Title: Introduction to the science and regulation concerning endocrine disrupting chemicals: Challenges ahead.

Running head: Science and regulation of endocrine disruption: challenges ahead.

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ABSTRACT

Presentations in session one of the Society of Environmental Toxicology and Chemistry (SETAC) North America Focused Topic Meeting: Endocrine Disruption (February 4 – 6, 2014) described where the science and the regulations have arrived and identified the key challenges that lie ahead. The first presentation gave an overview of where the endocrine disrupting chemical (EDC) issue currently stands in terms of science and policy. It introduced the significant debate about whether suspected EDCs should be evaluated using a hazard-based or a risk-based approach. Subsequent presentations provided a synopsis of the US-EPA Endocrine Disruption Screening Program (EDSP), including a description of the legislative origins of the program, its risk-based nature, its evolution and its future through the input of multi-stakeholder advisory groups. A presentation was given about the current status of potential regulatory activities in the European Union (EU) relative to EDCs and the fact that it is a highly political subject in Europe was highlighted. Finally an EU- industry perspective was given on the repercussions of hazard versus risk-based approaches for EDCs. Both European speakers noted that the regulatory situation in the EU is not set and that at present it is not possible to predict exactly how EDCs will be addressed.

Key words: Endocrine disruption, hazard, risk, criteria, testing programs.

INTRODUCTION:

Public and scientific concern for the potential endocrine disrupting properties of substances in humans and the environment has led to the development of regulatory approaches in certain regions. The most developed approach to screening and testing of chemicals has been implemented by the US-EPA in the form of the EDSP program. Presentations in the first session of the Society of Environmental Toxicology and Chemistry (SETAC) North America Focused Topic Meeting: Endocrine Disruption (February 4 – 6, 2014) described where the science and the regulations have arrived and identified the key challenges that lie ahead. Glen Van Der Kraak (University of Guelph, Canada) opened the meeting with an overview of science and policy, highlighting the considerable debate about whether suspected EDCs should be evaluated using a hazard-based or a risk-based approach. Over recent years significant work has been done to develop methodologies that allow transparency in assessing cause and effect relationship between exposure to EDCs and adverse outcomes, which form the basis for hazard- and risk-based approaches. However, some scientists are concerned that 'traditional' risk assessment does not address potential issues concerning low dose or non-threshold effects and specific life stage sensitivity. In the United States, USEPA has developed a risk-based approach for its Endocrine Disruption Screening Program (EDSP). Mary Manibusan (US EPA[1]) provided a synopsis of the EDSP, including a description of legislative origins of the program and its evolution. In the case of the European Union, efforts are on-going to develop criteria to identify endocrine disrupting properties of chemicals – until then identification will be based on interim toxicology classification criteria (for pesticides and biocides) and with case-by-case decisions (industrial chemicals). Niklas Andersson (European Chemical Agency) discussed the current status of

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potential regulatory activities in the EU relative to EDCs and the fact that it is a highly political subject. James Wheeler (Syngenta[2]) presented a European industry view, discussing some of the repercussions of hazard versus risk-based approaches. He emphasized that, in the absence of a scientific risk-based approach in Europe, hazard-based criteria need to be clear, fact based and consistent. Full summaries of the session are presented below.

SESSION PRESENTATION SUMMARIES:

Science and Policy of Endocrine Disruptors: Sitting at the Crossroads, by Glen Van Der Kraak

In 1991, scientists meeting at Wingspread issued the statement that "Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife, and humans" (Bern et al, 1992). This served as one of the origins of the endocrine disruptor hypothesis and the literally thousands of publications that followed. To date there remains considerable uncertainty and controversy as to how to use this information in regulation that is protective of apical endpoints including growth, reproduction and development. Despite studies spanning almost 25 years, the discipline remains highly polarized and there continues to be significant debate over a range of topics including the very definition of endocrine disruption, whether a hazard-based or a risk-based approach is appropriate when evaluating endocrine disrupting chemicals, and how to evaluate all the available information in the process of establishing whether there is a causal relationship between environmental exposures and health effects (Kortenkamp et al. 2011; Rhomberg et al, 2012, Dietrich et al 2013; Lamb et al, 2014; Zoeller et al. 2014).

[2] Currently Dow AgroSciences

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In 2002, the World Health Organization issued a report on the State of the Science of Endocrine Disrupting Chemicals (EDCs) which included an objective and transparent framework for assessing the relationship between potential endocrine disruptors and health outcomes (WHO, 2002). They proposed an organized framework, based on criteria modified by Bradford-Hill (1965), Fox (1991), and Ankley et al. (1997), to be used in the assessment of relationships between exposures to potential EDCs and altered health outcomes. The framework evaluated whether the outcome of concern (*e.g.*, a specific human disease or status of an ecological species) was linked to a putative stressor that is acting on the individual or population and that exposure to the stressor results in endocrine-mediated events that ultimately result in the outcome of concern. The evaluation of the scientific evidence utilized five aspects: 1) temporality, 2) strength of the association, 3) consistency of the observations, 4) biological plausibility of the effect, and 5) evidence for recovery following diminution of the stressor. In recent years there has been an increased focus in describing adverse outcomes pathways (AOPs) which are used as an approach to collect, organize and evaluate information on the chemical, biological and toxicological effects of chemicals including those that affect the endocrine system. An AOP portrays existing knowledge concerning the pathways of causal linkages between a molecular initiating event and final adverse effects at a biological level of organization that are relevant to a regulatory decision (Ankley 2010). A weight of evidence approach has been proposed to assess the AOP (OECD, 2013). Criteria that are used include: 1) concordance of the dose response relationship, 2) temporal concordance among the key events and adverse effect, 3) strength, consistency and specificity of association of adverse effect and initiating event, 4) biological plausibility coherence and consistency of the experimental evidence, 5) alternate mechanisms that logically present themselves and the extent to which they may distract

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112 from the postulated AOP and , 6) uncertainties, inconsistencies and data gaps. So collectively
113 these and related methodologies (Borgert et al. 2011; Meek et al. 2014) provide increased
114 transparency in assessing cause and effect relationships between exposure to EDCs and adverse
115 outcomes (Fig 1). These form the basis of risk-based approaches to assess the possible effects of
116 EDCs.

117 Some of the controversy in assessing the actions of EDCs has arisen when approaches
118 based on criteria other than those of Bradford Hill are employed. In a follow-up report published
119 in 2012, the World Health Organization in collaboration with the United Nations Environment
120 Programme moved away from a weight-of-evidence approach for the evaluation of data on
121 endocrine disruption and used "best professional judgment" in assessing the potential effects of
122 EDCs and the pattern of appearance of possible endocrine related effects in populations (WHO-
123 UNEP, 2012). The approach used in this assessment leaned heavily on disease trends to suggest
124 associations with EDCs, and largely ignored the role of exposure, dose and potency in endocrine
125 disruption. Significantly the authors in this report completed their assessment without evaluating
126 the totality of the evidence (Lamb et al. 2014). The approach taken in the report by the WHO-
127 UNEP, 2012 is hazard-based and is one that is favoured by some toxicologists and
128 endocrinologists that consider that traditional risk assessment may not always be appropriate
129 when considering unresolved issues including low-dose or non-threshold effects on portions of
130 the life cycle sensitive to exposure. In the hazard-based approach, the primary focus is whether
131 or not the chemical in question affects an endocrine dependent endpoint, regardless of whether a
132 response occurs at a concentration well above any known environmental exposure.

133 Over the last 20 years, much progress has been made in the development of standardized
134 and harmonized test guidelines for regulatory application that address the effects of chemicals on

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estrogen, androgen, and thyroid dependent pathways in lab animal and selected wildlife species. These studies are time consuming and costly from both a monetary and an animal use perspective and still come with their own technical challenges including uncertainty as to the predictive nature of test results and coverage of only a subset of endocrine effects. On the basic science side there has been much progress made in defining the mode of action of chemicals on aspects of endocrine physiology, but there continue to be gaps in making the linkages between effects seen at the molecular and cellular levels of biological organization and apical endpoints. This latter point is becoming highly charged given the pending legislation in Europe that would see regulation of agents that show endocrine-mediated effects in some experimental systems including *in silico*, *in vitro* and *in vivo* models. So while there have been major strides in identifying and defining the actions of endocrine disrupting chemicals, the field struggles on how to best use this information in regulatory decision-making.

Indeed one of the main purposes of the Focused Topic meeting was to publically recognize some of the controversies surrounding the developing science around EDCs and to further the debate concerning hazard- and risk-based approaches (Figure 1).

2013 a Critical Year in the Evolution of the Endocrine Disruptor Screening Program: from Vision to Implementation, by: Mary Manibusan

The USEPA EDSP (Endocrine Disruptor Screening Program) is located in the Office of Science, Coordination and Policy, the third office within the Office of Chemical Safety and Pollution and Prevention. At its start, the program was envisaged to be by natural extension of the USEPA, a "risk-based" program that sought to ensure human health and environmental

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157 health protection against chemicals that elicit an endocrine mediated adverse health outcome. As
158 interpreted under the legislative statutes, described below, the EDSP was not intended to be a
159 "hazard-based" program.

160 The 1996 Federal Food, Drug and Cosmetic Act, Section 408(p) requires the USEPA "to
161 develop a screening program using appropriate validated test systems and other scientifically
162 relevant methods to determine whether certain substances may have an effect in humans that is
163 similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as
164 the Administrator may designate". FFDCA 408(p), Section 3 specifies that the Agency "shall
165 provide for the testing of all pesticide chemicals" and Section 6 states that "…..the Administrator
166 shall, as appropriate, take action under such statutory authority as is available to the
167 Administrator….as is necessary to ensure the protection of public health." Different from
168 FFDCA, the 1996 Safe Drinking Water Act Amendments, Section 1457, requires the EDSP
169 testing of chemical substances that may be found in sources of drinking water, if substantial
170 human populations may be exposed. The explicit languages provided under these key statutes are
171 the fundamental components that influenced the development of the EDSP implementation plan.
172 To this end, the Agency leaned on the Federal Advisory Committee Act (FACA) which
173 represents an important process to achieve collaboration and build environmental consensus
174 among the Agency's diverse customers and stakeholders on complex environmental issues. In
175 1996, EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee
176 (EDSTAC) to provide recommendations on how to design the EDSP to operationalize the testing
177 and review process for thousands of chemicals. When initiated, EDSTAC was composed of
178 members from federal agencies, state agencies, industry sectors, water providers, worker
179 protection organizations, national environmental groups, environmental justice groups, public

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health groups, and research scientists. The committee's intense deliberations took place from October 1996 – 1998. In 1998, the Federal Advisory Committee provided the following key recommendations:

- The legislative mandate would be expanded to include human health and wildlife protection;
- Coverage of endocrine specific pathways would include estrogen, androgen and thyroid pathways, and
- The EDSP Conceptual Framework and "Analytical Blueprint" would be centered on a two-tiered screening and testing approach, consisting of a validated Tier 1 screening battery of assays to determine *potential* interaction with the endocrine system, and subsequent longer-term, definitive studies in Tier 2 to confirm endocrine mediated adverse health outcome(s) and provide quantitative dose/response relationships for risk assessment purposes.

EPA submitted a proposed battery of Tier 1 assays to the Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) for external peer review in March 2008, which found the proposed battery adequate to begin screening chemicals to detect the potential for interaction with the E, A or T hormonal systems. (http://www.epa.gov/endo/pubs/assayvalidation/tier1battery.htm). Table 1 provides and overview of the Tier 1 screening battery of tests and identified per test their ability to detect effects on the E, A or T hormonal systems.

The Data Evaluation Review (DER) process of the Tier 1 test data is an extensive internal review process involving multiple layers of individual and expert panel reviews. Similar for typical pesticide data review packages, a primary review is initiated for each Tier 1 assay by a

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technical contractor. A follow-up secondary review is then performed for each assay by senior level agency scientists. Subsequently, a Tier 1 Assessment Review Committee (T1ARC) performs a consistency review of the groups of assays – this comprehensive review is done by a cross-agency group of experts. Finally, lead scientists and an internal expert committee perform a weight of evidence evaluation of the totality of the data, inclusive of extant 40 CFR 158 pesticide submission data and relevant published data.

It is important to emphasize that the weight of evidence analysis is not a check-list, prescriptive process. It is a scientifically integrative and interpretive process and one that has been routinely used by EPA to evaluate the volume of health and ecological information, shifting in accordance with the availability of different data sets (Figure 2). Principles and criteria for weighing and integrating different lines of evidence to evaluate Tier 1 screening level data are not different from those currently used by USEPA to determine biological plausibility and coherence of data sets from health and ecological studies.

The regulatory requirement at the Tier 1 screening level is that hazard characterization should be clear and transparent with a descriptive rationale of whether there is sufficient demonstration of potential to interact with the endocrine system and what, if any, additional testing is warranted. The Adverse Outcome Pathway (AOP) (Figure 3) construct is typically relied upon to frame the available data from different biological layers of organization from molecular initiating event to effects at the cellular, tissue, and organ levels. The subsequent effects on the individual and population level is commonly relied upon for endpoint selection decisions, but in this case, the decision is whether the chemical has the potential to interact with the endocrine system and subsequently, whether additional studies are needed to ensure public health and environmental health protection.

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In those cases where additional testing is warranted following the data evaluation process at the Tier 1 stage, the following test methods are proposed for Tier 2 testing (Figure 4)**:**

- For mammals, the validated two-generation rat reproduction test (OCSPP 870.3800 and OECD TG 416) with the option of performing the extended F1-generation reproduction test (OECD 443) is already available.
- For birds the long-term effects of maternal transfer and *in ovo* exposure are determined in Avian Two-Generation Toxicity Test in the Japanese Quail (draft guideline OCSPP 890.2100).
- In fish, likened to the mammalian extended one generation reproduction test, the medaka extended one-generation reproduction test is now available in draft form (draft guideline OCSPP 890.2200).
- The Tier 2 amphibian test characterizes endocrine related perturbations in the Larval Amphibian Growth and Development Assay (draft guideline OCSPP 890.2300).
- Finally for invertebrates the existing mysid life cycle test (OCSPP 850.1350) has been adapted for Tier 2 testing.

Between 1998 and 2008 a number of critical scientific reviews took place. With the completion of the Endocrine Disruptor Screening Testing Advisory Committee (EDSTAC, USEPA, 1997) Conceptual Framework, in 1999, the joint FIFRA Scientific Advisory Panel (SAP) and USEPA Science Advisory Board (SAB) reviewed the EPA's Proposed Environmental EDSP at that time. Based on this review, the joint panels provided broad support for the existing Tier 1 battery if there was agreement on a mid-course evaluation of the Tier 1 battery of assays, with "an eye towards revising the process and eliminating those methods that don't work"(SAP, 1999). This instilled a very practical approach to evolving the EDSP with an interest in doing

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more with less; the economies of scale would become an iterative theme for the program in the coming years ahead with the incorporation of high throughput technologies.

Between 2009 and 2013 a number of programmatic implementation steps were taken. Prior to 2009, the initial EDSP list 1 was assembled based on the specific requirements under FFDCA 408(p), section 3 that required the Agency to test all pesticidal ingredients. Prioritization of which active ingredient would be screened first, was determined based on pesticides having three or more exposure pathways, occupational, residential, food and/or drinking water. The selection was not based on the likelihood or probability of a pesticide having endocrine activity. In 2009, EDSP Tier 1 test orders were issued for 67 pesticide chemicals. These test orders covered *in vitro* and *in vivo* assays for estrogen, androgen and thyroid pathways, and capturing both mammalian and aquatic species (*Pimephales promelas* – fathead minnow and *Xenopus laevis* – African clawed frog).

Due to logistical issues, the Tier 1 data were delayed in submission to the Agency which occurred between 2011 and 2013. During this two year time period, the Agency had released a number of significant documents: the 2011 Tier 1 Weight of Evidence Guidance Document (US-EPA 2011), the 2012 EDSP Comprehensive Management Plan (US-EPA , 2012), and the EDSP21 Work Plan a Summary overview prepared by EPA in September 2011, titled: *The Incorporation of In Silico Models and In Vitro High Throughput Assays in the Endocrine Disruptor Screening Program (EDSP) for Prioritization and Screening.* This is also an important part of the EDSP Comprehensive Management plan. All of these documents set the stage for the year 2013 when the Agency had initiated four SAP reviews on the infrastructure, methods and operations of the EDSP program.

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In 2013, several Science Advisory Panels were held (USEPA, 2013) with all final reports acccessible through the following website: http://www.epa.gov/scipoly/sap/meetings/2013. The first SAP review was held in January, 2013 and was titled: Scientific Issues Associated with Prioritizing the Universe of Endocrine Disruptor Screening Program (EDSP) Chemicals Using Computational Toxicology Tools. The prioritization approach discussed in the SAP includes the consideration of: 1) physico-chemical properties, 2) structure- activity relationships and chemical interpolation/extrapolation within the context of the chemical category approach, 3) exposure information (for some chemicals) 4) high through-put (HTP) *in vitro* assays and computational methods and 5) the application of the Adverse Outcome Pathway concept.

In May 2013, the second SAP review was held and it was titled: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Endocrine Disruptor Screening Program (EDSP) Tier 1 Screening Assays and Battery Performance. This SAP was entirely response to the 1999 SAP recommendation for a mid-course evaluation on whether the Tier 1 assays and battery were sufficiently adequate to support the decision of whether a chemical has the potential to elicit an endocrine activity. This SAP dealt with questions related to the Tier 1 assay and battery performance overall. Determinations by the panel were based on a limited of number of EDSP List 1 chemicals (n=21).

In June 2013, the third SAP review was held and titled: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Proposed Endocrine Disruptor Screening Program (EDSP) Tier 2 longer term, eco-toxicity test methods. For this SAP meeting, interlaboratory validation testing reports were presented on the multiple tests run across multiple labs using the study protocols for the birds, fish, frog, and invertebrate Tier 2 studies.

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293 Finally in the July 2013 SAP meeting, A Set of Scientific Issues Being Considered by the
294 Environmental Protection Agency Regarding: Weight-of-Evidence: Evaluating Results of EDSP
295 Tier 1 Screening. For this SAP meeting, five unique Tier 1 weight of evidence case studies were
296 presented in the context of the Adverse Outcome Pathways.

297 The General SAP Recommendations that came out of these 2013 SAP's included the
298 following points: 1) Provide full transparency in the decision logic; 2) Ensure scientific
299 reproducibility of test methods; 3) Adjust test methods to ensure regulatory acceptance of quality
300 data; 4) Systematically integrate all available scientific data; 5) Use the Adverse Outcome
301 Pathway framework and employ the understanding of biological pathways for the interpretation
302 and evaluation of the Tier 1 and published data.

303 While 2013 was a critical year for recalibrating the state of the science for the Tier 1 and
304 Tier 2 test methods, several additional SAP meetings were planned for 2014 that would
305 scientifically transform the program. [3].

306 In recognition of the current pace of screening and testing, the current operations is
307 neither efficient nor effective to address >10,000 chemicals. Computational toxicology heralds
308 an important "evolutionary turning point" which will be put to use to the screening program. An
309 EDSP21 vision (Figure 5) has been developed to implement a more strategic approach to
310 prioritize chemicals for targeted screening. This approach will include rapid screening, increase
311 in capacity and reduction in the use of whole animals. It is also clear that to instill this large scale
312 change to the EDSP, it will be critical to have a multi-stakeholder partnership with regulatory

[3] Note from the Guest Editor: This publication was completed 2,5 years after the Focused Topic Meeting took place and in the meantime there have been two more SAP's: One in June 2014, about: New High Throughput Methods to Estimate Chemical Exposure. The second one was held in December 2014 on: Endocrine Activity and Exposure-based Prioritization and Screening. (http://www.epa.gov/scipoly/sap/meetings/2014).

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313 programs across EPA, other federal and state agencies, industry, and non-governmental
314 organizations to validate and apply tools.

315 In the process of EDSP chemical prioritization multiple data streams will be considered,
316 including:

317 • Inherent chemical properties (pKa, LogP, etc.) and exposure data
318 • HTP assays for estrogen, androgen and thyroid
319 • Modeling predictions (e.g., QSAR and ER expert systems)
320 • Data from structural analogs (read across and chemical categories)
321 • Toxicity pathway anchored by biological mechanistically based understanding

322 The conceptual framework of the Strategic Testing Approach consists of three main steps:
323 1) A "risk-based" chemical prioritization pre-screen phase, 2) Tier 1 screening battery of assays
324 and weight of evidence, and 3) Tier 2 test methods, if necessary.

325 The EDSP21 work plan focuses on implementation through incremental stages of
326 demonstration and learning by doing. Critical to this implementation plan is having a clear
327 programmatic goal. For example, a prioritization process should be developed with criteria to
328 determine the order for screening of the universe of non-pesticide chemicals. The domain of
329 application and the regulatory decision contexts must be defined (*e.g.*, what is the degree of
330 uncertainty that will be tolerated?).

331 The universe of chemicals for EDSP screening and testing should be defined and
332 identified. This is essential in order to determine the longer term resource needs for the
333 completion of milestones for the program. A transparent strategy with a sound scientific basis
334 following OECD (Q) SAR Validation Principles is to be built. Scientific soundness and rigor is

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335 to be ensured and an open and transparent process for public outreach and multi-sector
336 involvement is to be provided.

337 ***Endocrine disruptors – ECHA's role and activities by: Niklas Andersson***[4]

338 According to the International Programme on Chemical Safety (IPCS)/World Health
339 Organisation (WHO), 2002 an endocrine disruptor is defined as follows: "*An endocrine disruptor*
340 *is an exogenous substance or mixture that alters function(s) of the endocrine system and*
341 *consequently can cause adverse health effects in an intact organism, or its progeny, or*
342 *(sub)populations."* While the IPCS/WHO definition of endocrine disruptors is widely accepted,
343 its interpretation can be challenging.

344 In Europe the Community Strategy for Endocrine Disrupters identifies the key
345 requirements of further research, international cooperation, communication to the public and
346 appropriate policy actions. As a result, EU legislation now addresses concerns of endocrine
347 disruption in several places, and this includes the Regulation on Registration, Evaluation,
348 Authorization and Restriction of Chemicals (REACH) (EC, 2006), Plant Protection Products
349 Regulation (PPPR) (EC, 2009), Biocidal Products Regulation (BPR) (EU, 2012)), Regulation on
350 Cosmetics (EC, 2009)) and the Water Framework Directive (EC, 2000).

351 How to identify endocrine disruptors in a regulatory context is currently under debate. In
352 order to facilitate identification of endocrine disruptors for regulatory action, efforts are on-going
353 at the EU level to develop a common set of criteria for identification of endocrine disruptors
354 under the REACH, BPR and PPPR. The European Commission is developing these

[4] This text reflects the view of the author and does not necessarily represent the official opinion of the European Chemicals Agency (ECHA).

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criteria.[5]Until these criteria are adopted interim criteria (based on toxicological classification) are in place in the PPPR and BPR while decisions under REACH are made on a case-by-case basis.

The European Chemicals Agency (ECHA) is managing the implementation of the REACH, BPR, and the Regulation on classification, labeling and packaging of substances and mixtures (CLP) (EC 2008) to ensure consistency at the EU/EEA level as well as credible science-based decision making. As a platform for scientific discussion on endocrine disruptors in the regulatory context, ECHA has established an Endocrine Disruptor Expert Group. It consists of nominated experts from Member State Competent Authorities, the European Commission and accredited stakeholders. The group provides scientific advice that does not anticipate or interfere with formal decision-making under the REACH Regulation. The REACH regulation includes the following steps:

- Evaluation: All substances registered under REACH are subjected to tonnage dependent standard information requirements. The standard information requirements under REACH cover some of the tests from the OECD conceptual framework for the assessment of endocrine disruptors, but they are not comprehensive and do not generally provide mechanistic data. Under dossier evaluation, ECHA may only request for standard information from the registrants, whereas the Member State competent authorities conducting substance evaluation can also request for additional information

[5] Note from the Guest Editor: This publication was completed 2,5 years after the Focused Topic Meeting took place. In the meantime the European Commission has, on the 15th of June, 2016, published two draft regulations setting out criteria to define enodocrine disruption (COM(2016) 250 Final). The focus is not on potency or risk but on intrinsic properties alone. It remains to be seen whether these criteria really provide sufficient clarity to inform regulatory decision making.

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beyond the standard information requirements of REACH. Therefore, substance evaluation is a more suitable process for generating information to investigate potential endocrine disrupting properties as the information needed in order to conclude often goes beyond the standard information requirements.

- Authorization: Substances with endocrine disrupting properties may be identified on a case-by-case basis as substances of very high concern (SVHCs) and added to the REACH Candidate List for Authorization. Currently, four substances or substance groups have been placed on the Candidate List due to endocrine disrupting properties with equivalent level of concern to CMR or PBT/vPvB substances. Authorization requirements apply to SVHCs that are included in Annex XIV of REACH. The objective is to progressively replace these substances with safer alternatives or other technologies where these are economically and technically viable. Unacceptable risks of substances with endocrine disrupting properties can also be dealt with through restriction, where the manufacture, placing on the market and use of substances can be controlled.

Under CLP, endocrine disruptors are not a specific hazard but endocrine disruption may be a mode of action, leading to classification for reproductive toxicity, carcinogenicity, or specific target organ toxicity. Adverse effects related to the environment and caused by an endocrine disruptive mode of action may also lead to classification. The provisional interim criteria under the PPPR and BPR make reference to CLP hazard classes toxic for reproduction category 2 (*Repro. 2)* and carcinogen category 2 (*Carc. 2*.). Therefore, CLP may play an indirect role in the identification of endocrine disruptors.

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Under the BPR endocrine disruption is addressed in the context of the approval of active substances and exclusion criteria. Risk assessment of biocides encompasses endocrine disruption. The BPR has exclusion criteria for the approval of active substances that considers endocrine disrupting properties. This means that the active substance is not approved if it has endocrine disrupting properties. The exact criteria of what encompasses endocrine disrupting properties are currently being developed at the commission level (see above). Pending these criteria, active substances that are classified in accordance with CLP as (or meet the criteria to be classified as) *Carc. 2*. and toxic for *Repro. 2*, are being considered as having endocrine-disrupting properties. However, derogation exists in case of *e.g.* public health concerns, negligible exposure or socio-economic consequences, where an approval may be granted for up to five years.

An EU industry perspective on endocrine disrupting chemicals: hazard vs risk assessment, by: James R. Wheeler

Endocrine disrupting properties require specific evaluation under the European regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH; 1907/2006), and the regulations on plant protection (Regulation (EC) No 1107/2009) and biocidal (528/2012/EC) products and Water Framework Directive (2000/60/EC). These regulations require that substances having endocrine disrupting properties are either severely restricted or removed from the market. This represents a significant regulatory shift from risk-based authorisation to one based on the intrinsic hazard of an endocrine mechanism irrespective of the dose/concentration at which it occurs. The development of specific criteria to 'identify

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endocrine disrupting properties' is underway to enable this hazard-based regulation in the EU. This process has culminated in a recent 'roadmap' document (EU, 2014) that outlines an impact assessment, four options for 'technical criteria' and three policy options to enable regulatory decision making. It is anticipated that draft criteria will be available in 2016 and come into force for pesticides in early 2017[5]. This represents a significant delay, but is required in order to conduct the impact assessment for pesticides and biocides. Impact assessments are now considered a standard element of policy-making in Europe for decisions which may have substantial impact. Until definitive criteria are in place, interim criteria for pesticides, based on toxicology classifications (no environmental criteria apply) will remain in place. In the meantime in the US (US-EPA, EDSP) and Japan (SPEED and ExTend programmes), scientific, risk-based approaches are being developed.

The technical criteria options are currently poorly defined. As such they could be open to different interpretations that might lead to inappropriate classification of chemicals as endocrine disrupters. This may lead to the removal from the market of useful and safe solutions. Therefore, criteria need to be developed that are robust and scientifically defensible. These must have clear guidance on the nature and quality of technical data underlying the criteria. [5]

From a purely scientific point of view, the evaluation of chemicals could encompass hazard identification, hazard characterisation, exposure assessment and risk assessment. Hazard identification requires assessment of whether a chemical has an endocrine mode-of-action that consequently leads to an adverse effect – *i.e.* it satisfies the widely accepted definition of endocrine disruption (IPCS, 2002). Next, the hazard can be characterised in terms of the nature of the effect. Properties such as potency, lead-toxicity, specificity, severity and irreversibility may be considered (see Bars et al, 2012; Weltje et al, 2013). However, only potency is

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considered in one of the EU criteria options (EU, 2014). Thereafter, exposure characterisation, in the form of prospective modelling and/or retrospective monitoring (measurement) in the environment, can be considered. Ultimately all the available information can be brought together to perform a risk assessment to conclude on the acceptability of risk to inform decision making.

During the process of consultation different European Member States (MS), regulatory authorities, Non-Government Organisations (NGOs) and industry have expressed their view or made proposals (Wheeler et al, 2012; EFSA, 2013). These overlay onto the range of options with some MSs and NGOs preferring a purely hazard based scheme, whilst others incorporate some aspects of hazard characterisation. However, the European Food Safety Authority favours a risk-based approach (EFSA, 2013) as do some geographies outside Europe (*e.g.* US and Japan). Industry would also prefer a full risk assessment option using all the available information. However, the constraints of the current legislative environment in the EU may not allow this. Consequently, aspects of hazard characterisation at least offer the power to distinguish chemicals of low and high regulatory concern in the absence of risk assessment.

A thorough and realistic impact assessment is difficult to perform without firm criteria in place. However, a number of proposals have been evaluated (Wheeler et al, 2012) and the European Commission will also have an impact assessment of the current options (EU, 2014). Further, the negative impact on global trade and commerce has also been investigated. A CropLife America commissioned report estimated that approximately $4.04 billion of U.S. exports to the EU of raw agricultural commodities could be affected (Brenner, 2013). However, beyond the head line of financial costs it is also important to remember the availability of chemistry solutions will impact on agriculture yield, resistance management and the development of new crop protection solutions.

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In terms of regulatory needs, the optimal solution from a purely scientific perspective is hazard identification and characterisation combined with an extensive exposure assessment and risk assessment. However, the current legislative environment explicitly does not allow for exposure considerations (with the exception of an undefined negligible exposure clause). Therefore, there remains a need for a clear, fact-based and consistent approach. This should allow for predictability in the outcome of an endocrine assessment enabling industry to focus its resources on creating space for innovation.

In conclusion a hazard based cut-off for endocrine disruption will be implemented in the EU. It will have an impact on the availability of chemistry solutions that are important for agriculture yield, resistance management and the development of new crop protection solutions. A robust impact assessment is therefore essential to fully understand the likely impact. Scientifically, risk assessment would be the optimal solution. But, in the absence of this, the hazard-based criteria need to be clear, fact based and consistent. This will be important to give all stakeholders predictability in the outcome of evaluations so that resources can be appropriately managed.

CONCLUSION

Over the past 20 years many standardized guidelines (*in vivo* and *in vivo*) have been developed to evaluate effects of chemicals on the estrogen, androgen and thyroid dependent pathways in mammals and selected wildlife species. The most developed approach to screening of chemicals has been implemented by the US-EPA in the form of the EDSP program. However, with the universe of chemicals that may need to be screened there is a concern that the battery is

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too costly (both in a monetary sense and in terms of and animal use) and time consuming. Hence approaches are being developed to use high through-put techniques (computational, *in vitro* bioactivity and exposure methods) to perform rapid screening. In addition, a framework to make sense of this is being developed in the form of the AOP approach. It is hoped that AOPs will enable an understanding of the chemical processes and linkages amongst initiating toxicity at the molecular, cellular, organ, organism and ultimately population levels. However, there continue to be gaps in making the linkages to demonstrate cause and effect. This latter point is becoming highly charged given debate that is currently ongoing in Europe on how to identify endocrine disruptors in a regulatory context using technical criteria. Given the fact that a hazard-based approach is likely to be implemented in the EU, it will be even more critical that these criteria need to robust and scientifically defensible. Therefore, this session of the Focused Topic Meeting highlighted scientific and regulatory achievements whilst acknowledging some of the current uncertainties that form the basis of the challenges ahead.

DISCLAIMER

This text reflects the views of the authors and does not necessarily represent the official position of the European Chemicals Agency (ECHA), or the OECD and its member countries. In addition, this text reflects the views of the authors and does not necessarily represent the official position of the EPA.

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689 Table 1. USEPA Endocrine Disruptor Screening Program: Tier 1 Screens and Interactions

Study Name	Study Number (OCSPP)					Steroid Synthesis			
		E	**E-**	**A**	**A-**	**A**	**E**	**HPG**	**HPT**
In vitro									
ER Binding	890.1250	**X**	**X**						
ER Transcriptional Activation (ERTA)	890.1300	**X**							
AR Binding	890.1150			**X**	**X**				
Steroidogenesis (H295R)	890.1550					**X**	**X**		
Aromatase (Recombinant)	890.1200						**X**		
In vivo									
Uterotrophic	890.1600	**X**							
Hershberger	890.1400			**X**	**X**				
Pubertal male	890.1500			**X**	**X**	**X**		**X**	**X**
Pubertal female	890.1450	**X**	**X**				**X**	**X**	**X**
Fish Reproductive Screen (FSTRA)	890.1350	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Amphibian Metamorphosis (AMA)	890.1100								**X**

690 ER = estrogen receptor
691 AR = androgen receptor
692

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694 Figure 1: Which criteria should be used to describe endocrine disruption?

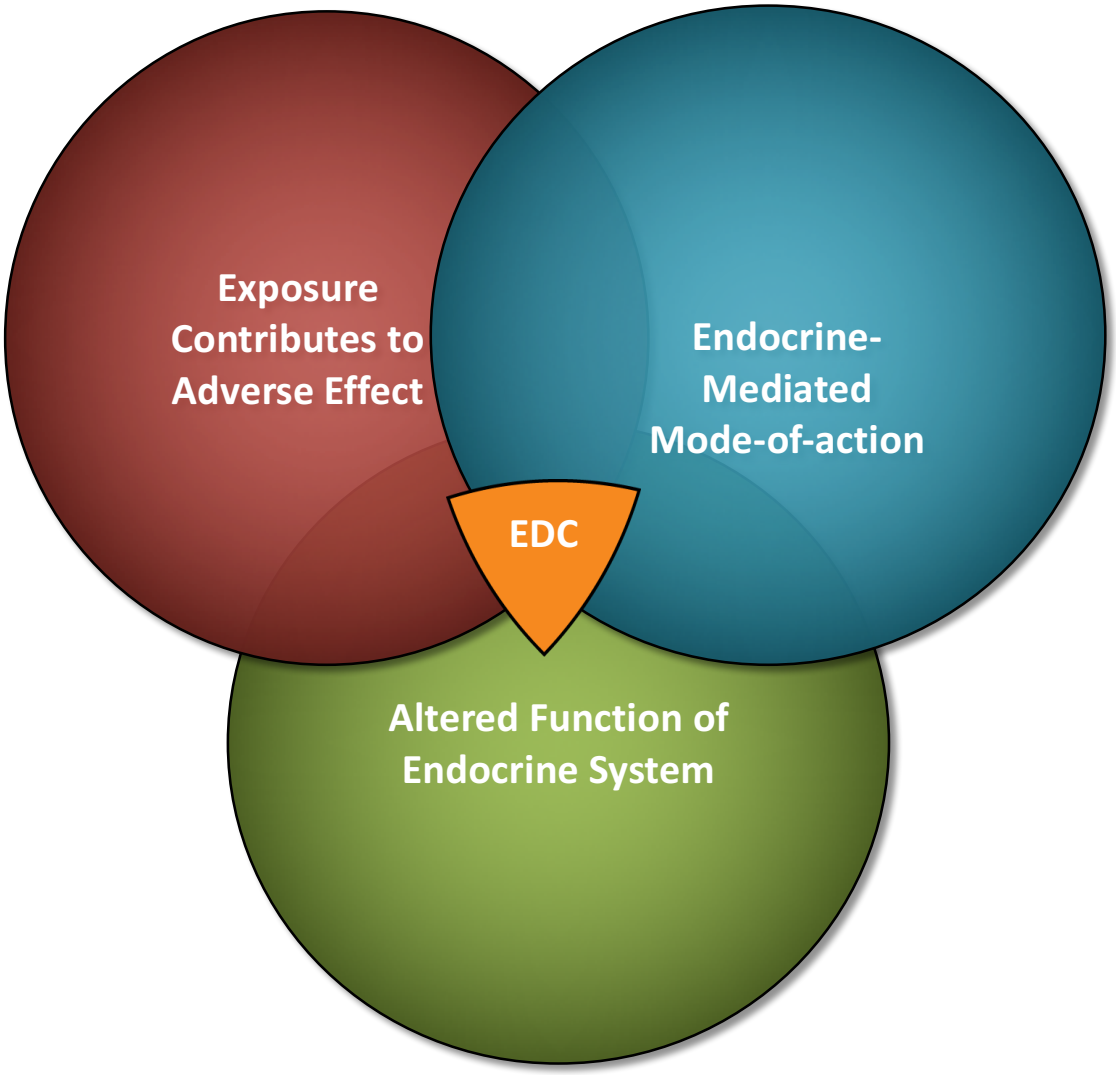

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Figure 2: Weight of All Available Scientific Evidence - Tier 1 and Other Scientifically Relevant Information (OSRI):

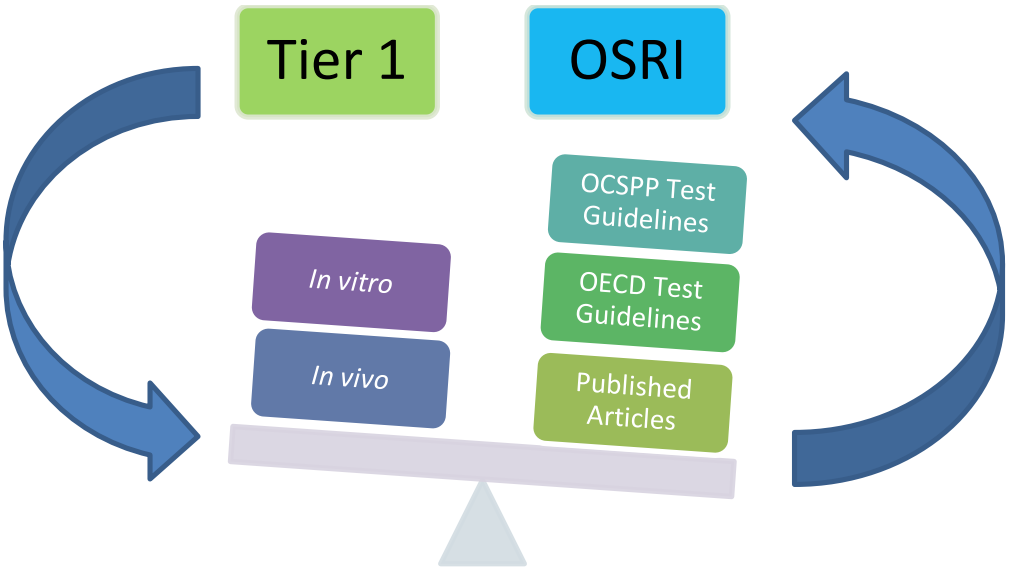

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Figure 3: Screening level characterization:

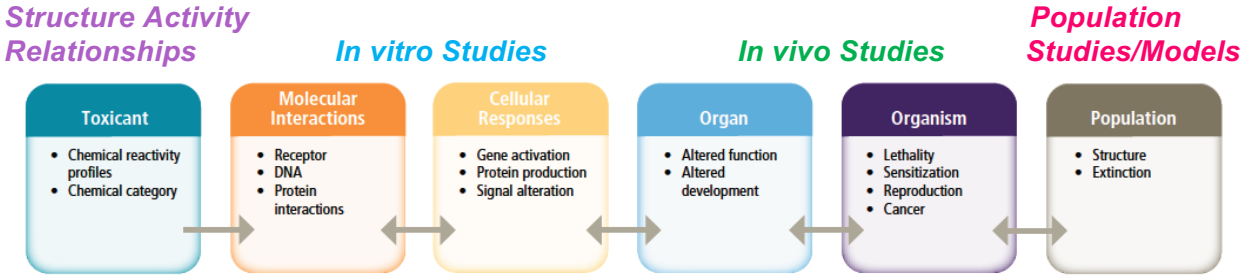
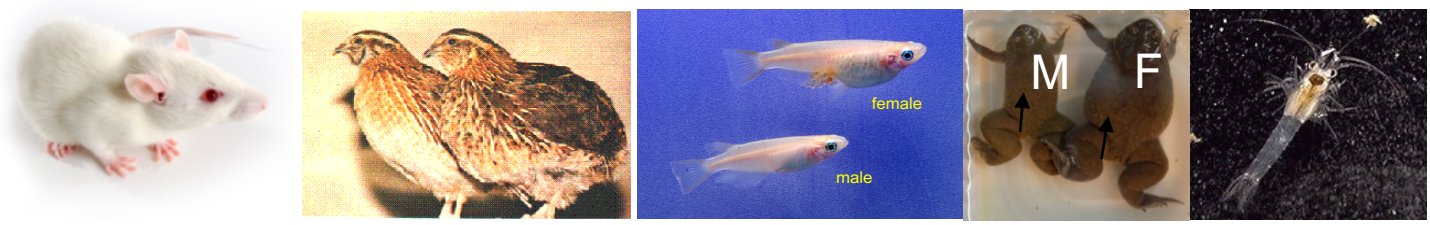


Figure 4: Mouse, *Coturnix japonica,* Japanese quail male (l) and female (r); *Oryzias latipes,* Japanese medaka; *Xenopus laevis,* African claw-toed frog male (l) and female (r); *Mysidopsis bahia*, mysid shrimp.



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726 Figure 5: The timing and approach described in the Work Plan.

727 http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf

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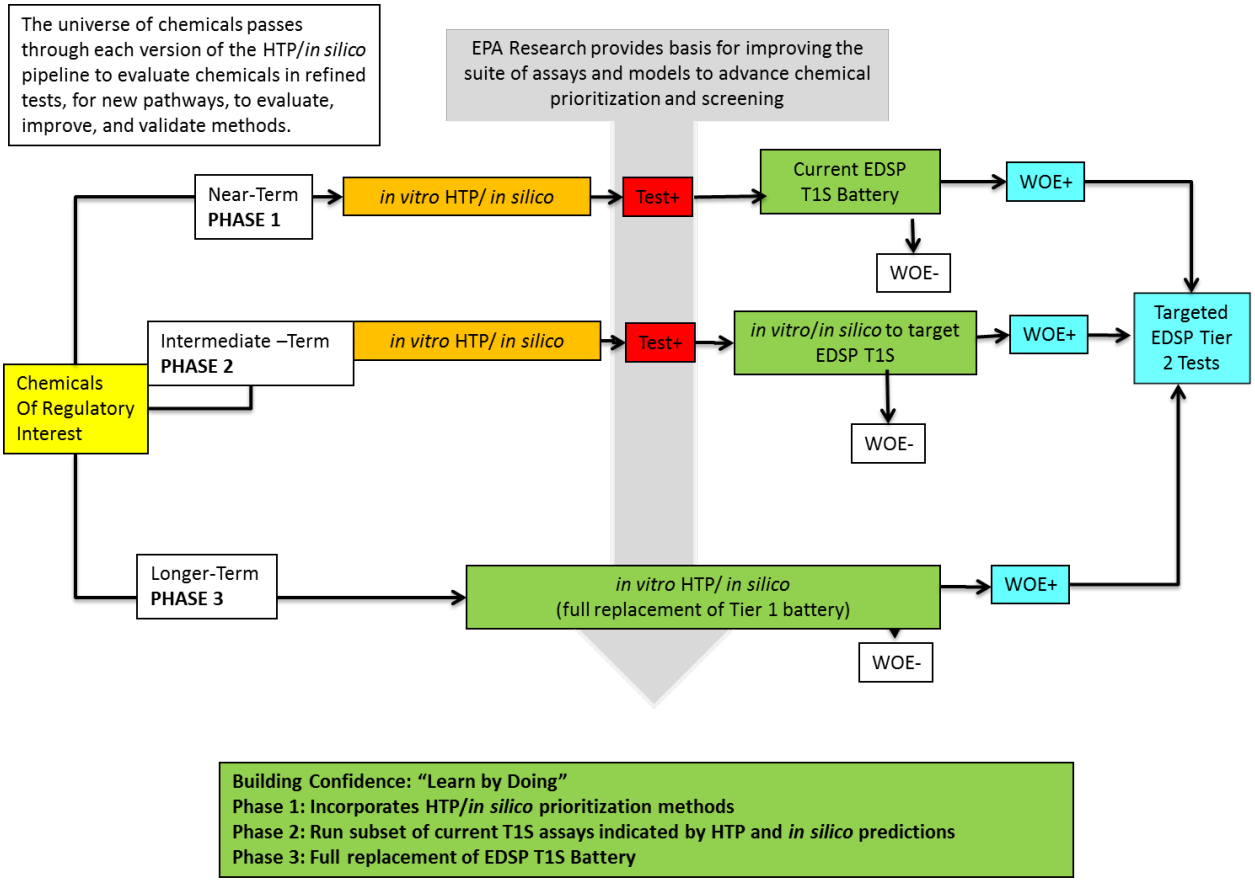

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