Ecotoxicological Hazard and Risk Assessment of Endocrine Active Substances

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ABSTRACT
This collection of papers provides state-of-the-art science on a complex topic that has been challenging for scientists and regulators for a long time. The papers emanated from the Society of Environmental Toxicology and Chemistry (SETAC) Pellston Workshop “Environmental Hazard and Risk Assessment Approaches for Endocrine-Active Substances (EHRA).” Forty-eight international experts met in early February 2016 to discuss whether the environmental risks posed by endocrine-disrupting substances (EDS) can be reliably assessed. The primary conclusion of the workshop was that if data on environmental exposure, effects on sensitive species and life-stages, delayed effects, and effects at low concentrations are robust, initiating environmental risk assessment of EDS is scientifically sound and reliable. Integr Environ Assess Manag 2017;13:264–266. © 2016 The Authors. Integrated Environmental Assessment and Management published by Wiley Periodicals, Inc. on behalf of Society of Environmental Toxicology & Chemistry (SETAC)

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BACKGROUND
Over the past 20 y, concern over the impact of endocrine-disrupting substances (EDS) (WHO/IPCS 2002; WHO/UNEP 2012) has led individual countries and international governments and organizations, including Japan, the United States (US), the European Union (EU), and the Organisation for Economic Co-operation and Development (OECD), to initiate programs to assess impacts of endocrine-active substances (EAS) and EDS to wildlife (as well as human health) (Coady et al. this issue) (EAS are not necessarily proven EDS, but are substances known to interact directly with the endocrine system). Several jurisdictions have developed regulatory approaches, but these vary, partly because there has been little consensus on key scientific questions (Matthiessen et al. this issue). Some scientists believe that EDS can be reliably evaluated using risk assessment, whereas others do not believe this is sufficiently precautionary and propose to manage EDS on the basis of hazard characteristics alone (Endocrine Society 2009, 2015).

A key question is “How are regulators and policy makers to decide whether to select a hazard- or a risk-based approach for a given EDS under review?” Although some (inter)governmental guidance already is available on evaluating the (eco)toxicological properties of potential EAS or EDS (e.g., DK EPA 2011; USEPA 2011; OECD 2012), there has not been a scientific consensus on whether this information can be used, together with a characterization of exposure, to come to an assessment of risk. The 2016 SETAC Pellston Workshop “Environmental Hazard and Risk Assessment Approaches for Endocrine-Active Substances (EHRA)” and resulting papers address a clear need for objective advice, based on the current level of scientific understanding, to allow regulators and policy makers to make comprehensive, science-based decisions (Matthiessen et al. this issue).

OVERVIEW OF THE SPECIAL SERIES
Case studies on the following 6 chemicals (all of them EAS) were performed prior to the workshop:

• 17α-ethinyl estradiol,
• 17β-trenbolone,
• perchlorate,
• propiconazole,
• tributyltin, and
• vinclozolin.

The papers emanated from the expert discussions that were held at the workshop, with the case studies as the starting point. Each of the papers represents a consensus...
reached among the authors. The first paper discusses recommended approaches for the scientific evaluation of environmental hazards and risks of EAS, and the 4 companion papers each deal with a series of crosscutting issues that emerged from the evaluation of the case studies. It is unique to have all the key issues that make the evaluation of EAS and EDS such a highly debated topic discussed together in a special series.

The first paper, by Matthiessen et al. (this issue), “Recommended Approaches to the Scientific Evaluation of Environmental Hazards and Risks of Endocrine-Active Substances,” provides an overview and summary of the entire workshop, so it is the first place where readers should look for the workshop’s conclusions. The paper addresses a crucial and controversial issue in current ecotoxicology: Under what circumstances is it feasible to conduct environmental risk assessments of EDS? The conclusions are founded on the 6 case studies and are evidence based. Matthiessen et al. (this issue) provide explicit guidance for chemical risk assessors and refer readers to the other papers in the series for detailed information underpinning this guidance. The primary conclusion of this paper is that if data on environmental exposure, effects on relevant species and life-stages, delayed effects, and effects at low concentrations are robust, initiating environmental risk assessment of EDS is scientifically sound and sufficiently reliable.

A recent Learned Discourse in IEAM essentially began the data interpretation discussion by asking “Are all chemicals endocrine disruptors?” (Wheeler and Coady 2016). Mihaich et al. (this issue) deal in further depth with the need for reliable study design and data interpretation to distinguish between endocrine- and nonendocrine-specific responses in “Challenges in Assigning Endocrine Specific Modes of Action: Recommendations for Researchers and Regulators.” Mihaich et al. (this issue) identify and describe potentially confounding factors in assessing endocrine effects such as stress, parasites, husbandry, systemic or overt toxicity, and organ system toxicity resulting in secondary endocrine responses. Both in vitro and in vivo mechanistic and apical data for establishing biological plausibility of adverse effects are described and considered in an adverse outcome pathway (AOP) approach. This paper is expected to be of high value to scientists and regulatory authorities who interpret the responses from screens and tests to characterize the likelihood that an adverse outcome is endocrine mediated.

The third paper, by Parrott et al. (this issue), “Uncertainties in Biological Responses that Influence Hazard or Risk Approaches to the Regulation of Endocrine Active Substances,” aims to provide guidance on issues that have been fueling an intense scientific debate around the management of EDS. Examples of these issues include delayed effects, multigenerational effects, and nonmonotonic dose–response relationships (NMDRs) that require careful consideration when determining environmental hazards. A major step is taken in the scientific discussion of how to deal with the occurrence of nonmonotonic dose– or concentration–response relationships, which can be considered one of the limiting factors for a reliable risk assessment of EDS. Substantial data reviews are underway elsewhere to inform on their occurrence (Vandenberg et al. 2012; NRC 2014). However, evidence to date indicates they are more prevalent in vitro and in mechanistic data, and do not often translate into adverse apical endpoints that would be employed in risk assessment. The paper provides a proposal of how to evaluate NMDFRs in the context of endocrine hazard and risk assessment procedures. Provided that delayed, multigenerational, and NMDR effects are carefully considered, it is feasible to assess environmental endocrine hazards and derive robust apical endpoints for risk assessment procedures, which ensure a high level of environmental protection.

The fourth paper, by Coady et al. (this issue), “Current Limitations and Recommendations to Improve Testing for the Environmental Assessment of Endocrine-Active Substances,” 1) briefly describes current tests and testing frameworks for EAS, with an emphasis on nonmammalian assays; 2) identifies difficulties, shortcomings, and challenges associated with these assays; and 3) proposes a variety of “fixes,” ranging from short-term, relatively easy modifications to method developmental work that will require longer-term research. This is a novel paper in that no other publications to date have systematically and comprehensively attempted to address this important and complex issue. Efficient and defensible assays are critical for assessing the hazards and risks of EDS; the topic is therefore of substantial regulatory interest. This paper was co-authored by 14 internationally recognized experts representing all the stakeholders involved in the EDS issue, that is, regulators and risk assessors, scientists from industry, contract research organization representatives, and academic partners.

The fifth and final paper, by Marty et al. (this issue), “Population-Relevant Endpoints in the Evaluation of Endocrine-Active Substances (EAS) for Ecotoxicological Hazard and Risk Assessment,” 1) briefly describes the current status regarding ecotoxicological testing pertinent to population-relevant endpoints and to biomarkers used to inform on modes of action; 2) illustrates strengths and limitations of invertebrate, fish, amphibian, avian, and mammalian toxicity endpoints that may be collected to support ecotoxicological hazard and risk assessment of EDS; and 3) briefly describes areas of ongoing research and critical knowledge gaps hindering the understanding of population relevance. While other papers on AOP frameworks have discussed endpoints relevant for populations (Ankley et al. 2010; Groh et al. 2015), the focus of those papers is much narrower within the limits of the presented AOP. Marty et al. (this issue) discusses population relevance of endpoints across multiple taxa and modes of action using the case study chemicals evaluated at the workshop. Marty et al. has an authorship of 11 internationally recognized experts representing all the stakeholders in the EAS and/or EDS discussion.
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Data availability—Not applicable.

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