

# 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 ( $<1 \mu\text{g}/\text{kg}$  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

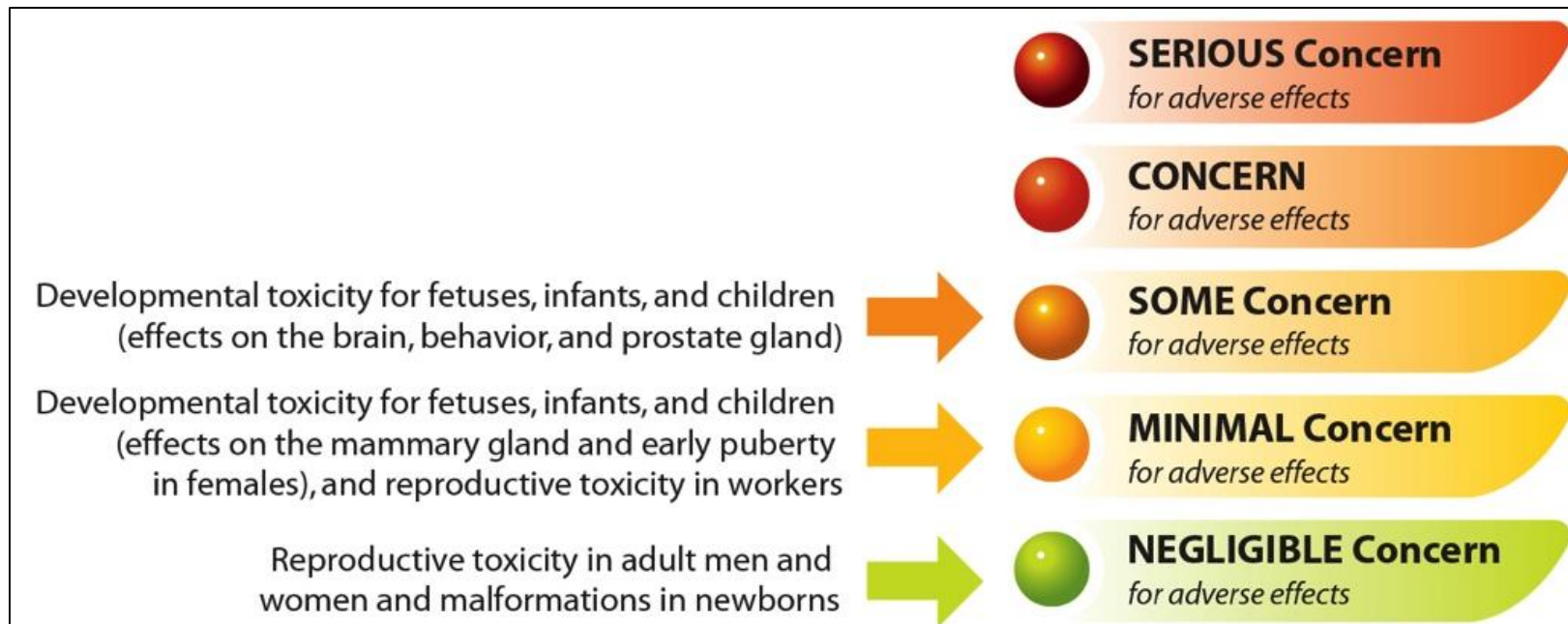
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- The U.S. Food and Drug Administration (FDA) maintains that BPA is safe at the current levels occurring in foods
- FDA also supports currently-approved uses of BPA in food containers and packaging
- Conclusions based on FDA assessments
  - Progressive series of “cumulative” formal evaluations from 2009-2014
  - Ongoing review of scientific evidence (2014-present)



# Historical NTP Context

- National Toxicology Program (NTP) Monograph (2008)
- Evaluated the available scientific literature about the possible effects of BPA on human development and reproduction
- Conclusions





# Historical Regulatory Context

- FDA Draft Assessment (2008) concluded the appropriate no-observed-adverse-effect-level (NOAEL) was 5,000  $\mu\text{g}/\text{kg}$  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



# FDA Science Board Key Recommendations

- 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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- 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

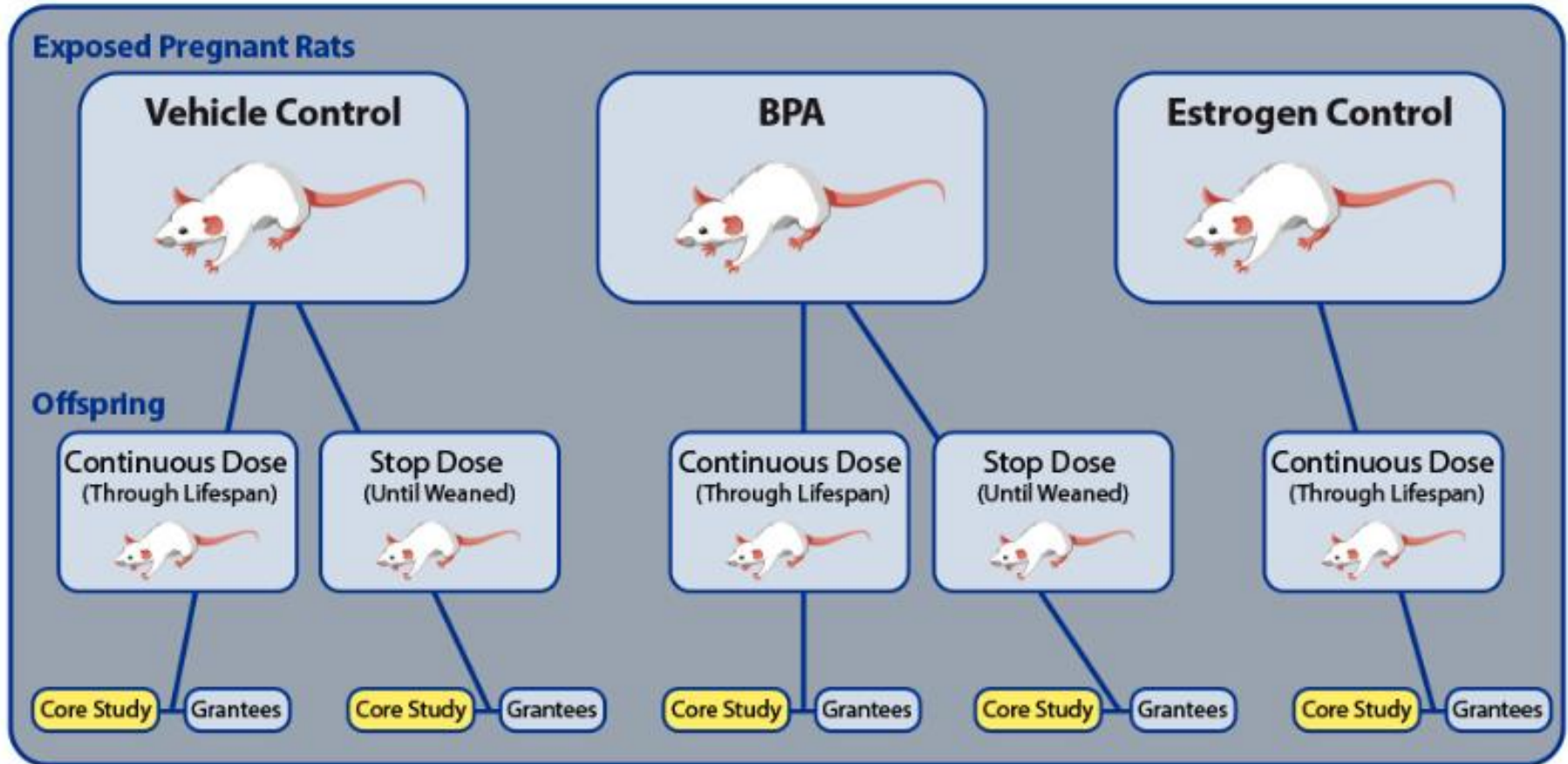


# CLARITY-BPA: Key Components

- “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





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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  $\mu\text{g}/\text{kg}$  bw/day, but not at  $\leq 2,700$   $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$  bw/day ethinyl estradiol ( $\text{EE}_2$ )
- Dose informed by effects observed in prior studies of  $\text{EE}_2$  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



# NIEHS CLARITY-BPA Grantees

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



# 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

CLARITY-BPA Program

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[https://ntp.niehs.nih.gov/go/clarity\\_bpa](https://ntp.niehs.nih.gov/go/clarity_bpa)

The draft NTP Research Report presenting Core Study results will undergo peer review by an external expert panel on April 26, 2018. The draft report and additional details are available on the [meeting](#) and [study data](#) webpages.

In order to study the full range of potential health effects from exposure to Bisphenol A (BPA) and to provide data that can be used for regulatory decisions, NIEHS, NTP, and the U.S. Food and Drug Administration (FDA) developed a research program called Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA).

CLARITY-BPA aims to create a mutually beneficial partnership that unites standard research practices used by regulators with innovative studies conducted at universities.

CLARITY-BPA has two components:

- **Core Study:** A two-year guideline-compliant study of potential BPA toxicity in rats, which was conducted according to federal regulatory and statutory guidelines for toxicity testing.
- **Grantee Studies:** Studies conducted by university researchers but testing a broader range of health endpoints, including genetic impacts, cardiovascular disease, obesity, and behavior. The Grantee Studies used animals raised in the same conditions and exposed to the same doses of BPA as the Core Study.

These two components combined to produce a robust [study design](#). One key strength was identical BPA exposure conditions for both components of the study, which were provided at the same facility in the FDA's National Center for Toxicological Research (NCTR). A second strength was that grantees received blinded Core Study samples, meaning they did not know whether samples had been dosed with BPA or how much, to minimize the potential for bias.

Final CLARITY-BPA conclusions, expected from NTP in 2019 as shown in the timeline, will be drawn from the integration of the Core Study and Grantee Studies.

**CLARITY-BPA Timeline**

Feb 2012: CLARITY-BPA Convened

Feb 2018: Draft Core Study Report Released

Mar: Draft Core Study Report Peer Review

Apr

May

Jun

Jul

Aug: Final Core Study Report Released

Aug: Grantee Data Released

Aug 2019: Final CLARITY-BPA Conclusions

[https://ntp.niehs.nih.gov/go/clarity\\_bpa](https://ntp.niehs.nih.gov/go/clarity_bpa)