

SETAC PELLSTON WORKSHOP®

# The take home message for you:



48 global experts with equal representation from government, academia, industry and consultancies from 9 countries came together and addressed the controversy at the heart of environmental safety assessment of endocrine disrupting substances (EDS)

Disclaimer: The views or statements expressed in this presentation do not necessarily represent the views of the organisations to which the participants are affiliated

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# SETAC Pellston Workshop<sup>®</sup> - Pensacola, FL, SETAC



### February 2016

48 participants

Academia: 27% Government: 27% Independent consultants: 25% Industry: 21%

North America (48%) Europe (42%) Japan (6%) Australia (4%)



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### What is SETAC?



**The Society of Environmental Toxicology and Chemistry (SETAC)** is a not-for-profit, global professional organization comprised of some 6,000 individual members and institutions from academia, business and government.

Founded in 1979 the SETAC provides a forum for scientists, managers and other professionals to exchange information on, study, analyze and solve environmental problems through multidisciplinary approaches and provide environmental education.

Science-based objectivity is a key founding principle.

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# Against the background of:



- Continuing scientific concern, public debate, and media attention over some EDS that are, or have been, present in the environment at concentrations harmful to wildlife populations,
- Some jurisdictions initiating regulatory approaches but
- Lack of consensus about the most appropriate approaches:
  - Some scientists believe that EDS can be reliably assessed using the standard risk assessment paradigm,
  - others do not believe this is sufficiently precautionary and propose risk management on the basis of hazard alone

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# The EHRA SETAC Pellston Workshop

was held with the aim of:

Trying to find scientific agreement on how best to assess the impact of endocrine active substances (EAS) on wildlife.

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- developing guidance, assisting regulators and policy makers in their decision making, thereby contributing to speeding up the global progress in controlling these chemicals.
- identifying areas of uncertainty and knowledge gaps.

# Workshop Approach: Cross-cutting Issues from Six Case Studies



 Case studies summaries are included as SI to Matthiessen et al. IEAM (In Review)



- Endocrine active
- Data rich (several taxa; multiple levels of biological organisation; well studied)
- Covering range of ED pathways of concern
- NOT full safety evaluations but mechanism for identifying issues

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# Workshop Approach: Six Case Study chemicals:



- Focus for literature search based on use,
  exposure routes, MOA of chemicals; for example:
  - EE2: focus on aquatic environment (initially 15000 papers -> 1371 and from there focus on fish – vertebrate taxon with estrogen receptors.
  - Perchlorate: from 6945 ref. -> app. 180. Focus on repro/dev tox studies because development is sensitive lifestage for thyroid insuficciency. Focus on population level effects; confirm similar MOA across species.

# Workshop Approach: Six Case Study chemicals:



- TBT: From 965 regulatory reports + open and grey literature to 160. Fish (45 ref.), molluscs (55) and other taxonomic groups (60).
- Trenbolone: 805 ref. -> 155. Hazard and risk assessment focused on aquatic vertebrate species, because MOA of TRB is steroid hormone activity + major route of exposure is via animal waste run-off into aquatic systems.





## **Case study approach:**



- Quality evaluation of relevant data: selected papers were:
- Toxicological Data Reliability Assessment Tool (ToxRTool -Schneider et al, 2009) and/or
- Klimisch criteria (Klimisch et al., 1997). Klimisch 1 and 2 used in the analysis, Klimisch score of 3 or 4 were not used.
- Histopath data addressed more specifically in parallel exercise and results incorporated in case study evaluations.

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## Cross Cutting Issues: Uncertainties in Biological Responses



### $\odot$ For example:

- effects manifest at a later life stage, following exposure during sensitive windows of life cycle, eg sex reversal in fish;
- multigenerational effects reflected in design of extended one-generation designs for fish and mammals;
- transgenerational effects
- non-monotonic dose relationships (NMDRs)/thresholds.

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### **Threshold issues and NMDR's encountered**

#### – EE2:

## in the case studies: \*

- NMDR for egg production (zebra fish, FHM).
- NOECs for fish repro endpoints sometimes not determined due to effects seen at lowest conc test
- But: sufficient fish full life cycle studies with LOEC/NOEC -> able to do risk assessment

#### Perchlorate

 NMDR in one study in stickleback T3 and T4 levels were affected at low concentrations but not at two higher concentrations across life stages (larval, juvenile and adult stages) No apical endpoints evaluated in this study -> relevance could not be determined.

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- NMDR in mammalian 2-gen: T4 but inconsistent across dose, gender and generation.
- NMDR not seen population relevant endpoints -> no impact on risk assessment in case study.
- TBT: Inverted U shaped responses:
  - mainly involve gene expression studies
  - In vivo: eg effect on bw in fish and mammals -> different modes of action operating at different does.
- Trenbolone -
  - U-shaped dr relationship for plasma T, E2 and VTG conc in female FHM exp to TRB for 21 days. Conc > PEC conc -> little significance.
  - NMDRs seen for steroid synthesis/ concentration and or HPG gene expression I in FHM. Biological basis given by Ankley & Villeneuve, 2015 relates to compensatory responses during exposure and early recovery after removal of chemical stressor.

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## Conclusion Regarding Threshold Issues and NMDR's encountered in the case studies: \*



Are the responses significant, plausible, repeatable, across species; endocrine mediated, multiple MOA's, adaptive process, exposure artefacts?

- NMDRs seen in case studies were not considered to impede an environmental risk assessment.
- In nearly all cases threshold determination was straightforward. In other words: studies that scored a Klimisch rating of 1 or 2 described experiments with apical endpoints and exposure concentration ranges that allowed thresholds to be resolved for adverse population-relevant effects. In all of these case studies, for apical population-relevant endpoints we were able to determine clear thresholds for endocrine mediated adverse effects for the purpose of risk assessment.

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Fig 1A (from Parrott et al, 2017): Flowchart for evaluation of NMDR's for mechanistic endpoints (in vitro and biomarkers

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### Uncertainties in biological responses eg NMDRs



Fig 1B (from Parrott et al, 2017): Flowchart for evaluation of NMDR's for in vivo apical and/or population level endpoints

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### Cross Cutting Issues: Improved methods for assessment of EAS/EDS \*

Opportunities to improve approaches to, and guidance for existing test methods, and reduce uncertainty eg:

*in vitro* high throughput screening to prioritize chemicals for testing and provide insights as to the most appropriate assay(s) for characterizing hazard and risk.

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- adding endpoints for elucidating connections between mechanistic effects and adverse outcomes,
- identifying potentially sensitive taxa for which test methods currently do not exist
- addressing key endocrine pathways of possible concern in addition to those associated with estrogen, androgen and thyroid (EAT) signalling.

\* Coady et al, 2017

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### Cross Cutting Issues: Identifying Population-relevant Endpoints in the Evaluation of EAS \*

- There are a few examples of population level impacts from EAS exposure (eg gastropods and TBT; Fish and EE2)
- Greater understanding of relationship between mechanistic (in vitro, non-apical) endpoints and adverse population-level effects is needed.
- Consider severity and prevalence of response
- Use newer endpoints (eg behaviour) from current / newly designed studies.
- Development of adverse outcome pathways (AOPs) and population modeling will increase this understanding.
- Recovery process should be considered when evaluating populationlevel effects.

#### \* Marty et al, 2017.

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**Proposed Decision**making Strategy to Support **Endocrine Disrupter Ecotoxicological Hazard** and Risk Assessment

(Matthiessen et al, 2017)



### **Main Conclusions of the Workshop**

### Provided:

- o environmental exposure,
- effects on relevant taxa and life-stages,
- o delayed effects,
- o dose- and concentration-response relationships
  are adequately characterized, then conducting
  environmental risk assessment of endocrine disrupting
  substances is scientifically sound; expected to be the case
  for most EAS;
- IF data do not allow proper scientific assessment (YET) a hazard based decision is scientifically justified



# **Topics for Further Research**



- Consideration of further endocrine pathways
- Test methods for under-represented taxa and pathways
- Methodological gaps for tiered progression
- Potentially sensitive (behavioural?) endpoints to link to population-level effects
- Determining adversity of effects
- Consider sensitive species/life stages/windows of exposure
- Methods to predict no-effect concentration/thresholds

### http://onlinelibrary.wiley.com/doi/10.1002/ieam.v13.2/issuetoc

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**Special Series** 

Integrated Environmental Assessment and Managemer Received: 2 September 2016 Revised: 3 October 2016

### Ecotoxicological Hazard and Risk Assessment of Endocrine Annegaaike Leopold, \* j Mike Roberts, j and Peter Matthiessen§

Integrated Environmental Assessment and Management — Volume 13, Number 2—pp. 267–279 Received: 5 August 2016 Revised: 12 September 2016 Accepted: 28 November 2016

#### **Special Series** searches to the Scientific Evaluation of

Integrated Environmental Assessment and Management — Volume 13, Number 2—pp. 280-292 Received: 5 August 2016 Revised: 22 September 2016 Accepted: 1 December 2016 gaard,<sup>4</sup> Christopher Borgert,<sup>5</sup> Coady,<sup>9</sup> Lisa Constantine,<sup>10</sup> y,<sup>13</sup> L Earl Gray,<sup>14</sup> Melanie Gross,<sup>15</sup>

#### Challenges in Assigning Endocrine-Specific Modes of Action: Recommendations for Researchers and Regulators

Ellen M Mihaich, \* | Christoph Schafers, | David A Dreier, § Markus Hecker, || Lisa Ortego, # Yukio Kawashima, † Zhi-Chao Dang, ‡ and Keith Solomon§§ itmironnental and Regulatory Resource, Durham, North Carolina, USA fraunhofer IME Applied Ecology, Schnallenberg, Germany

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11RIVM, Billhoven, The Netherlands \$\$Centre for Toxicology, School of Environmental Sciences, University of Guelph, Guelph, Ontal Uncertainties in Biological Responses that Influence Hazard and Bick Approaches to the Perulation of Enderrine Active Substance Uncertainties in Biological Responses that Influence Hazard and Risk Approaches to the Regulation of Endocrine Active Substances Received: 8 August 2016 Revised: Integrated Environm

#### EDITOR'S NOTE:

This is 1 of 5 articles generated from the SETAC Pellston Workshop = Approaches for Endocrine-Active Substances (EHRA)" (February 2016, Pens workshop was to provide objective advice, based on current scientific under whether in industry, government, or academia. The goal is to make considered, ecotoxicological hazard. or risk based approach for regulating a given endocrin

#### Special Series

Integrated Environmental Assessment and Management — Volume 13, Number 2—pp. 302-316

# Contraction - Revised 2015 / Revised 22 September 2016 / Accested 20 October 2016

Active Substances

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Current Limitations and Recommendations to Improve Testing for the Environmental Assessment of Endocrine Active Substan Katherine K Coady, \*; Ronald C Blever; Nancy D Denslow, § Melanie Gross, Patri Hannik Unikark & Alantia K Katharia Baning to International Statements of the State State State State State State Katherine K Coady, \*† Rohald C Biever, I Nancy D Denslow, § Melanie Gross, © Path Henrik Holbech, †† Natalje K Karouna-Renier, †† Ioanna Katsiadaki, §§ Hank Kruege Henrik Holbech, †† Natalie K Karouna-Renier, †† Ioanna Katsiadaki, §§ Hank K Gerd Maack, ††† Mike Williams, ††† Jeffrey C Wolf, §§§ and Gerald T Ankley///

- Serd Maack; fff Mike Williams; fff Jeffrey C Wolf; 555 and Gerald T Ankley//// ffhe Dow Chemical Company: Toxicology and Environmental Research and Consulting. Midland, Mid Smithes Visenti Aboratories, Wareham, Masachusets, USA Shindia, USA Findia, USA Aorda, USA Morda, USA Morda, JSA Mathematical and Emronmental Transicology Center, University of Wacorsin, Madison, Madison, Wacorsi (UCA) Morantment of Budy Walding International Diversion of and Aquactivities Maryland Morante for Environment Advances (Sector, Dorse United Kingdom (Mathematical Science, Science, Dorse), Staton, Maryland, USA Professional Diversion of and Calaboratories Staton, Maryland, USA (Foreman Environment Agency, Dessau-Rollau, Cermany

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#### SETAC PELLSTON WORK Environmental Hazard and Risk As



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Outcome

# Take home message:

### Provided:

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- effects on relevant taxa and life-stages,
- o delayed effects,
- dose- and concentration-response relationships
  are adequately characterized, then conducting
  environmental risk assessment of endocrine disrupting
  substances is scientifically sound; expected to be the case
  for most EAS.
- IF data do not allow proper scientific assessment (YET) a hazard based decision is scientifically justified.



### Thank you for your attention!

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