NTP
National Toxicology Program

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

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NTP Research Report Peer-Review Meeting
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# Outline

- Background
- CLARITY-BPA
- Core Study
- Program Management and Next Steps

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# Bisphenol-A (BPA)

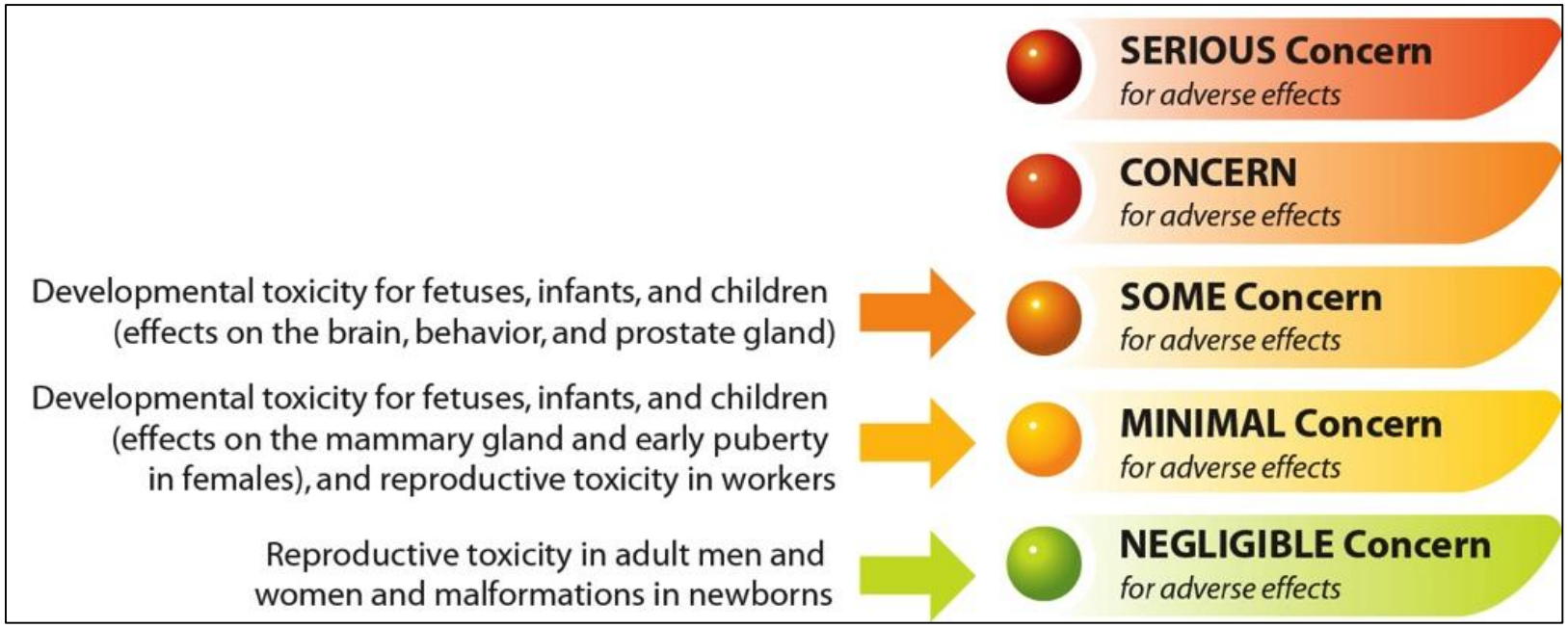
- Chemical widely used to make polycarbonate plastics and epoxy resins
- Widespread low exposure (<1 µg/kg body weight (bw)/day) from migration of small amounts into foods from food contact materials
- Considerable debate over risk posed by “low level” exposure
- Guideline studies conducted under Good 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)

# 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 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

# 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

https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-05.pdf

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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

# CLARITY-BPA

- 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)

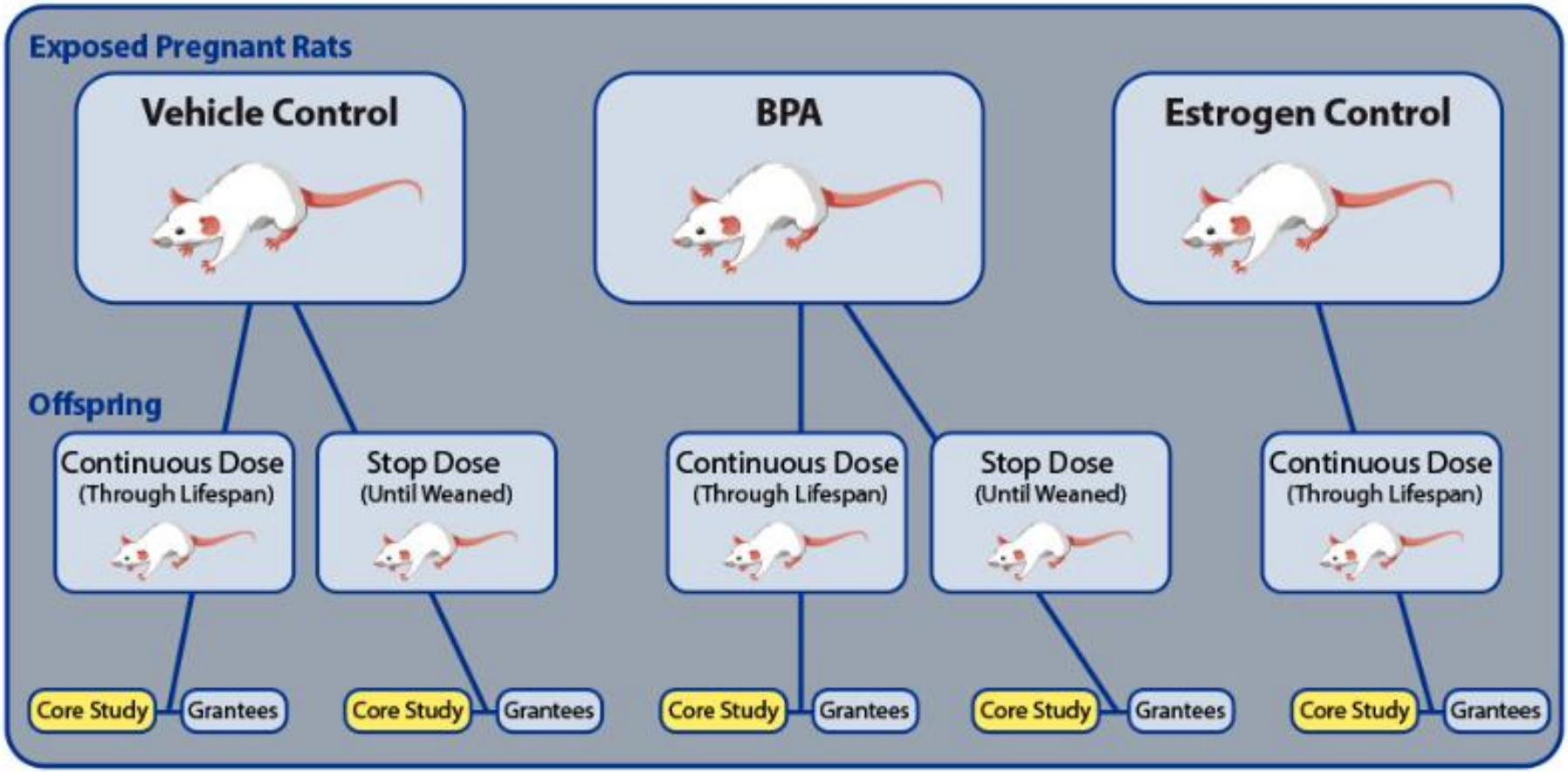
# CLARITY-BPA: Project Development

- 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 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 ($EE_2$)
- Dose informed by effects observed in prior studies of $EE_2$ 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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# 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 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

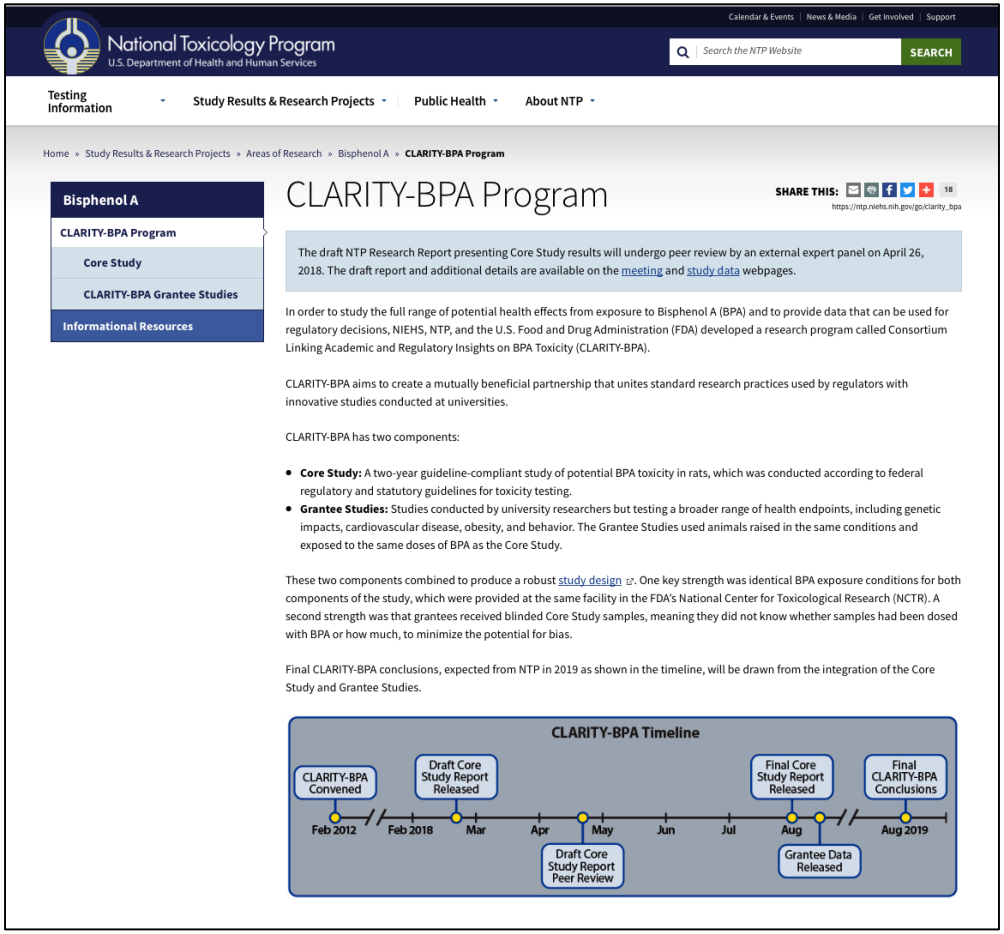
| Principal Investigator | Institution | Health Endpoint |
|---|---|---|
| Scott Belcher | NC State University | Cardiovascular |
| Nira Ben-Jonathan | University of Cincinnati | Obesity/adipose tissue |
| Kim Boekelheide | Brown University | Testis function/sperm count |
| Jodi Flaws | University of 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 |

# 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