a priority, and that there is a need to improve the interdisciplinary communication of endocrinologists, toxicologists and risk assessors to better evaluate these implications.

At a European Commission conference on "Endocrine Disruptors: Current challenges in science and policy" in June 2012 with over 300 participants including policy makers, academics, regulatory risk assessors, industry and NGO groups there was a general recognition by most attendees that the current scientific evidence on risks of EDC to human health and the environment supported the need for action and that the knowledge and tools exist to identify substances with endocrine disrupting properties (http://ec.europa.eu/environment/endocrine/index_en.htm).

Shortly thereafter the European Food Safety Authority (EFSA) held a scientific colloquium with approximately 100 risk assessors and researchers to discuss low dose response in toxicology and risk assessment. Although the different views from different disciplines did not allow for a consensus some pertinent conclusions were noted in the report, (http://www.efsa.europa.eu/de/events/event/120614.htm):

1. An adequate and generally accepted definition of "low-dose effects" and of NMDRC is needed in order to facilitate discussions.
2. The amount of evidence needed to decide if in a particular case a "low-dose effect" or an NMDRC has to be taken into account should be defined.
3. Information may be obtained from *in vitro* and *in vivo* studies to determine biological plausibility.
4. Data on toxicokinetics, MoA and toxicodynamics will be helpful to understand the nature of the observations and to link internal dose estimates to occurrence of adverse effects.
5. The criteria for adversity should be the same for all types of effects.
6. It should be possible to derive Points of Departure (PoDs, NOAEL/BMDL) for risk assessment in studies with an adequate (extended range) number of dose levels, in particular in the lower dose range and even if there is a NMDR.
7. Information should be obtained from well-designed studies covering wide dose ranges with more than usual dose groups and sufficient animals per group.
8. Dose selection may be based on observations in epidemiological studies or on estimates of human exposure to cover the low exposure ranges more adequately.
9. It was noted that although the established principles of toxicological risk assessment would still be applicable, adaptation of these techniques might be needed.
10. It was generally considered that tiered approaches for hazard assessment guided by exposure estimates might not be adequate for substances for which an NMDRC is suspected.