



# Emerging Issues in Endocrine Disruption

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## What will be discussed?

- EDSP
- EPA Risk Assessment
- 21<sup>st</sup> Century Science
- TSCA Reform
- Interactions of politics and regulation





## **EDSP – What is EPA looking at?**

- **Estrogen**
  - **Androgen**
  - **Thyroid**
- 1. Review Available data – OSRI**
  - 2. Tier 1 Screen**
    - Priority setting (not for risk assessment or management)
  - 3. Tier 2 Testing**
    - Develop data that might be used for regulation (studies not defined yet)

# Endocrine Disruptors

- **Is this the right database?**
  - Scope and cost
  - Existing data
  - New screens in new species (ecotox)
  - Highly specific protocols
- **What is the second tier?**
  - Tough to determine relevance when the purpose is not specified
  - EDSTAC called for a by-pass of tier 1 in certain cases





## Strategic Confusion

**How can you implement a proper Tier 1 Screen  
if you do not know what the  
T2 tests will be, or criteria for moving to Tier 2  
or risk assessment will look like???**



## **ABCs of EDSP and OSRI**

- **Agonizingly slow to be implemented**
- **Beginning to collect data**
- **Complicated studies**
- **Don't know how they will be interpreted**
- **Endocrine system is more than 3 hormones**



## Tier 1 Screens (T1S)

### ■ *In vitro*

- Estrogen receptor (ER) binding – rat uterine cytosol
- Estrogen receptor - (hER $\alpha$ ) transcriptional activation - Human cell line (HeLa-9903)
- Androgen receptor (AR) binding – rat prostate cytosol
- Steroidogenesis – Human cell line (H295R)
- Aromatase – Human recombinant microsomes

### ■ *In vivo*

- Uterotrophic (rat)
- Hershberger (rat)
- Pubertal female (rat)
- Pubertal male (rat)
- Amphibian metamorphosis (frog)
- Fish short-term reproduction



## **Tier 2 – In Vivo Definitive Studies**

- **Rat multigeneration (or extended one generation) study**

**NOT DEFINED YET, BUT WILL INCLUDE:**

- **Fish**
- **Birds**
- **Daphnid**



## Other Scientifically Relevant Information

- **OSRI has been submitted**
  - In depth review of certain guideline studies
  - Review relevant published literature
  - EPA Toxcast data
  - Develop a weight-of-the-evidence approach
  - Develop a response for each assay or hormone



## **OMB, EPA and OSRI or Other Scientifically Relevant Information**

- OMB “encouraged” EPA to consider OSRI in deciding whether any Tier 1 assays could be waived
- EPA issued very limited guidance on what would be considered acceptable OSRI
- Functionally equivalent data exist for many Tier 1 assays for pesticides
- Weight of the Evidence (WoE) document (2 ½ pages of substance) has been published



# EPA OSRI Evaluation Process Ongoing and Late

- OSRI for **>40** chemicals evaluated by EPA to date; responses for some are published
  - [http://www.epa.gov/endo/pubs/EDSP\\_OSRI\\_Response\\_Table.pdf](http://www.epa.gov/endo/pubs/EDSP_OSRI_Response_Table.pdf)
- Many EPA OSRI responses are more than 6 months late; EPA initial estimate 90 days for evaluation from receipt
  - EPA indicated challenges: “the diversity of approaches to OSRI, as well as the volume and frequency of the order/DCI responses and short time frame (90 days). Including OSRI from public.”
- EPA Data table for OSRI responses incomplete
  - Some reviews unavailable; no links provided
  - Some link to incorrect chemicals



## OSRI Evaluation Process at EPA Ongoing and Changing

- **Appears to be improvisational approach to OSRI evaluation and approved options**
  - Confusion at EPA? Inconsistent responses
  - Example: Bypass option (move directly to Tier 2) issued for several chemicals, then withdrawn
- **As noted above, still a limited number of OSRI evaluations to draw conclusions from, but some patterns appear to be emerging**



## Patterns in OSRI Responses—ToxCast Data

- EPA ToxCast data uniformly rejected, even in context of extensive other supporting information
- ToxCast assays include *in vitro* ER and AR binding and transactivation; multiplex assay; thyroid activity; aromatase
- ToxCast assays used to screen potential endocrine toxicity of oil dispersants used in the Gulf, though not acceptable for T1S



# Patterns in EPA OSRI Evaluations

- **No WoE process evident for OSRI evaluation**
  - Studies considered individually, without consideration of other studies with the same or closely functionally-related endpoints
  - without consideration of any Tier 1 assays the registrant has promised to perform
- **Weak non-specific positive responses, or responses in poor quality studies, have been used as indications that an EAT pathway may be affected**



## Registrant and Producer Perspective

- **Collection of assays to be conducted**
  - Expectation in FQPA was cheap and quick T1S
  - Not cheap
  - Not quick
- **67 chemicals on first list (many pesticides)**
  - Responses submitted to EPA
  - Some reviews by EPA have been completed
  - OSRI reviews do not appear even-handed
- **Over 100 on the new list (SDWA-driven)**



## Political Pressures on EPA re EDSP

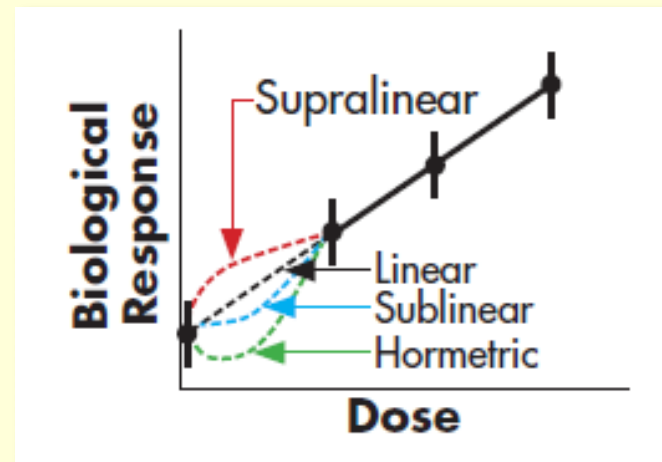
- Legislative and EPA action to screen on 100 more chemicals quickly

### *HOWEVER*

- Need to look and see whether the battery really works for priority setting or not
- OSRI review process is not consistent or based on a WoE evaluation
- Not just about hormone activity, key is ultimate value in risk assessment and risk management

# Risk Assessment and Risk Management

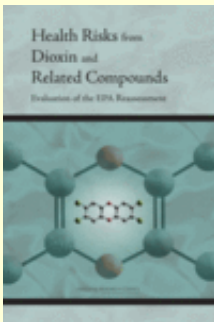
- Hazard identification and dose response
- Exposure assessment
- Risk characterization



- Regulatory action and communication

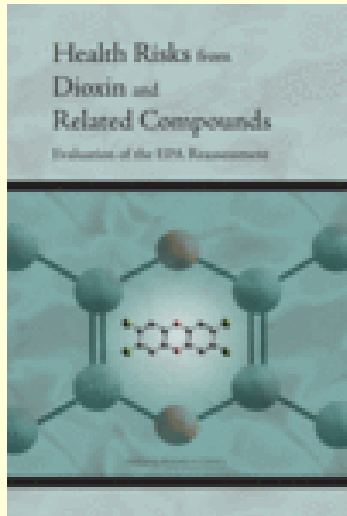
# Risk Assessment Paradigm

- NAS publications as guidance to assessing EDC risk

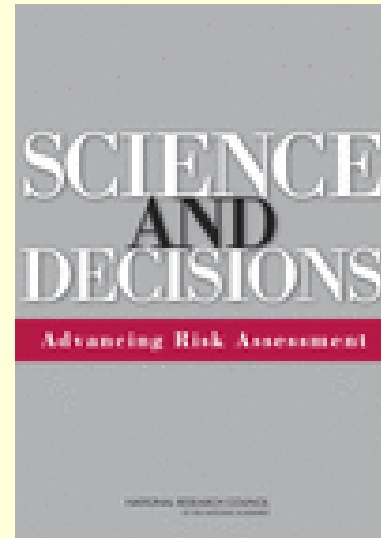




# Linear vs. Non-linear Risk Assessment



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## **Risk Assessment and Regulatory Paradigm**

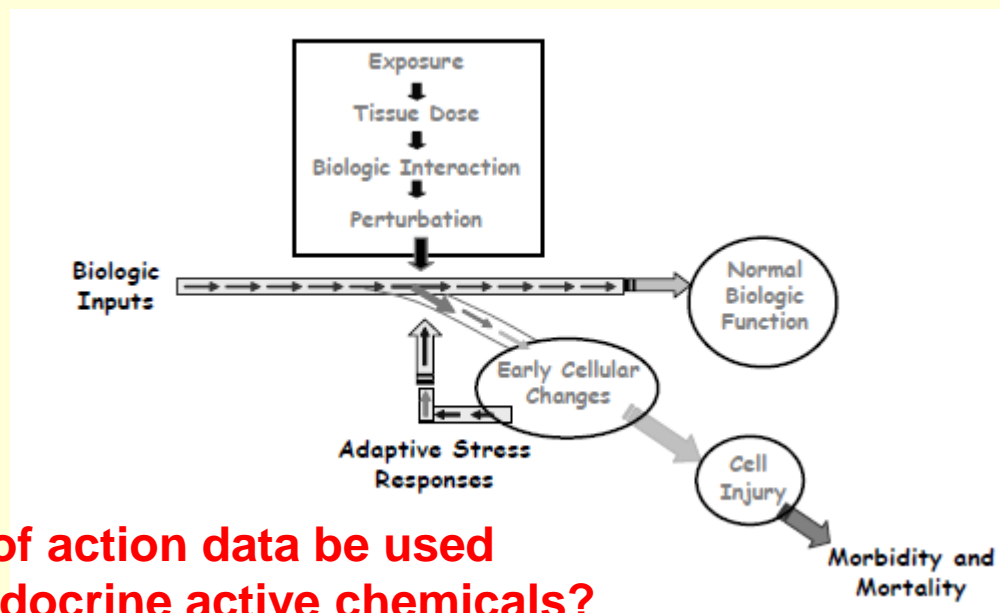
- **NOT a simple-minded conclusion about low level hormonal activity**
- **T1S is NOT sufficient for Risk Assessment or Management (per EDSTAC)**
- **Must develop T2T within the context of all the data available**



## How will EPA Assess Risks for Endocrine Effects?

- **Currently no change**
- **Tier 1 will not be used**
- **Tier 2 will develop data for risk assessment and risk management**

# Toxicity Testing in the 21<sup>st</sup> Century



**How will mode of action data be used in assessing endocrine active chemicals?**



## TSCA Reform and EDCs

- Opportunity for another look at this issue in a different context
- Move towards Tox in the 21<sup>st</sup> Century?
- Regulate by hazard or by risk?
- Can hormone binding or influence on the endocrine system become Scarlet Letters?

# EDCs



## Interactions of Politics and Regulation

- **More data and better information does not necessarily lead to easier decisions in regulation**
  - Dioxin
- **Politics have increased the pressure within EPA**
- **Political solutions (e.g., legislative bans) have been sought to ban certain EDCs**
  - Bisphenol A
  - Phthalates

## Conclusions

- New data and protocols provide opportunities to continue to improve risk assessment and risk management
- Apical studies still determine hazard, dose response and risk
- Increased use of the mode of action framework for various substances
- Many questions remain in science and process
- Endocrine activity may explain a mode of action, but is it going to be treated as an adverse effect?