Endocrine Disruptors and Their Regulatory Treatment

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- Reproductive and developmental toxicology background
- Directed ED testing for medical devices and agricultural, environmental discharges
- Trained NICNAS (Australia) staff on OECD testing methods for ED

RAMBOLL

Overview

- **Endocrine disruption status in EU and US product regulatory programs**
- **Hazard Communication Programs *vs* hazard communication expectations**
- **Complexities of EDCs explained**

Summing it all up…

- Endocrine disruption is NOT its own hazard classification under GHS
- Generally fall into reproductive or developmental hazard categories
- Extra effort/complexity for hazard communication

Simplifying Generalizations

- US and USEPA
  - Conceptually old fashioned and slow to update on hazard
  - Technologically – at the forefront of driving testing results into a comparable data structure
- EU, ECHA and EFSA
  - Effectively capturing updated scientific framework and goals
  - Waiting for testing submissions
  - Adopt workarounds to achieve hazard reduction goals

USEPA Description

"Endocrine disrupting chemicals can interfere with the normal functions of the endocrine system and lead to problems with reproduction (i.e. egg and sperm production) and development (i.e. healthy fetal growth) in both humans and wildlife."

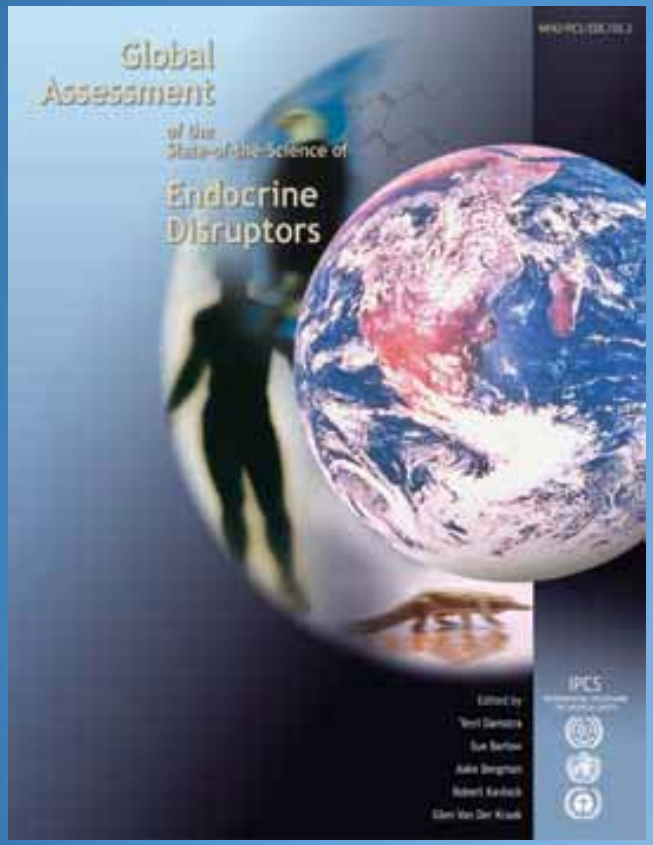
USEPA.gov - Research on Endocrine Disruptors
https://www.epa.gov/chemical-research/research-endocrine-disruptors#:~:text=Endocrine%20disrupting%20chemicals%20can%20interfere,in%20both%20humans%20and%20wildlife

- Focused on the outcome – reproduction and development
- Specifically distinguishes humans and wildlife

US Still Looking Beyond Hazard

- Assessments include hazard AND exposure
- Key research leadership on:
  - Low-dose effects
  - Non-typical (nonmonotonic) dose-response relationships
- USEPA Focus – Endocrine Disruptor Screening Program (EDSP)
  - Tier 1 screening – endocrine activity/potential
  - Tier 2 testing – adverse effects AND dose-response

WHO-IPCS - Global Assessment of the State-of-the-Science of Endocrine Disruptors (2002)



ED Definition:

"An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations

Defining the Next Level

- An Adverse Effect: causes a change in
  - Morphology
  - Physiology
  - Growth
  - Development
  - Reproduction
  - Life span
- Results in impairment of functional capacity, capacity to compensate for additional stress or an increased susceptibility to other influences
- Plausibly linked to an endocrine mode of action

ED Mechanisms/Modes of Action

- Mimic the biological activity of hormone (agonist)
  - Bind to receptor
  - Produce the expected cellular response, but excessively or mistimed
  - Leading to unexpected/adverse sequence of signaling and outcomes
- Block the activity of hormone (antagonist)
  - Bind to the receptor– but not activate it
  - Prevent binding of the hormone
- Alter normal hormone circulation/signaling
  - Bind to transport proteins in the blood
  - Reducing capacity for transport of hormones
- Interfere with the metabolic processes signaling or controlling synthesis or breakdown of hormones

EU Framework for Designating ED

- Screening assessments – frequently rely on structure : activity expectations
- Systematic review of relevant and reliable studies, testing
- Weight-of-evidence evaluation
  - Adverse effects
  - Endocrine mode of action
  - Plausible link between the adverse effects and the mode of action
- Excludes effects that are secondary to other toxicities

Official Endocrine Disruptors in EU

- Multiple EU Regulations include ED as hazard characteristic to consider
  - REACH, BPR, Plant Protection (Cosmetics, Water Framework)
  - Forcing function to reach designations
- Formally designated
  - Substances of Very High Concern (SVHC) listed and categorized – more than 60 EDs
  - Recent notable listings – BPA, PFOA
  - Germany has lead proposals and research

Complexities of Classification vs Expectations of Safety Information

- Hazard Communication Programs
  - Characterizing ED activity is technically complex
  - Establishing regulatory requirements or actions is a protracted process
- hazard communication expectations (note the lower case…)
  - Customers & public want clear, simple messages
  - Expect programs that are directive, not investigative

Endocrine Disruption Seen as Particularly Hazardous

- General perceptions/intuitions about vulnerability of endocrine system
  - Connections to reproduction and development
  - Understanding of general homeostatic, metabolic role
- Concern and “slow” progress capitalized on by advocacy messaging

Programs in the US – Endocrine Disruptor Screening Program

- Scope
  - Pesticides and substances that may have a cumulative effect with pesticides
  - Substances in sources of drinking water
- A two-tiered approach to screen
  - Estrogen, androgen and thyroid hormone systems
  - Tier 1 results finalized in 2015
  - Tier 2 testing is on hold

EDSP Tier 1 Test Guidelines

890.1100 – Amphibian Metamorphosis (Frog)

890.1150 – Androgen Receptor Binding (Rat Prostate)

890.1200 – Aromatase (Human Recombinant)

890.1250 – Estrogen Receptor Binding

890.1300 – Estrogen Receptor Transcriptional Activation (Human Cell Line HeLa-9903)

890.1350 – Fish Short-Term Reproduction

890.1400 – Hershberger (Rat)

890.1450 – Female Pubertal (Rat)

890.1500 – Male Pubertal (Rat)

890.1550 – Steroidogenesis (Human Cell Line – H295R)

890.1600 – Uterotrophic (Rat)

EDSP Tier 2 Test Guidelines

890.2100 – Avian Two-Generation Toxicity Test in the Japanese Quail

890.2200 – Medaka Extended One Generation Reproduction Test

890.2300 – Larval Amphibian Growth and Development Assay (LAGDA)

EDSP – the next generation

- Faster
  - Full battery and process for thousands of chemicals impractically slow
  - Increase use of high throughput screening tests
  - Tox21 database - estrogen receptor activity for 1800 chemicals
- Cheaper– in vitro, in silico, reduced animal use
- Better ??
  - Good for starting point, prioritizing chemicals
  - Does the default, single information point lead to presumptive conclusions?

US Programs That Can Take Action

- USEPA Administrator – granted authority to act if substance has endocrine effect
- Under FIFRA - pesticides
  - Registrations/re-registration
  - Can add ED testing requirements
- Under updated TSCA program – chemical products
  - Specification to consider reproductive and developmental endpoints
  - New chemical reviews
  - Existing chemical reviews (first 10)

EU Programs – ED Not a Hazard Classification

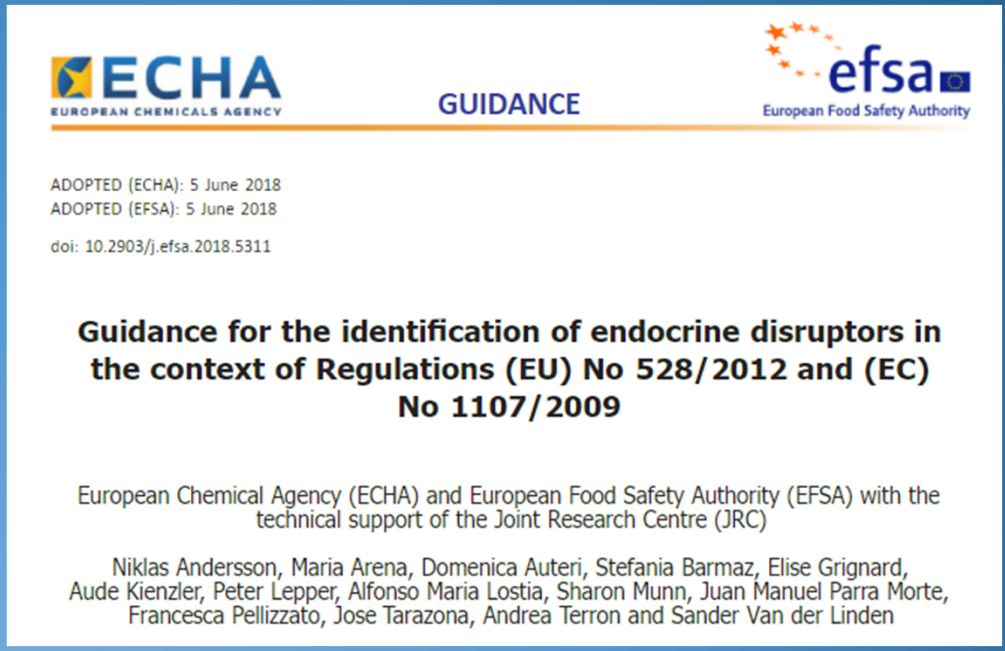
- EU has detailed, specific hazard communication requirements related to classification, labeling, packaging and safety information (Regulation (EC) No 1272 /2008)
  - ED not included among 15 categories for classification
  - Program relies on testing metrics to assign classification – acknowledges that there are not yet agreed test methods for ED
- Indirectly addressed via some classifications
  - Reproductive hazards
  - Ecotoxicity hazards

EU – REACH Program Uses SVHC Designation

- REACH applies to broad groups of chemicals in commerce and imported into EU
- SVHC designation by ED properties determined on case-by-case basis
  - No one test – use the framework and weight of evidence
  - Other ED effects considered analogous hazard to reproductive-based determination (CMR), i.e., can be an SVHC for these effects
- Structured around hazard-based restrictions or pressure to eliminate
- Risk-based considerations come in for exemptions by specific use (Authorisation)

EU Pesticide Programs Provide Specific Guidance

- Joint guidance with regulatory authority
  - Biocidal Products Regulation (BPR)
  - Plant Protection Products Regulation (PPPR)
- Joint agency adoption 2018
  - ECHA – chemicals generally
  - EFSA – food safety
  - Specified goal of having aligned definition and determinations



ECHA
EUROPEAN CHEMICALS AGENCY

GUIDANCE

efsa
European Food Safety Authority

ADOPTED (ECHA): 5 June 2018
ADOPTED (EFSA): 5 June 2018

doi: 10.2903/j.efsa.2018.5311

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Niklas Andersson, Maria Arena, Domenica Auteri, Stefania Barmaz, Elise Grignard, Aude Kienzler, Peter Lepper, Alfonso Maria Lostia, Sharon Munn, Juan Manuel Parra Morte, Francesca Pellizzato, Jose Tarazona, Andrea Terron and Sander Van der Linden

ECHA/EFSA Applies Framework Definition

"Substance shall be considered as having ED properties if it meets all of the following criteria:

a) it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

c) the adverse effect is a consequence of the endocrine mode of action

EU Testing and Interpretations

- Testing Focus
  - EATS – Estrogen, Androgen, Thyroid, Steroidal
  - In vivo testing for establishing adverse effect
  - Mode of action can be in vivo or in vitro/in silico testing
- Interpretation
  - Default assumption that an endocrine MoA is relevant to humans

Guidance for the identification of endocrine disruptors in the context of regulations (EU) No 528/2012 and (EC) No 1107/2009
[https://www.efsa.europa.eu/en/efsajournal/pub/5311]

Guidance document on standardized test guidelines for evaluating chemicals for endocrine disruption, Series on Testing and Assessment, No. 150
[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2012)22&doclanguage=en]

Summary of Programmatic Progress

- US
  - Broad set of validated (?) tests available for use
  - Large database and listing (Tox21) based on single metric – estrogen receptor binding
- EU
  - In-depth, well constructed framework for evaluations
  - First set of directive guidance for decision-making, will be precedent

In the eyes of scientists – substantial innovation and progress

In the eyes of public – slow and side-tracked by industry involvement

Complexities of the Endocrine System and EDCs

- EDC topic complicated because the endocrine system is
  - Signaling and feedback loops for metabolic, growth, reproductive processes
  - Endocrine processes highly dynamic – by time and level
  - Extraordinary capacity for plasticity and accommodation – responses aren't necessarily adverse effects
- EDCs are weak substitutes for endogenous hormones
  - Partial fit to receptors, poor activation of downstream events
  - Orders of magnitude less effective at triggering signals
  - Signal to noise dilemma

Word Association –

Endocrine Disruption

Word Association –

Endocrine Disruption

First Hormone That Pops Into Your Head

Word Association –

Estrogen

Maybe Testosterone…

Sex Steroids – Starting Point - Not Where Toxicology Ends Up

- Unambiguous wildlife incidents involved sex steroids
  - Santa Barbara gull colony behaviour and sex ratio - DDT
  - Alligators in Lake Apopka- DDT spill
  - Intersex fish in the Potomac River
- A function of what you can (first) measure
  - Generally a new science from analytical standpoint
  - Early assays and identification of receptors focused on estrogen, progesterone, testosterone
- Fear and outrage factor particularly high with the public

Emerging Sensitive Endpoints and Pathways for ED

- Thyroid (e.g., PCBs, PFOA)
  - Metabolism, Reproductive, Developmental, Cardiovascular
  - Top EU priority for methods advancement
- Neuro-Developmental
  - The brain on hormones (Hypothalamic-Pituitary-Thyroid axis)
  - Life-long hormonal responsiveness patterned during development

Setting priorities for further development and validation of test methods and testing approaches for evaluating endocrine disruptors
https://publications.europa.eu/en/publication-detail/-/publication/6b464845-4833-11e8-be1d-01aa75ed71a1

Takeaways – Hazard Communication and Endocrine Disruptors

- Scientific and regulatory answers are not going to come easily
  - Underlying biology is inherently complex
  - Regulatory efforts will involve more chemicals and more endpoints
  - Be sceptical of proposed shortcuts
- Customers and consumers won't wait
  - Substitution and elimination initiatives will use whatever information is available
  - Will focus on the available "lists" – estrogen receptor activity in the US
  - Who defines the metrics and makes the lists????