NTP
National Toxicology Program

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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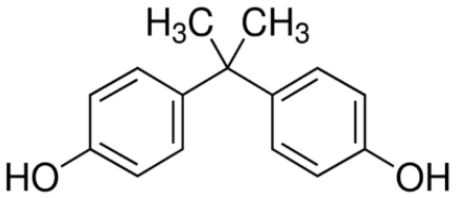
Outline

- 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)

Bisphenol A (BPA)

- 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



Historical NTP Context

- NTP Center for the Evaluation of Risks to Human Reproduction Monograph (2008)
- 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

U.S. Regulatory Position

- 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)

CLARITY-BPA Inception

- 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)

CLARITY-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 CLARITY-BPA consortium members (2012)

CLARITY-BPA: Key Components

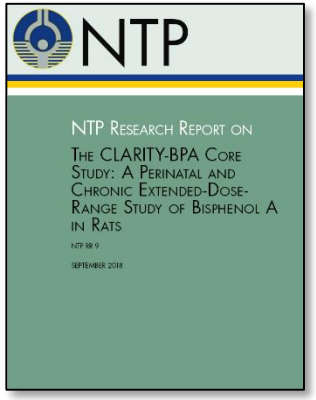
- "Core Study" 2-year chronic study conducted under GLP at FDA/NCTR
  - Designed in accordance with accepted guidelines for assessing chronic toxicity and carcinogenicity
  - Draft report peer reviewed April, final Report released September 2018
- "Grantee Studies"
  - 14 Academic investigators selected 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

Program Management

- 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/datasearch
  - 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
  - https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/rr09_508.pdf



“Core Study” Conclusions

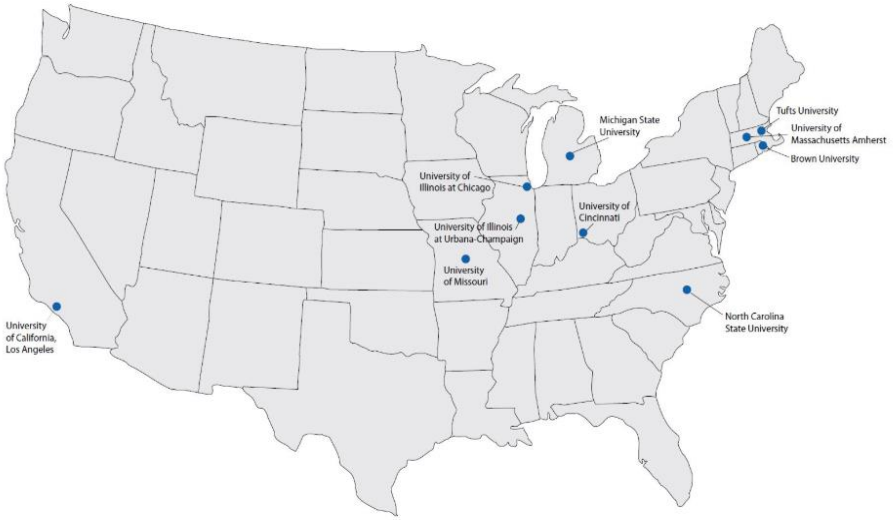
- In conclusion,… statistical differences between BPA treatment groups, particularly below 25,000 µg/kg bw/day, and the vehicle control group detected by the low-stringency statistical tests applied to histopathology lesions, were not dose responsive, sometimes occurring in only one low or intermediate 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

Principal Investigator	Institution	Health Endpoint
Scott Belcher	NC State University	Cardiovascular
Nira Ben-Jonathan	University of Cincinnati	Obesity/adipose tissue
Kim Boekelheide	Brown University	Testis function/sperm count
Jodi Flaws	University of Illinois	Ovarian function
Nestor Gonzalez-Cadavid	University of California Los-Angeles	Penile function
Andrew Greenberg	Tufts University	Diabetes, blood glucose, pancreas, liver
Shuk-mei Ho	University of Cincinnati	Uterine cancer
Norbert Kaminski	Michigan State University	Immune function
Heather Patisaul	NC State University	Learning and behavior
Gail Prins	University of Illinois	Prostate cancer
Cheryl Rosenfeld	University of Missouri	Learning and behavior
Ana Soto	Tufts University	Breast cancer
Frederick vom Saal	University of Missouri	Male urogenital abnormalities
Thomas Zoeller	University of Massachusetts	Thyroid and brain anatomy

Next Steps-First Objective

- *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)



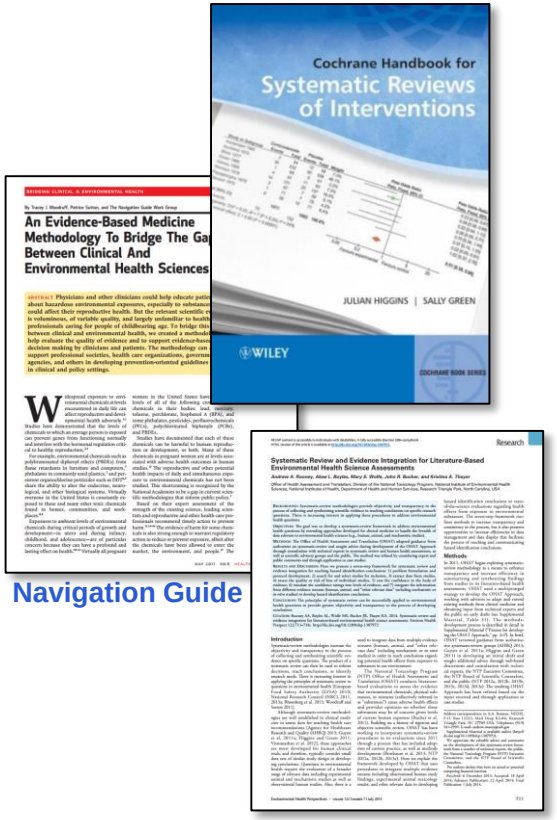
- *Synthesize* findings for endpoints using elements of systematic review
- *Develop* consensus confidence statements for association of health effects with BPA exposures and for evidence of non-monotonic dose response

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.



Navigation Guide

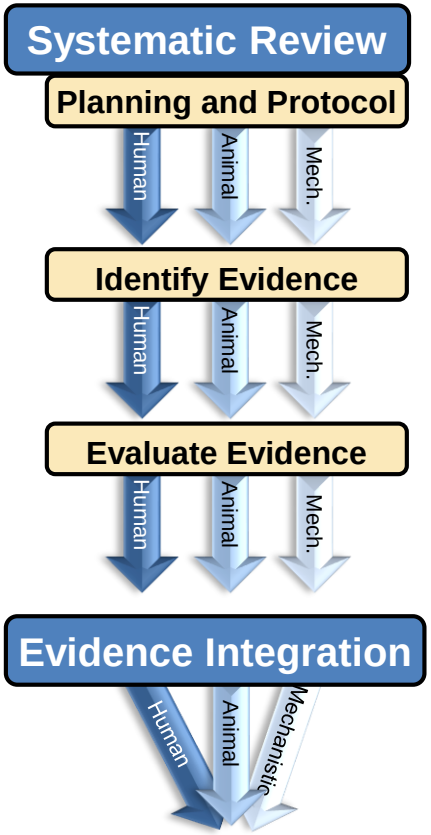
OHAT Method

Systematic Review

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

OHAT Method, Rooney *et al.* (2014) EHP 122:711-718.

Elements of Systematic Review for CLARITY-BPA

Systematic Review Process

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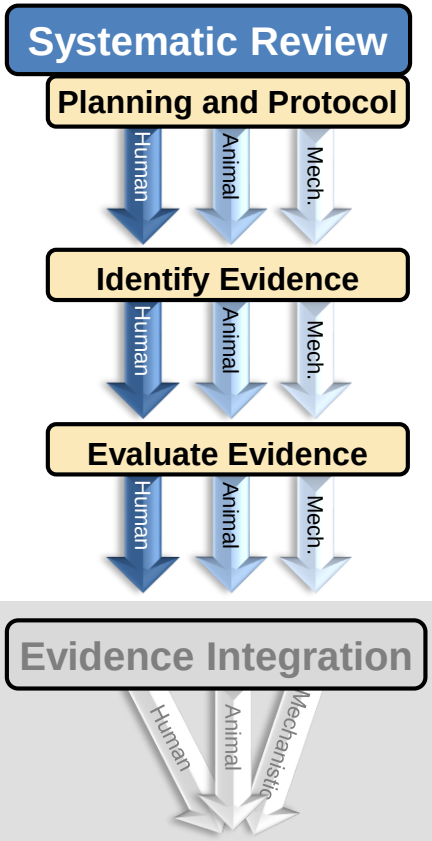

No plans for evidence integration steps

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

Organization of Reports

- 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

Timeline

- 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
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Questions?