Introduction to Special Series on Endocrine Disruption: Chemical Testing, Risk Assessment Approaches and Implications; Guest Editor: Katherine Coady

Endocrine Disruption Chemical Testing; Risk Assessment Approaches and Implications
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ABSTRACT

This special series of six papers (this introductory paper and 5 other papers) is about the Focused Topic Meeting on Endocrine Disruption Chemical Testing; Risk Assessment Approaches and Implications (4 – 6 February, 2014, Raleigh, North Carolina). The workshop was composed of five sessions that each dealt with a specific topic. Broadly speaking the following themes were addressed: a) the status of the USEPA Endocrine Disruptor Screening Program, b) how data from how data from both EDSP-directed testing and other sources may be interpreted and applied in regulatory settings and c) approaches for moving beyond estrogen, androgen and thyroid pathways to address current challenges and expanding future approaches to EDC testing. The series of publications summarizes the knowledge presented and discussed at the Focused Topic Meeting and organizes the information by session. Where relevant, the summaries are enhanced beyond the original ideas of the presentations during the meeting. It is the intention of the Steering Committee that these publications will act not only as a record of the proceedings of the meeting, but also as a valuable resource.

Key words: endocrine disruption, risk and hazard assessment, estrogen, androgen, thyroid,

INTRODUCTION

Concern both from the public and the scientific community regarding potential endocrine disruption in humans and wildlife due to exposure to exogenous chemicals has led to the implementation of endocrine testing programs for regulatory purposes in certain regions of the world. The most developed approach to screening and testing to date has been implemented by the USEPA in the form of the Endocrine Disruption Screening Program (EDSP). In Europe chemical substances are also starting to be evaluated for potential endocrine activity/disruption. This is leading to a debate about whether or not endocrine disrupting chemicals (EDCs) can be safely assessed by taking the usual approach involving identification of intrinsic hazards, prediction of exposure and consequent calculation of risk or if hazard based assessments are more appropriate for EDCs. Substantial progress is also being made at the crossroads of the academic and regulatory world in developing new and alternate tests looking at a broader range of taxa, including invertebrate ED mechanistic assays (OECD, 2014). Many other potential types of vertebrate endocrine disrupting effects (*e.g.* corticosteroid effects) are being investigated for which screening assays still need to be developed and/or validated. Genomics and binding assays are in development, and the sequence of biological events describing how chemical damages in and around cells leads to adverse effects to various tissues, organs and individuals and subsequently populations is being examined in the Adverse Outcome Pathway (AOP) approach (Ankley et al, 2010). Against this background the SETAC North America Focused Topic Meeting (FTM) on Endocrine Disruption: Chemical Testing and Risk Assessment Approaches and Implications was held in Research Triangle Park, NC from 4 -6 February 2014. The meeting, which was co-chaired by Annegaaike Leopold (Wildlife International, EAG [1]Calidris Environment BV)

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and Holly Zahner (US Food and Drug Administration; FDA), was co-supported by more than 20 sponsors representing the private sector and government. More than 200 participants attended, representing industry, government, and academia from 10 countries which accounted for four of the five SETAC Geographic Units.

MEETING OVERVIEW

This meeting was a follow-up to a similar workshop held 24-25 October, 2012 in Brussels. The focus of that meeting was on research and regulatory issues for endocrine-disrupting chemicals (EDCs), with emphasis on the European perspective. The FTM provided an opportunity to explore EDC issues from a North American perspective which differs somewhat from other parts of the world. As such, an important emphasis of the meeting was the status of the USEPA Endocrine Disruptor Screening Program (EDSP).

Session one set the stage of the science and regulations around endocrine disrupting chemicals and identified the challenges that lie ahead. The current debate on whether suspected EDCs should be evaluated using a hazard-based or a risk-based approach was presented. Subsequently an introduction was given to the USEPA EDSP. The legislative mandate, risk-based nature, and multi-stake holder development process of the EDSP was described. The EDSP is applied to a defined universe of chemical substances and focuses on potential perturbations of the hypothalamic pituitary-gonadal and -thyroidal (HPG/T) axes. The debate currently going on in the EU on how to identify EDCs in a regulatory context using technical criteria was highlighted (European Commission, 2014), and the fact that it is a highly political subject in Europe was explained. Finally an EU- industry perspective was given on the repercussions of hazard versus risk-based approaches for EDCs. The regulatory situation in the EU still is evolving and it is not possible to predict exactly how EDC's will

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ultimately be addressed. It was emphasized that in the absence of a risk-based approach, hazard-based criteria need to be clear, fact based and consistent.[2]

The USEPA's EDSP was discussed in detail in Sessions two and three of the FTM. The EDSP is a two-tiered screening and testing program consisting of Tier 1 to determine potential endocrine activity and Tier 2 to confirm interaction and provide dose/response relationships of endocrine active chemicals via the hypothalamic-pituitary-gonadal axis and the hypothalamus-pituitary-thyroidal axis. Session two of the meeting was entitled: "The Endocrine Disruptor Screening Program: Where have we been: Data interpretation and Lessons learnt from Tier 1". In this session, the background and implementation of Tier 1 of the EDSP was discussed as well as the weight of evidence approach that is used in the evaluation of data. Tier 1 of the EDSP consists of 11 *in vitro* and *in vivo* assays designed to determine the presence of endocrine activity (*i.e.* interactions with the estrogen, androgen, steroidogenesis, and thyroid pathways) in both humans and wildlife. Session three of the Focused Topic Meeting was entitled: "The Endocrine Disruptor Screening Program: Where are we now: Tier 2 testing". In this session, Tier 2 EDSP test designs and interpretations were discussed. Tier 2 is composed of several long-term, and in most cases, multigenerational study designs conducted with both mammalian and environmental species. The Tier 2 studies are designed to involve more intensive testing of potentially active chemicals to determine if activity at Tier 1 translates into adverse effects, and collect data (e.g., dose-response relationships in full life-cycle tests) suitable for conducting formal risk assessments.

Session four of the meeting entitled: "Endocrine Disruption: Where are we with hazard and risk assessment?", addressed how data from both EDSP-directed testing and other sources may be interpreted and applied in regulatory settings and various chemical case

[2] Note from the Guest Editor: In the meantime the European Commission has, on the 15th of June, 2016, published two draft regulations setting out criteria to define enodocrine disruption.

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studies were presented. Processes for regulating EDCs are still under consideration or are still in the early stages of implementation. Various viewpoints exist globally as to whether chemicals with endocrine activity or meeting the definition of an ED should be managed via a hazard or risk-based framework. An outcome of session four was the drafting of a SETAC Outreach Statement that summarizes the overarching themes of a risk vs. hazard approach to regulating EDCs. A further outcome of session 4 was a proposal to organize a SETAC Pellston workshop™ that was to address the scientific questions surrounding the evaluation of chemicals with suspected or known endocrine activity. This would be done through the evaluation of some comprehensive case studies. The intention is for the workshop was to develop a guidance document which can be used by chemical companies and regulators when evaluating chemicals.[3]

In session five, entitled: "Where do we go from here: the future and challenges of EDC testing", approaches for moving beyond estrogen, androgen and thyroid pathways to address current challenges and expanding future approaches to EDC testing was discussed. This session focused on possibilities for expanding the working universe of endocrine assays in regard to the biological target/endocrine pathway (OECD, 2014) as well as incorporating new technologies and new assessment techniques.

Each of the five manuscripts in this special series is aimed at disseminating the knowledge presented and discussed in each of the five sessions of the meeting, and where

[3] Note from the Guest Editor: The SETAC Pellston Workshop™ 'Environmental Hazard and Risk Assessment Approaches for Endocrine-Active Substances (EHRA)' was held from 31st January to 5th February 2016 in Pensacola, Florida, USA. The primary aim of the workshop was to provide objective advice, based on current scientific understanding, to regulators and policy makers, whether in industry, government or academia; the aim being to make considered, informed decisions on whether to select an ecotoxicological hazard- or a risk-based approach for regulating a given endocrine-disrupting substance (EDS) under review. The workshop additionally considered recent developments in the identification of EDS. Case studies were undertaken on six endocrine active substances (EAS – not necessarily proven EDS), that are representative of a range of perturbations of endocrine system and considered to be data-rich in relevant information at multiple biological levels of organisation for one or more ecologically-relevant taxa. The workshop was successful in developing consensus. Scientific papers are being prepared for publication.

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relevant, enhanced beyond the original ideas of the presentations during the meeting. It is the intention of the Steering Committee that these manuscripts will serve not only as a record of the proceedings of the meeting, but also as a valuable resource.

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