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>
<th>Bisphenol A Chemical</th>
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</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Bisphenol P</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>BPS-MPE</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Pergafast 201</td>
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*Red = potential use in thermal paper*
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Green = flame retardants  
Orange = plastic/resins/dental polymers
## Testing Program

**Blue = detected in environment or human samples**

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• **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:**
  Air, hand wipe, and surface wipe sampling for BPA among workers…  

  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)
Binding of bisphenol A, bisphenol AF, and bisphenol S on the androgen receptor: Coregulator recruitment and stimulation of potential interaction sites

Lalith Perera\textsuperscript{1,2}, Yin Li\textsuperscript{3}, Laurel A. Coone\textsuperscript{4}, Rene Houman\textsuperscript{4}, Rinie van der Beek\textsuperscript{5}, Bonnie Goodwin\textsuperscript{6}, Scott S. Auerbach\textsuperscript{7}, Christina T. Teng\textsuperscript{6,8}

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

Mona I. Churchwell, Luisa Camacho, Michelle M. Vanlandingham, Nathan C. Twaddle, Estatir S. Sepehr, K. Barry Delcos, Jeffrey W. Fisher, and Daniel R. Dorcey

Pharmacokinetics of bisphenol A in neonates

Danila R. Doerze\textsuperscript{a,1}, Nathan C. Twaddle\textsuperscript{a}, Michelle M. Vanlandingham\textsuperscript{a}, K. Barry Delcos\textsuperscript{a}, W. W. Ching\textsuperscript{a}, Ying Li\textsuperscript{a}, Lotte B. van der Beek\textsuperscript{a}, Scott S. Auerbach\textsuperscript{a}, Christina T. Teng\textsuperscript{a,8}

Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague Dawley Rats From Gestation Day 6 Through Postnatal Day 90

K. Barry Delcos\textsuperscript{a,1}, Luisa Camacho\textsuperscript{a}, Sherry M. Lewis\textsuperscript{a}, Michelle M. Vanlandingham\textsuperscript{a}, John R. Latendresse\textsuperscript{a}, Greg R. Olson\textsuperscript{a}, Kolly J. Davis\textsuperscript{a}, Ralph E. Patton\textsuperscript{a}, Gonçalo Gambão de Costa\textsuperscript{a}, Kellie A. Woodling\textsuperscript{a}, Matthew B. Bryant\textsuperscript{a}, Mani Chidambaram\textsuperscript{a}, Real T. Trijewicz\textsuperscript{a}, Beth E. Julian\textsuperscript{a}, Robert P. Felton\textsuperscript{a}, and Brett T. Thoms\textsuperscript{a}

Review

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

Thaddeus T. Schug\textsuperscript{a,1}, Jerrold J. Heindel\textsuperscript{2}, Luisa Camacho\textsuperscript{2}, K. Barry Delcos\textsuperscript{2}, Paul Howard\textsuperscript{1}, Anne F. Johnson\textsuperscript{1}, Jason Aungst\textsuperscript{1}, Dennis Kelle\textsuperscript{1}, Retha Newbold\textsuperscript{1}, Nigel J. Walker\textsuperscript{1}, R. Thomas Zoeller\textsuperscript{1}, John R. Bucher\textsuperscript{1}

Review

NIHES/FDA CLARITY-BPA research program update

Jerrold J. Heindel\textsuperscript{2,1}, Retha R. Newbold\textsuperscript{1}, John R. Bucher\textsuperscript{1}, Luisa Camacho\textsuperscript{2}, K. Barry Delcos\textsuperscript{2}, Sherry M. Lewis\textsuperscript{1}, Michelle Vanlandingham\textsuperscript{1}, Mona I. Churchwell\textsuperscript{1}, Nathan C. Twaddle\textsuperscript{1}, Michelle McLellen\textsuperscript{1}, Mani Chidambaram\textsuperscript{1}, Matthew Bryant\textsuperscript{1}, Kellie Woodling\textsuperscript{1}, Gonçalo Gambão de Costa\textsuperscript{1}, Sherry A. Ferguson\textsuperscript{1}, Joel Flaws\textsuperscript{1}, Paul C. Howard\textsuperscript{1}, Nigel J. Walker\textsuperscript{1}, R. Thomas Zoeller\textsuperscript{1}, Jennifer Foster\textsuperscript{1}, Carolyn Favaro\textsuperscript{1}, Thaddeus T. Schug\textsuperscript{1}

Disposition of bisphenol A, 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

Sarayma Waidyanatha, James M. Mathews, Purvi R. Patel, Sherry R. Black, Rodney W. Snyder & Timothy R. Fennell
**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 different: De novo data needed:
Data from reference chemicals does not apply, further testing of analogue(s) needed

Analogue(s) are similar: Comprehensive characterization not needed:
Use data from reference bisphenols
Sufficient Similarity Framework

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

Integrate data and evaluate similarity of analogue(s) to reference chemicals (e.g., structural and biological information plotted relative to BPA)
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
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<td></td>
<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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*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
### In Vivo Comparisons, Rats

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#### In-life
- Body weight gain: ≥ 100 mg/kg, 300 mg/kg
- Pup survival: ≥ 300 mg/kg, ≥ 560 mg/kg, ≥ 80 mg/kg, ≥ 25 mg/kg
- No F2 generation at 280 mg/kg

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#### Endocrine Endpoints:

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<td></td>
</tr>
<tr>
<td>Balanopreputial</td>
<td>No effect at doses tested</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Separation</td>
<td></td>
<td></td>
<td>Delated</td>
</tr>
<tr>
<td>Vaginal Opening</td>
<td>No effect at doses tested</td>
<td>Na</td>
<td>Accelerated</td>
</tr>
</tbody>
</table>
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

Bisphenol analogues

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Fit for purpose products

Longer-term in vivo Tests

Short-term in vivo Tests

Inform Public Health Decisions
Combining Old and New

Define Hypotheses & Design a Testing Strategy

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Hazard assessment, Dose response

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High Throughput Screening, TOXCAST

Alternative Models (e.g., zebrafish)

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

ADME/TK

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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?