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

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NTP Research Report Peer-Review Meeting
April 26, 2018
• Background
• CLARITY-BPA
• Core Study
• Program Management and Next Steps
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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
• 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

Historical NTP Context

- Developmental toxicity for fetuses, infants, and children (effects on the brain, behavior, and prostate gland)
- Developmental toxicity for fetuses, infants, and children (effects on the mammary gland and early puberty in females), and reproductive toxicity in workers
- Reproductive toxicity in adult men and women and malformations in newborns
• 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)
CLARITY-BPA: Project Development

• 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
• “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
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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
Core Study: Dose Choice and Rationale

- 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
Core Study: Reference Control

- 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
  – 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>
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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>
<td>NC State University</td>
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<td>Gail Prins</td>
<td>University of Illinois</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>Breast cancer</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
Data Availability

• Program overview

• Link to Core Study data
  – LIVE

• Links to Grantee data sets
  – August 2018

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