Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA)

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NTP Research Report Peer-Review Meeting
April 26, 2018
Outline

• Background
• CLARITY-BPA
• Core Study
• Program Management and Next Steps
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Bisphenol-A (BPA)

- Chemical widely used to make polycarbonate plastics and epoxy resins
- Widespread low exposure (<1 µg/kg body weight (bw)/day) from migration of small amounts into foods from food contact materials
- Considerable debate over risk posed by “low level” exposure
- Guideline studies conducted under Good Laboratory Practices (GLP) show no effects of concern at “low doses”
- Academic “investigative” studies report that BPA induces a variety of effects in a variety of model systems at low exposures
Current U.S. Regulatory Landscape

• The U.S. Food and Drug Administration (FDA) maintains that BPA is safe at the current levels occurring in foods

• FDA also supports currently-approved uses of BPA in food containers and packaging

• Conclusions based on FDA assessments
  – Progressive series of “cumulative” formal evaluations from 2009-2014
  – Ongoing review of scientific evidence (2014-present)
• National Toxicology Program (NTP) Monograph (2008)
• Evaluated the available scientific literature about the possible effects of BPA on human development and reproduction
• Conclusions
• FDA Draft Assessment (2008) concluded the appropriate no-observed-adverse-effect-level (NOAEL) was 5,000 µg/kg bw/day for systemic toxicity
  – Concluded that an adequate margin of safety existed for BPA at estimated levels of exposure from food contact uses
  – Noted information were insufficient to support other endpoints as a point of departure for estimating margins of safety for developmental prostate gland toxicology, developmental neural or behavioral toxicology

• FDA Science Board (2008) recommended further research to address the central question of the developmental toxicity of BPA
• Rodent study should be considered….designed to:
  – Meet criteria for acceptance established by FDA or reasonable criteria applied by the scientific community for study evaluation that FDA should adopt
  – Address the endocrine mechanism-based concerns of the scientific community
  – Use endpoints and models validated for the study of endocrine-mediated developmental processes

• Develop physiologically based pharmacokinetic (PBPK) models for model species and humans
  – Enable comparisons of dose to be made across species in a rational, quantitative manner

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CLARITY-BPA Inception

- Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA)
- Developed by National Institute of Environmental Health Sciences (NIEHS) and FDA in response to the FDA Science Board recommendation

- Principles
  - Address scientific uncertainties about BPA toxicity
  - Use a relevant long-term oral dosing protocol that includes developmental exposure
  - Interrogate additional endpoints not typically assessed in guideline studies available for assessing BPA hazards
  - Common “core” exposure paradigm across all studies, conducted according to GLP
• Novel collaborative research model that draws upon the strengths of investigative and applied-regulatory science research

• Consortium of NIEHS-funded academic researchers with federal scientists and regulators
  – NIEHS
    • Division of the National Toxicology Program (DNTP)
    • Division of Extramural Research and Training (DERT)
  – NIEHS-funded academic grantees
  – FDA
    • National Center for Toxicological Research (NCTR)
    • Center for Food Safety and Applied Nutrition (CFSAN)
• 2010: NIEHS Funding Opportunity Announcement
  – RFA-ES-10-009
  – Develop a consortium of researchers to work with the NCTR and NTP in final design of chronic gavage toxicity study of BPA in NCTR-SD rats following developmental and direct rather than lactational exposure of pups
  – Proposals solicited for hypothesis-driven mechanistic studies focusing on disease/dysfunction endpoints which can be added to the chronic study design

• 2011: Applicants selected via NIH scientific peer review
  – Proposed grantee projects subsequently assessed for technical feasibility by NIEHS and NCTR

• 2012: Final Core Study design developed and agreed upon by all CLARITY-BPA consortium members
CLARITY-BPA: Key Components

• “Core Study” (Subject of THIS peer-review meeting)
  – 2-Year chronic study conducted under GLP at FDA/NCTR
  – Designed in accordance with accepted guidelines for assessing chronic toxicity and carcinogenicity

• “Grantee Studies”
  – 14 Academic investigators selected from applications following competitive NIH scientific peer review
  – Focus on a range of molecular, structural, and functional endpoints not usually assessed in guideline-compliant GLP studies
  – Used siblings born to Core Study females and raised in the same conditions and exposed to the same doses as for the Core Study

• “Integration Report”
  – Interpretative integration of findings from both the Core Study and the Grantee Studies
CLARITY-BPA: Overview

Exposed Pregnant Rats

- Vehicle Control
- BPA
- Estrogen Control

Offspring

- Continuous Dose (Through Lifespan)
- Stop Dose (Until Weaned)

Core Study Grantees

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Core Study: Model Choice and Rationale

- NCTR Sprague-Dawley Rat (CD23/NctrBR)
  - NCTR breeding colony established in 1972 using Sprague-Dawley rats from the Charles River Laboratories

- Responsive to estrogens
  - Used for NTPs “Endocrine Disruptor Initiative” examining short-term, multigenerational, and long-term exposures to estrogenic agents in developmentally exposed Sprague-Dawley rat pups
  - Ethinyl-estradiol, genistein, nonylphenol

- Responsive to BPA
  - BPA causes adverse effects in this strain after 90 days at 100,000 and 300,000 µg/kg bw/day, but not at ≤2,700 µg/kg bw/day
    - Delclos et al., 2014: https://doi.org/10.1093/toxsci/kfu022

- Strain used for comprehensive evaluations of the pharmacokinetics of BPA across life stages
Main study goal: dose-response assessment
  - Cover wide range of BPA doses with reported effects in the scientific literature
    - 2.5, 25, 250, 2,500, or 25,000 µg/kg bw/day
  - Doses informed by prior NCTR 90-day BPA study
    - Delclos et al., 2014: https://doi.org/10.1093/toxsci/kfu022
  - Top dose: provided sufficient margin of exposure to estimated human exposure
    - Not based on a “minimally toxic dose” from a prior 90-day study
  - Low dose: 10-fold higher than the allowed dietary exposure of BPA of the study animals
Assess response to a classic estrogen for comparison with response to BPA

- 0.05 or 0.5 µg/kg bw/day ethinyl estradiol (EE₂)

- Dose informed by effects observed in prior studies of EE₂ in the NCTR Sprague-Dawley rat
  - NTP technical report TR-548: https://ntp.niehs.nih.gov/go/tr548ab
  - Delclos et al., 2014: https://doi.org/10.1093/toxsci/kfu022
Challenges for Interpretations

- 56 exposure groups
  - Seven times the number of exposure groups of a standard NTP rat 2-year study
  - Statistical and interpretive challenge

- 10,000x dose-response range
  - “Guideline” chronic studies usually cover only 3 doses over a 4x to 10x dose range
  - Challenges expectations of what a “dose-dependent” response should look like

- Historical experience
  - Few recent long-term studies in this strain
  - NTP has never done an in vivo study with this number of groups with as wide a range in a study longer than 90 days
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• **Scientific oversight**
  
  – Steering committee: representatives from NTP, NIEHS, NCTR, CFSAN, and researchers from the grantee institutions
  
  – External scientific panel

• **Grantee data management**
  
  – Grantees were blinded to the doses of BPA that the animals or tissues received
  
  – Blinded data deposited directly into NTP’s Chemical Effects in Biological Systems (CEBS) database
    - [https://ntp.niehs.nih.gov/go/datasearch](https://ntp.niehs.nih.gov/go/datasearch)
  
  – Decoding team (NIEHS/NCTR) ensured all data collected and missing data explanations provided prior to decoding and sending decoded data to grantees
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<th>Principal Investigator</th>
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<th>Health Endpoint</th>
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<td>Scott Belcher</td>
<td>NC State University</td>
<td>Cardiovascular</td>
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<td>Nira Ben-Jonathan</td>
<td>University of Cincinnati</td>
<td>Obesity/adipose tissue</td>
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<td>Kim Boekelheide</td>
<td>Brown University</td>
<td>Testis function/sperm count</td>
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<td>Jodi Flaws</td>
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<td>Nestor Gonzalez-Cadavid</td>
<td>University of California Los-Angeles</td>
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<td>Andrew Greenberg</td>
<td>Tufts University</td>
<td>Diabetes, blood glucose, pancreas, liver</td>
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<td>Shuk-mei Ho</td>
<td>University of Cincinnati</td>
<td>Uterine cancer</td>
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<td>Norbert Kaminski</td>
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<td>Heather Patisaul</td>
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<td>Gail Prins</td>
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<td>Cheryl Rosenfeld</td>
<td>University of Missouri</td>
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<td>Ana Soto</td>
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<td>Frederick vom Saal</td>
<td>University of Missouri</td>
<td>Male urogenital abnormalities</td>
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<td>Thomas Zoeller</td>
<td>University of Massachusetts</td>
<td>Thyroid and brain anatomy</td>
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Program Status and Next Steps

- NTP Research Report
  - Draft being reviewed at THIS meeting
  - Final report: anticipated to be completed by summer 2018
- Grantee publications
  - Ongoing
- Grantee data sets
  - Data reformatting to common format is ongoing
  - Methods prepared and in review
  - Anticipate all data available by August 2018
- Integrated interpretation of all datasets and publications
  - To occur after release of grantee datasets
  - Report anticipated in 2019: will be peer-reviewed
• Program overview

• Link to Core Study data
  – LIVE

• Links to Grantee data sets
  – August 2018

https://ntp.niehs.nih.gov/go/clarity_bpa