Endocrine Disruptors
Emerging Hazard Communication Topics

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21 September 2022

Presenter

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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

- **Status in EU and US product regulatory programs**
- **Hazard Communication Programs *vs* hazard communication expectations**
- **Complexities of EDCs**

Background and Breadth: Endocrinology

- **Two-bit word: Homeostasis**
- **Endocrine system regulates all of physiology**

Waking up to hormone changes

Cortisol : Melatonin

Regulatory Status - Simplifying Generalizations

- US and USEPA
  - Conceptually old fashioned, slow to update on hazard
  - Technologically – at the forefront driving testing results into standardized database
- EU, ECHA and EFSA
  - Proposed Hazard Categories for use in HazComm
  - Waiting for testing results from others
  - Workarounds to achieve hazard reduction

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 Programs That Can Take Action

- USEPA Administrator – granted authority to act if substance has endocrine effect
- Updated TSCA program – chemical products
  - Specification to consider reproductive and developmental endpoints
  - New and existing chemical reviews
- FIFRA – pesticide registration/re-registration
  - Can add ED testing requirements

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 – endocrine activity potential
  - Tier 2 – effects on organisms

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 for thousands of chemicals impractically slow
  - High-throughput screening tests
  - Tox21 database - estrogen receptor activity for 1800 chemicals
- Cheaper– in vitro, in silico, reduced animal use
- Better ??
  - Good for prioritizing chemicals
  - Does single test outcome lead to presumptive conclusions?

USEPA Progress Stalled – OIG Report July 2021

- 1996 Food Quality Protection Act required USEPA to test all pesticide chemicals for endocrine disruptor activity

  "Without the required testing and an effective system of internal controls, the EPA cannot make measurable progress toward compliance with statutory requirements or safeguard human health and the environment against risk from endocrine-disrupting chemicals. " (p.15, https://www.epa.gov/system/files/documents/2021-07/_epaoig_20210728-21-e-0186.pdf)

- OIG recommends moving ahead with testing.

Breakfast… Lunch and Dinner

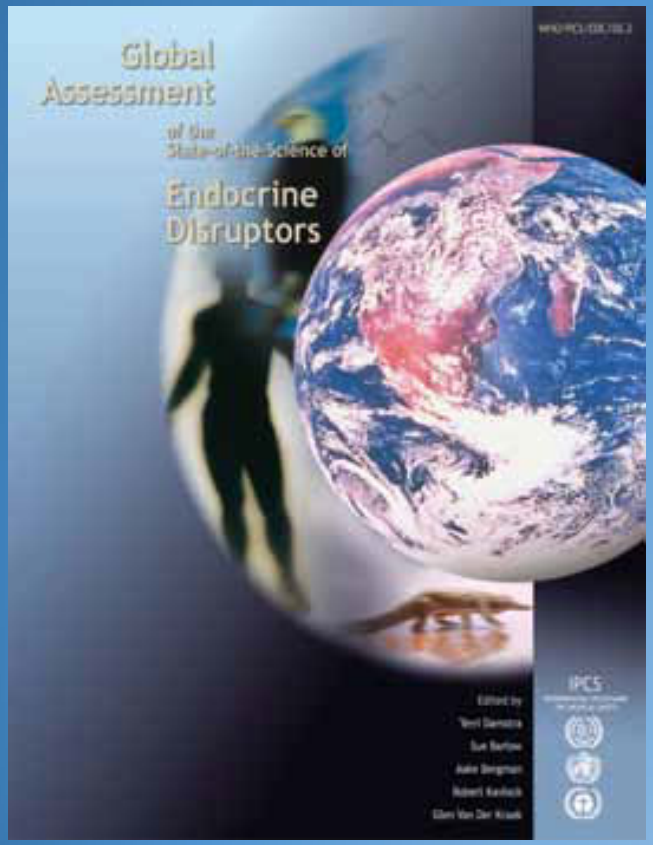
Hormonally Regulated

- **Hormones control energy storage – energy use (metabolism)**

Thyroid function critical

- **T4 (thyroxine) – inactive**
- **T3 (triiodothyronine - active**

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

EU Framework for Designating ED

- Screening frequently relies on structure : activity expectations
- Systematic review and weight-of-evidence evaluation
  - Adverse effects
  - Endocrine mode of action
  - Plausible link between the adverse effects and the mode of action
- Excludes secondary toxic responses

Direct Hazcomm Implications – CLP Update

- 2021 proposed updates to EU Hazard Classification Labelling and Packaging regulation
- New hazard categories for endocrine disruption
  - Category 1 - Known or presumed endocrine disruptors for human health
  - Category 2 - Suspected endocrine disruptors for human health
- Committee (CASG-ED) review – at least through 2022

Ongoing Committee Review

- Category 1 - Known or presumed endocrine disruptors for human health
  - Signal word - Danger
  - Hazard statement – “may cause endocrine disruption in humans”
  - Threshold level – 0.1%
- Category 2 - Suspected endocrine disruptors for human health
  - Signal word - Warning
  - Hazard statement – “Suspected of causing endocrine disruption in humans”
  - Threshold level – 1%

SCHC Homework

- Pictogram Pick-It!

Subgroup requests alternative to the “exploding man”

Official Endocrine Disruptors in EU

- EU Regulations include ED as hazard characteristic
  - REACH, BPR, Plant Protection (Cosmetics, Water Framework)
  - Forcing function to reach designations
- Substances of Very High Concern (SVHC)
  - 107 listed ED candidates
  - 33 reviews concluded
    - 6 - concluded Not ED
    - 11 – concluded Human Health ED
    - 13 – concluded Environmental ED

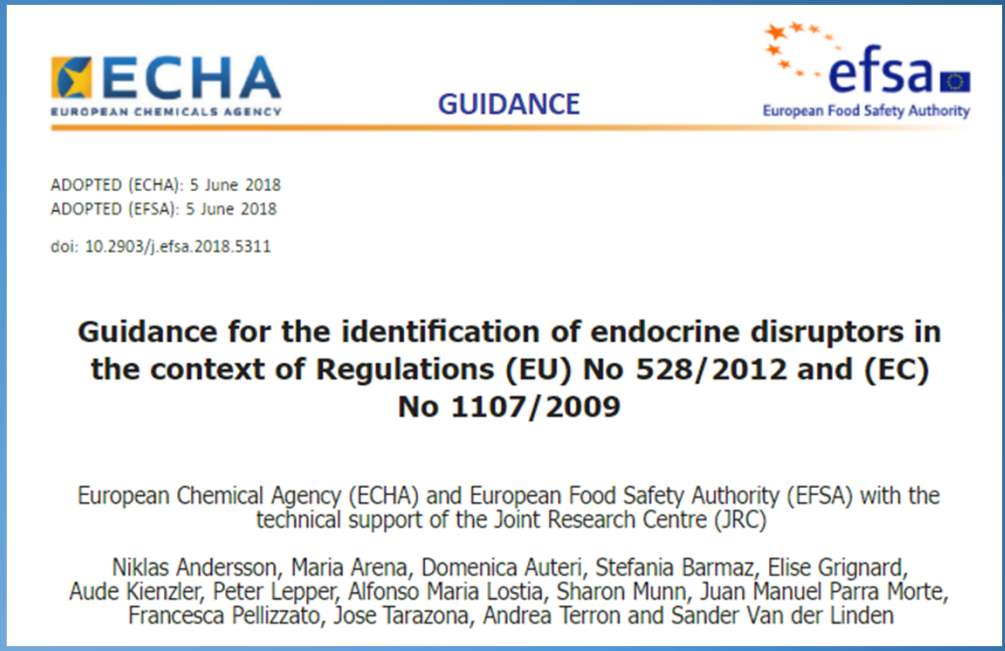
REACH Uses SVHC Designation to Trigger De-Selection or Restrictions

- 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
  - ED effects considered analogous reproductive hazard – allows for SVHC designation

EU Pesticide Programs Specific ED Guidance

- Joint guidance
  - Biocidal Products Regulation (BPR)
  - Plant Protection Products Regulation (PPPR)

- Joint agency adoption 2018
  - ECHA – chemicals generally
  - EFSA – food safety
  - Applies framework definition



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

EU Testing and Interpretations

- Testing Focus
  - EATS – Estrogen, Androgen, Thyroid, Steroidal
  - *In vivo* to establish adverse effect
  - *In vivo, in vitro, in silico* for mode of action
- 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 based on single metric – estrogen receptor binding (Tox21)
  - TSCA the analogy to REACH?
- EU
  - CLP – Hazard communication updates in process
  - In-depth framework for evaluations
  - First sets of directive guidance – will be precedent

Fear, Fleeing and Fighting

Rapid responses to the brain

Neuroendocrine signal for energy use, circulatory and musculoskeletal systems

- **Hormone/neurotransmitter double-duty – noradrenaline**
- **Rapid signal for adrenaline release**

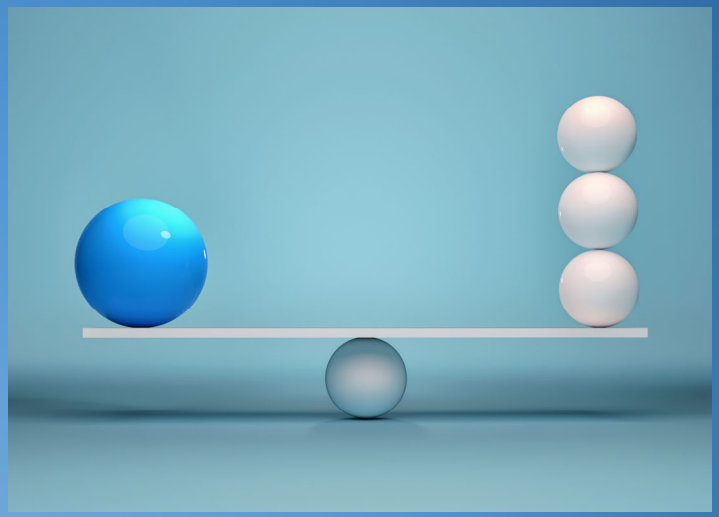
Expectations of Safety Information

- Hazard Communication Programs
  - Characterizing ED is complex
  - Establishing regulatory requirements takes time
- hazard communication expectations
  - Customers & public want clear, simple messages
  - Programs that are directive, not investigative

Endocrine Disruption Seen as Particularly Hazardous

- Perceptions/intuitions about vulnerability of endocrine system
  - Connections to reproduction and development
  - Association with stress responses
- Concern and “slow” progress capitalized on by advocacy messaging

Where we are today depends on your perspective



In the eyes of scientists
substantial innovation and progress

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

Word Association Homework

Endocrine Disruption

First Hormone That Pops Into Your Head

Sex Steroids
It's all about the base…line

Same hormones – different roles depending on levels and ratios

- **Pre-pubertal – growth**
- **Regular reproductive cycling**
- **Pregnancy – interrupting regular function**

Sex Steroids – Starting Point - Not Where Toxicology Ends Up

- Unambiguous wildlife incidents involved sex steroids
  - Intersex fish in the Potomac River
  - Santa Barbara gull colony behaviour and sex ratio - DDT
  - Alligators in Lake Apopka, FL- DDT spill

- A function of what you can (first) measure
  - Early assays and identification of receptors focused on estrogen, progesterone, testosterone

Sensitive ED Endpoints

- 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

Complexities of the Endocrine System and EDCs

- Endocrine system complexities
  - Breadth of function
  - Highly dynamic
  - Extraordinary capacity for accommodation – responses aren't necessarily adverse effects

- EDCs are weak hormonal substitutes
  - Partial fit to receptors, poor activation of downstream events
  - Orders of magnitude less effective
  - Signal-to-noise dilemma

ED Mechanisms/Modes of Action

- Hormone mimicry
  - Bind to receptor
  - Produce the expected cellular response, but excessively or mistimed
- Hormone blocking
  - Bind to the receptor– but not activate it
  - Prevent binding of the actual hormone
- Altering production or circulation of hormone
  - Interfere with synthesis or recycling
  - Block transport proteins in the blood

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 skeptical of 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 makes the lists????

Summing it all up…

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