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

Integration Report Preparation Update

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NTP Board of Scientific Counselors
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• Bisphenol A and origins of the CLARITY-BPA program
• CLARITY-BPA key components
• CLARITY-BPA “core study” peer review and report conclusions
• Academic “investigational” arm, laboratories, endpoints, and publications to date
• Objectives of the integration report(s)
• Elements of systematic review applied to the CLARITY-BPA publications
• Components of Integration report(s)
• Widely used to make polycarbonate plastics and epoxy resins

• Low human exposure (<1 µg/kg body weight/day) primarily from food contact materials

• Considerable debate over risk as an endocrine disruptor

• Guideline rodent studies conducted under Good Laboratory Practices (GLP) show no effects of concern at “low doses”

• Academic hypothesis-driven studies report that BPA induces effects in a variety of model systems at low exposures

• Suggestive findings from human epidemiology studies

• Widespread agreement that there is disagreement on human health significance

• Evaluated available scientific literature for possible effects of BPA on human development and reproduction

• Conclusions:
  
  – **Some concern**: brain, behavior, and prostate gland in fetuses, infants, and children at current exposure levels

  – **Minimal concern**: Developmental toxicity for fetuses, infants and children (effects on mammary gland and early puberty in females), and reproductive toxicity in workers

  – **Negligible concern**: Reproductive toxicity in adult men and women, fetal or neonatal mortality, birth defects, or reduced birth weight and growth
• FDA Draft Assessment (2008) concluded the no-observed-adverse-effect-level (NOAEL) was 5,000 µg/kg bw/day for systemic toxicity

• FDA Science Board (2008) recommended further research to address the potential developmental toxicity of BPA
  
  – “a large rodent study should be considered to address the central question of developmental toxicity of BPA. To this end, the study must be designed;

  1) to meet criteria for acceptance established by the FDA or reasonable criteria applied by the scientific community for study evaluation that FDA should adopt,

  2) to address the endocrine mechanism-based concerns of the scientific community, and

  3) to use endpoints and models validated for the study of endocrine-mediated developmental processes.”

• The FDA considers BPA safe at current levels occurring in foods and food packaging based on:

  – Progressive series of “cumulative” formal evaluations from 2009-2014
  – Ongoing review of scientific evidence (2014-present)
Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA)

Developed by NIEHS and FDA in response to the FDA Science Board recommendation

Elements

- Address scientific uncertainties about BPA toxicity
- Use a long-term oral dosing protocol with developmental exposure
- Include additional endpoints not typically assessed in guideline studies assessing BPA and endocrine hazards
- Use a common “core” exposure paradigm across all studies, conducted according to GLP with “positive” EE2 control
- Use a broad dose range (2.5, 25, 250, 2500, 25000 μg/kg bw/day)
CLARITY-BPA Organization

- 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)
CLARIY-BPA: Project Development

- NIEHS Funding Opportunity Announcement (2010)
  - Develop a consortium of researchers to work with the NCTR and NTP in the design of a chronic toxicity study of BPA in NCTR-SD rats with *in utero*, and direct gavage exposures to pups from PND 1 through weaning, or two years
  - Proposals solicited for hypothesis-driven mechanistic studies focusing on disease/dysfunction endpoints to add to the chronic study design

- Applicants selected via NIH scientific peer review (2011)
  - Proposed grantee projects subsequently assessed for technical feasibility by NIEHS and NCTR

- Final Core Study design developed and agreed upon by CLARIY-BPA consortium members (2012)
“Core Study” 2-year chronic study conducted under GLP at FDA/NCTR
- Designed in accordance with accepted guidelines for assessing chronic toxicity and carcinogenicity
- Draft report peer reviewed April, final Report released September 2018

“Grantee Studies”
- 14 Academic investigators selected from applications
- 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 academic investigational studies
• 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 received
  – All data deposited directly into NTP’s Chemical Effects in Biological Systems (CEBS) database
    • https://ntp.niehs.nih.gov/go/datasetsearch
  – Decoding team (NIEHS/NCTR) ensured all data collected and missing data explanations were provided prior to decoding and sending decoded data to grantees
“Core Study” Peer Review

• Peer review meeting - April 26, 2018 at NIEHS
  – Six member panel chaired by Dr. David Dorman, NCSU
  – Robust discussion
  – Narrative conclusions rather than “levels of evidence”
  – Revised final report issued as part of the NTP Research Report series

• NTP Research Report on the CLARITY-BPA Core Study: A Perinatal and Chronic Extended-Dose Range Study of Bisphenol A in Rats, NTP RR 9, September 2018
In conclusion,… statistical differences between BPA treatment groups, particularly below 25,000 μg/kg bw/day, and the vehicle control group detected by the low-stringency statistical tests applied to histopathology lesions, were not dose responsive, sometimes occurring in only one low or intermediate dose group, and did not demonstrate a clear pattern of consistent responses within or across organs within the stop- and continuous-dose arms and sacrifice times.

In contrast, the high EE2-dose elicited several estrogenic effects in females in a clearly interpretable and biologically plausible manner.

Several observations at 25,000 μg BPA/kg bw/day may be treatment related, including effects in the female reproductive tract (ovary, uterus, and vagina) and in the male pituitary.
# NIEHS CLARITY-BPA Grantees

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Health Endpoint</th>
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<tbody>
<tr>
<td>Scott Belcher</td>
<td>NC State University</td>
<td>Cardiovascular</td>
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<tr>
<td>Nira Ben-Jonathan</td>
<td>University of Cincinnati</td>
<td>Obesity/adipose tissue</td>
</tr>
<tr>
<td>Kim Boekelheide</td>
<td>Brown University</td>
<td>Testis function/sperm count</td>
</tr>
<tr>
<td>Jodi Flaws</td>
<td>University of Illinois</td>
<td>Ovarian function</td>
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<tr>
<td>Nestor Gonzalez-Cadavid</td>
<td>University of California Los-Angeles</td>
<td>Penile function</td>
</tr>
<tr>
<td>Andrew Greenberg</td>
<td>Tufts University</td>
<td>Diabetes, blood glucose, pancreas, liver</td>
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<tr>
<td>Shuk-mei Ho</td>
<td>University of Cincinnati</td>
<td>Uterine cancer</td>
</tr>
<tr>
<td>Norbert Kaminski</td>
<td>Michigan State University</td>
<td>Immune function</td>
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<tr>
<td>Heather Patisaul</td>
<td>NC State University</td>
<td>Learning and behavior</td>
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<tr>
<td>Gail Prins</td>
<td>University of Illinois</td>
<td>Prostate cancer</td>
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<tr>
<td>Cheryl Rosenfeld</td>
<td>University of Missouri</td>
<td>Learning and behavior</td>
</tr>
<tr>
<td>Ana Soto</td>
<td>Tufts University</td>
<td>Breast cancer</td>
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<tr>
<td>Frederick vom Saal</td>
<td>University of Missouri</td>
<td>Male urogenital abnormalities</td>
</tr>
<tr>
<td>Thomas Zoeller</td>
<td>University of Massachusetts</td>
<td>Thyroid and brain anatomy</td>
</tr>
</tbody>
</table>
• **Collate** information from core studies with academic investigational studies published or (pending publication) for each organ system
  
  – Brain/behavior 6
  – Cardiac 1
  – Diabetes (pancreas, liver) (1)
  – Immune 2
  – Mammary (1)
  – Ovary 1
  – Prostate/penis 1 (2)
  – Testis/sperm 1
  – Thyroid (1)
  – Uterus (1)

• **Synthesize** findings for endpoints using elements of systematic review

• **Develop** consensus confidence statements for association of health effects with BPA exposures and for evidence of non-monotonic dose response
Second Objective

• “While the study is expected to contribute to our understanding of potential effects of BPA, it also has ramifications beyond this specific focus.” Schug et al (2013)
  
  – “By drawing upon the strengths of academic and regulatory expertise and research approaches, CLARITY-BPA represents a potential new model for filling knowledge gaps, enhancing quality control, informing chemical risk assessment, and identifying new methods or endpoints for regulatory hazard assessments.”

• Compare findings and methods from the core and academic CLARITY-BPA consortium studies with prior published studies on BPA by participants in the consortium, using elements of systematic review.

• Identify technologies or enhanced endpoint measures that may improve our capacity to detect endocrine-related effects in guideline studies.

• Discuss strengths and limitations of the CLARITY-BPA approach to an academic-regulatory partnership.
Systematic Review - What is it and why use it?

- Systematic reviews, pioneered in the clinical field, provide a transparent, methodologically rigorous and reproducible means of summarizing the available evidence on a precisely framed research question.

- Systematic-review methodologies provide objectivity and transparency to the process of collecting and synthesizing scientific evidence in reaching conclusions on specific research questions.

- The product of a systematic review can then be used to inform decisions, reach conclusions, or identify research needs.
Systematic Review Process

- Problem formulation and protocol development
- Comprehensive literature search
- Select relevant studies and extract data
- Assess individual study quality/risk of bias*/utility
- Rate confidence in the body of evidence

*Risk of bias is defined as a measure of whether features of the design, conduct or analysis of a study may cause systematic error in the study’s results

Evidence Integration

- Process for developing hazard conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data

Systematic Review Process
- Problem formulation and protocol development
- Comprehensive literature search
- Select relevant studies and extract data
- Assess individual study quality/risk of bias/utility
- Rate confidence in the body of evidence

No plans for evidence integration steps

Evidence Integration
- Process for developing hazard conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data
Introduction – purpose, methods
Results of the CLARITY-BPA study
Consensus conclusions of the CLARITY-BPA consortium

Assess prior published studies on BPA from laboratories participating in CLARITY-BPA
Recommend changes to “guideline” studies for endocrine active agents if appropriate
Determine strengths and limitations of the linkage of academic and guideline studies under the CLARITY-BPA design
Suggest future ways to integrate academic and guideline compliant studies of endocrine active agents

Appendices
- Systematic review protocols for each endpoint evaluated
- Study quality/risk of bias evaluations
• Published study evaluations (underway)
• Waiting on final publications
• Consortium review and consensus conclusions (Spring 2019)
• Public Peer Review (Summer 2019)
Acknowledgments

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• NTP/NIEHS Nigel Walker, Mary Wolfe, and many others

• DERT/NIEHS Thad Schug, Jerry Heindel

• The Chemical Effects in Biological Systems (CEBS) team

• Integration report preparation team: Kembra Howdeshell, Andrew Rooney, Brandy Beverly, Retha Newbold, Vickie Walker, and ICF contract support
Questions?