Evaluation of Bisphenol Analogues

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Toxicology Branch
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
June 20, 2018
Presentation Outline

• Goals

• Portfolio – analogues/derivatives and evaluations

• Highlights from our data

• Future plans
Bisphenol Analogue & Derivatives Program

1. What are the toxicological concerns related to the bisphenol analogues & derivatives?

2. How to develop an approach for analyzing classes of chemicals, avoiding full characterization of each chemical in that class?

3. How does this feed into public health?
<table>
<thead>
<tr>
<th>Structure</th>
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Green = flame retardants  
Orange = plastic/resins/dental polymers
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*Blue = detected in environment or human samples*
Testing Program

- **Bisphenol A** – Traditional carcinogenic evaluation (1982)
  NTP-CERHR report (2008) on developmental and reproductive toxicity
  Emerging issue …are there concerns with others in this class?

- **Bisphenol AF** – Survey of literature showing strong activity at ER and AR
  ADME/TK likely different
  When compared to other analogues, could this be the worst?

- **Bisphenol S** – Measurements reported in literature
  Limited *in vitro* activity
  Concern about use of analogues

*Proposed Plan: use these 3 as the initial chemicals from this class for evaluation*
Three primary workstreams for an integrated assessment of bisphenols:

1. **Literature & in vitro evaluations – all analogues**
   - a) Literature
   - b) *In silico*, high throughput screening (HTS), TOXCAST, *in vitro*, alternative models, etc.

2. **In vivo studies – initial chemicals first**
   - a) BPA – CLARITY project with NCTR, ADME/TK
   - b) BPAF – Dose range-finding (DRF) and definitive modified one-generation (MOG) study, ADME/TK
   - c) BPS – DRF and definitive repro study, metabolomics (rat & human), ADME/TK

3. **Integrative Assessment – using all data**
   - a) Develop a database for read-across/model (e.g., database showing which chemicals are structurally and biologically similar)
   - b) Iterative process – what we learn will feed back into improving the process and model
Initial Testing Paradigm

Compare & contrast assays and data from BPA, BPAF, & BPS with information from other analogues to build a database of bisphenols.
• Leadscope QSAR profiling

• **Literature Review of Bisphenol Analogues (2017):**
  NTP Research Report on Biological Activity of Bisphenols…
**NIOSH Activities:**


Urinary BPA concentrations among industry workers…  https://academic.oup.com/annweh/article/61/2/164/2769471
In Vitro Assessments

- **Laboratory experiments on analogues**
  *In vitro* (genetic toxicology, ER/AR assays, Hepatic clearance, etc.)

- **HTS Similarity profiling of analogues**
  Tox21 & ToxCast structural and biological similarity profiling

- **Metabolomics**

- **Alternative assay evaluations**
  *C. elegans* and zebrafish
**In Vivo Assessments**

- **Short-term evaluations**
  - Uterotrophic & Hershberger assays
  - Dose Range-Finding studies
  - 2-week evaluations
  - Assessment of endocrine responsive tissues
  - ADME/TK

- **Long-term evaluations**
  - Subchronic studies
  - Modified One-Generation assays
  - Immunotoxicity assessments
  - Neurobehavioral evaluations
  - Human LifeCodes birth cohort biomonitoring (NIEHS, DIR)
In Vivo Assessments

Comparison of Life-Stage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague Dawley Rats

Mona L. Churchwell, Luisa Camacho, Michelle M. Vanlandingham, Nathen C. Twaddle, Estarin Sepehr, K. Barry Delcos, Jeffrey W. Fisher, and Daniel R. Deoerge

Disposition and metabolism of the bisphenol analogue Harlan Sprague Dawley rats and B6C3F1/N mice and from rats, mice, and humans

Mona L. Churchwell, Luisa Camacho, Michelle M. Vanlandingham, Nathen C. Twaddle, Estarin Sepehr, K. Barry Delcos, Jeffrey W. Fisher, and Daniel R. Deoerge

Pharmacokinetics of bisphenol A in neonates and adults

Daniel R. Doerne1,2, Nathan C. Twaddle4, Michelle M. Vanlandingham2,3, and K. Barry Delcos5

Disposition of bisphenol AF, a bisphenol A analogue, in hepatocytes in vitro and in male and female Harlan Sprague-Dawley rats and B6C3F1/N mice following oral and intravenous administration

Suryama Waidyanatha, James M. Mathews, Purvi R. Patel, Sherry R. Black, Rodney W. Snyder & Timothy R. Fenell

Review

A new approach to synergize academic and guideline-compliant research: The CLARITY-BPA research program

Thaddeus T. Schug1,2, Jerrold J. Heindel4, Luisa Camacho2, K. Barry Delcos3, Paul Howard4, Anne F. Johnson5, Jason Aungst6, Dennis Keele7, Retha Newbold7, Nigel J. Walker1, R. Thomas Zoeller2, John R. Bucher1

Review

NIH/FDA CLARITY-BPA research program update

Jerrold J. Heindel1,4, Retha R. Newbold3, John R. Bucher1, Luisa Camacho2, K. Barry Delcos3, Sherry M. Lewis1, Michelle Vanlandingham2, Mona L. Churchwell4, Nathen C. Twaddle4, Michelle McLellan7, Mani Chidambaram4, Matthew Bryant7, Kellie Woodling1, Gonçalo Gamba da Costa7, Sherry A. Ferguson4, Jodi Flaws1, Paul C. Howard4, Nigel J. Walker1, R. Thomas Zoeller2, Jennifer Foster6, Carolyn Favaro1, Thaddeus T. Schug1
Compounds

- Bisphenol A (BPA)
  - Literature & QSAR
  - HTS & in vitro assessments
  - Alternative models
  - ADME/TK
  - Subchronic assessments
  - Chronic CLARITY-BPA program

- Bisphenol AF (BPAF)
  - Literature & QSAR
  - HTS & in vitro assessments
  - Alternative models
  - ADME/TK
  - Modified OneGen assessment
  - Immunotoxicity evaluation
  - Neurobehavioral tests

- Bisphenol S (BPS)
  - Literature & QSAR
  - HTS & in vitro assessments
  - Alternative models
  - ADME/TK
  - Reproductive assessment
  - Additional tests as needed

Italicized – not completed
Bisphenol analogues are sufficiently similar to the reference bisphenols (BPA, BPAF, and/or BPS)

Reference Bisphenols & analogues:
Compare within & across datastreams:
- Physiochemical/Structural
- Biological activity

Integrate data and evaluate similarity of analogue(s) to reference chemicals

Analogue(s) are similar

Reference bisphenols data is adequate
Comprehensive characterization not needed: Use data from reference bisphenols

Analogue(s) are different

De novo data needed:
Data from reference chemicals does not apply, further testing of analogue(s) needed
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Reference Bisphenols & analogues:
Compare within & across datastreams:
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Integrate data and evaluate similarity of analogue(s) to reference chemicals
(e.g., structural and biological information plotted relative to BPA)
HTS Network Analysis

Thayer et al. 2016
Respective relationship of analogues relative to BPA - chemical and biological similarity
Respective relationship of analogues relative to BPA - chemical and biological similarity

- Where should the lines cross to best determine which analogues are most similar to BPA?
- What does the plot look like for each of the analogues?
- How do the analogues compare to other Tox21 chemicals?
- What does this look like when other data (e.g., in vivo) is added?
Bisphenol comparisons of Tox21 activities (including nuclear receptor and stress response pathways):

- Strong overlap for BPA and BPAF
- BPS activity only at ER
### In Vivo Comparisons, Rats

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<td><strong>Dosing Equivalents</strong></td>
<td>1.31 mmol/kg</td>
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*Mean chemical consumption during gestation was used to convert ppm to mg/kg

- Dosing equivalence is based on ~300 mg/kg
- BPAF is lower than BPS and BPA
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<td>↓ Pup survival</td>
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<td>≥ 560 mg/kg</td>
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<td>No F2 generation at 280 mg/kg</td>
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<td>0.0025, 0.008, 0.025, 0.08, 0.26, 0.84, 2.7, 100, or 300 mg/kg</td>
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**Endocrine Endpoints:**

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<td><strong>Balanopreputial Separation</strong></td>
<td>No effect at doses tested</td>
<td>na</td>
<td>Delayed</td>
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<td><strong>Vaginal Opening</strong></td>
<td>No effect at doses tested</td>
<td>Na</td>
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BPA, BPS, and BPAF:

- Well absorbed following a single gavage administration (≥ 90%)
- Low oral bioavailability:
  - BPA ≤ 5%
  - BPS ≤ 16%
  - BPAF ≤ 3%
- Dose normalized $C_{\text{max}}$ and AUC follow the rank order BPS >> BPAF > BPA
- Comparable plasma elimination half-lives:
  - BPA 3-5hrs
  - BPS 4-12hrs
  - BPAF 2-3hrs
- Metabolism is similar with glucuronide and sulfate conjugates being the major metabolites
Work is ongoing….

- Review of the literature, Tox21/TOXCAST structural and biological comparisons, and *in vitro* evaluations
  - NTP research report
  - Publications

- In vivo assessments of the initial compounds (reference chemicals):
  - BPA studies almost complete
  - BPAF and BPS studies ongoing
  - ADME/TK is ongoing
Assessment Plan

Define Hypotheses & Design a Testing Strategy

Fit for purpose products

Bisphenol analogues

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Longer-term in vivo Tests

Short-term in vivo Tests

Inform Public Health Decisions

In vitro Studies
Combining Old and New

Define Hypotheses & Design a Testing Strategy

Bisphenol analogues

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Hazard assessment, Dose response

Longer-term in vivo Tests

Short-term in vivo Tests

Fit for purpose products

Literature reviews

In silico

Inform Public Health Decisions

High Throughput Screening, TOXCAST

Alternative Models (e.g., zebrafish)

In vitro (e.g., ER/AR assays)

ADME/TK

In vivo studies

Short-term Studies (e.g., Uterotrophic)

Combining Old and New

Fit for purpose products

Literature reviews

In silico

Inform Public Health Decisions

High Throughput Screening, TOXCAST

Alternative Models (e.g., zebrafish)

In vitro (e.g., ER/AR assays)

ADME/TK

In vivo studies

Short-term Studies (e.g., Uterotrophic)
Plans

- Finish collecting *in vivo* data for the initial reference chemicals
- In depth comparison of all data streams for the analogues
- Work to develop an integrative assessment of the bisphenol class
- Iterative process – what we learn will feed back into improving class evaluations
It takes a village
Questions?