US Regulatory Perspective on Developmental Neurotoxicity Testing with Special Focus on Endocrine Disrupting and Industrial Chemicals

October 18, 2016

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What is the problem and how big is it?

- Broad chemical space and broad biological space required for testing of potential neurotoxicants and especially developmental neurotoxicants.
- Huge number (~10K) of substances which excludes pesticides and drugs with known mode of action and target sites.
- Approaches Needed for Prioritization, Screening, Testing and Assessment.
TSCA Major Improvements in 2016

- Mandatory duty on EPA to evaluate existing chemicals with clear and enforceable deadlines
  - Old TSCA – no duty to review; no deadlines for action

- Chemicals assessed against a risk-based safety standard
  - Old TSCA – risk-benefit balancing standard

- Unreasonable risks identified in the risk evaluation must be eliminated
  - Old TSCA – Significant risks might not be addressed due to cost/benefit balancing and no mandate to act

- Expanded authority to more quickly require development of chemical information when needed
  - Old TSCA – Required lengthy rulemaking
TSCA New Chemicals

- TSCA 21 requires EPA to make affirmative finding on new chemicals or significant new uses of existing chemicals.
- Before the chemical can enter the market, EPA must find that the chemical:
  - “presents an unreasonable risk” and issue a 5(f) order to address such risk;
  - “information...is insufficient to permit a reasoned evaluation...” and issue a 5(e) order;
  - “may present an unreasonable risk” and issue a 5(e) order; or
  - is “not likely to present an unreasonable risk”
Prioritizing Chemicals for Assessment

- Establish a risk-based process to identify “high” and “low” priority substances.
- High priority – the chemical may present an unreasonable risk of injury to health or the environment due to potential hazard and route of exposure, including to susceptible subpopulations.
- Low priority – the chemical use does not meet the standard for high-priority.
TSCA Alternative Testing

Section 4

When requiring the development of new information relating to a chemical substance or mixture under paragraph (2), the Administrator shall identify the need for the new information, describe how information reasonably available to the Administrator was used to inform the decision to require new information, explain the basis for any decision that requires the use of vertebrate animals, and, as applicable, explain why issuance of an order is warranted instead of promulgating a rule or entering into a consent agreement.
When requiring the development of new information under this subsection, the Administrator shall employ a tiered screening and testing process, under which the results of screening-level tests or assessments of available information inform the decision as to whether 1 or more additional tests are necessary, unless information available to the Administrator justifies more advanced testing of potential health or environmental effects or potential exposure without first conducting screening-level testing.
What is the scope of the problem?

- Can we estimate how many chemicals in commerce are neurotoxic (NTX)?
- Best estimates:
  
  OTA estimates (1990) that the number of chemicals (> 65,000) in commerce with NTX potential ranged from 3-28% (2,000-20,000). Majority of over 500 registered pesticides have NTX mechanism/mode of action.
Endocrine Disruptor Screening Program

• **Mission:** To protect public health and wildlife by screening and testing chemicals and taking appropriate actions for those chemicals that are found to have endocrine effects.

• Based on two legislative mandates:
  – 1996 Federal Food, Drug and Cosmetic Act, Section 408(p)
  – 1996 Safe Drinking Water Act Amendments, Section 1457

• Focus on Estrogen, Androgen, Steroidogenesis and Thyroid Pathways

• Program based on a Tiered Approach:
  – **Tier 1:** Screening to identify chemicals that have potential to interact with the endocrine system using a battery of assays
  – **Tier 2:** If found to have potential, then Tier 2 testing may be required to identify and establish doses at which adverse effects may occur
### EDSP Universe of Chemicals

<table>
<thead>
<tr>
<th>Chemical List</th>
<th>Number of Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Active Ingredients</td>
<td>838</td>
</tr>
<tr>
<td>Antimicrobial Active Ingredients</td>
<td>324</td>
</tr>
<tr>
<td>Biological Pesticide Active Ingredients</td>
<td>287</td>
</tr>
<tr>
<td>Non Food Use Inert Ingredients</td>
<td>2,211</td>
</tr>
<tr>
<td>Food Use Inert Ingredients</td>
<td>1,536</td>
</tr>
<tr>
<td>Fragrances used as Inert Ingredients</td>
<td>1,529</td>
</tr>
<tr>
<td>Safe Drinking Water Act Chemicals</td>
<td>3,616</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>10,341</strong></td>
</tr>
</tbody>
</table>
Based on current pace it could take decades to screen all 10,000 chemicals in EDSP Universe

Employ high throughput assays and predictive models to rapidly screen chemicals for potential bioactivity and exposure
Is Assessment of Developmental Neurotoxicity Necessary?

- Do we assess the structural and/or functional integrity of the nervous system following developmental exposure in Multigen/Extended 1 Gen or Developmental Guideline studies.

- If you don’t look you don’t see (Goldey et al., 1995; Ulbrich and Palmer, 1996, Makris et al., 1999, DNT Retrospective study).
NTX related testing

- EDSP Tiered screening recommendations for CTA (comparative thyroid assay) 4 pesticides from EDSP list 1
- Pesticide actives -101 DNT data evaluation records (DERs) with 24 DNT endpoints serving as regulatory endpoints
- Requests for TSCA new chemicals NTX testing since 1979-2016---1,010 consent orders covering 1,666 PMNs out roughly 22,000 PMNs- ---testing triggered
- 5 out of 55 New chemical categories identify NTX as CE possible NTX testing; 2/5 developmental NTX
- NTX for existing chemicals not required but one of screening criteria in OPPT work plan was NTX potential
Summary of NTX in IRIS data base of Existing Chemicals (Tilson, 2000)

- **Sufficient data base for NTX**: 392
  - Critical effect (CE) was NTX: 74
    - DNT endpoint critical effect: 2 out of 74
  - NTX reported but not CE: 46
  - Non NTX: 272

- **Insufficient data base for NTX**: 145
  - Cancer assessments: 57
  - Noncancer assessments: 1
  - No values listed: 87

**TOTAL**: 537
Challenges in Developmental Neurotoxicology

- Complexity of Nervous System.
  - number of cells.
  - number of cell phenotypes.
  - number of connections.
- Baseline may change rapidly with Time.
  - each region has different time scale.
- Patency of blood-brain barrier limited during early development
- Potential for Compensation and Recovery.
- “Silent damage”
  - Not expressed till later in life or
  - Not revealed until challenged
Development is Temporally and Regionally Determined by Multiple Processes.

DNT Testing Battery Needs

- Screening of high volume of chemicals
- Coverage of a broad number of biological processes and targets
- Well characterized performance based criteria for test of battery
- Reference list of chemicals for tests
- Predictive of adverse outcomes
- Informative of chemical categories, SAR and QSAR for prioritizing further testing
Summary of Use of NTX and Developmental NTX in Decision Context

- Screening and prioritization of thousands of chemicals
- Testing of chemicals based upon insight of AOPs - potential to reduce number of animals used in testing
- Setting up biological context for read across approaches using AOP’s and HTS
- Informing weight of evidence analysis
- Inform risk decision using SAR, QSAR, read across approaches in New Chemicals context
Acknowledgements

- EPA OSCP/OPP
- EPA ORD

https://www.epa.gov/endocrine-disruption
References

- USEPA Neurotoxicity Risk assessment guidelines 1998

- OTA, 1990, *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System*
  - [http://www.wws.princeton.edu/~ota/ns20/year_f.html](http://www.wws.princeton.edu/~ota/ns20/year_f.html)

- OTA, 1995: *Screening and Testing Chemicals in Commerce* (Chapter 4)
  - [http://www.wws.princeton.edu/~ota/ns20/year_f.html](http://www.wws.princeton.edu/~ota/ns20/year_f.html)
### Recommended Additional Testing including TIER 2 for Chemicals that Showed Potential Interaction with E, A and/or T

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Human Health</th>
<th>Wildlife</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Carbaryl</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>2 Chlorothalonil</td>
<td>None</td>
<td>LAGDA</td>
</tr>
<tr>
<td>3 Cypermethrin</td>
<td>Special study: Assess androgen-related effects in adult males</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>4 DCPA</td>
<td>CTA (comparative thyroid assay)</td>
<td>LAGDA</td>
</tr>
<tr>
<td>5 Dichlobenil</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>6 Dimethoate</td>
<td>CTA</td>
<td>None</td>
</tr>
<tr>
<td>7 Flutolanil</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>8 Folpet</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>9 Iprodione</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>10 Linuron</td>
<td>CTA</td>
<td>MEOGRT, LAGDA</td>
</tr>
<tr>
<td>11 Metalaxyl</td>
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<td>MEOGRT</td>
</tr>
<tr>
<td>12 Metribuzin</td>
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<td>LAGDA</td>
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<tr>
<td>13 Myclobutanil</td>
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<td>MEOGRT</td>
</tr>
<tr>
<td>14 O-phenylphenol</td>
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<td>MEOGRT</td>
</tr>
<tr>
<td>15 PCNB</td>
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<td>MEOGRT</td>
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<tr>
<td>16 Propargite</td>
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<td>LAGDA</td>
</tr>
<tr>
<td>17 Propiconazole</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
<tr>
<td>18 Tebuconazole</td>
<td>None</td>
<td>MEOGRT</td>
</tr>
</tbody>
</table>
EDSP “Pivot” Announcement

June 19, 2015
FRL-9928-69

“Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment”