NTP
National Toxicology Program

"Integrating regulatory and academic investigations in hazard assessments by the US National Toxicology Program. Lessons learned from the CLARITY-BPA initiative

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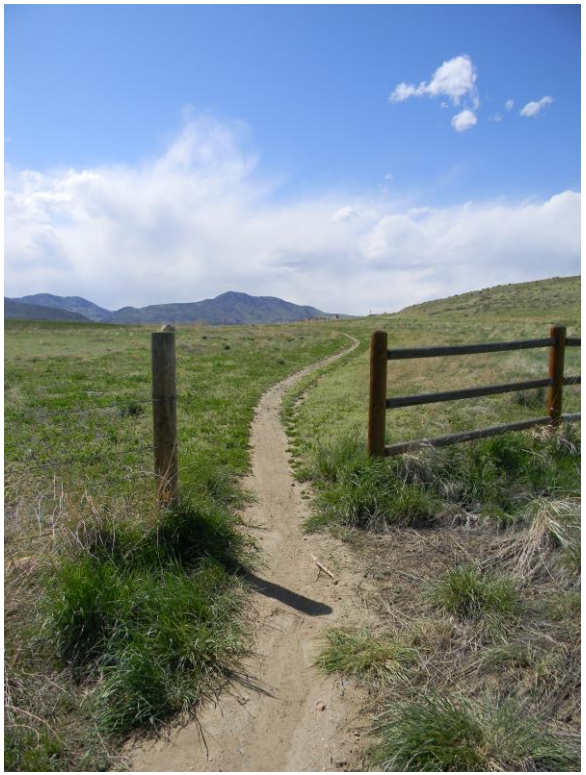
Conflict of Interest Statement

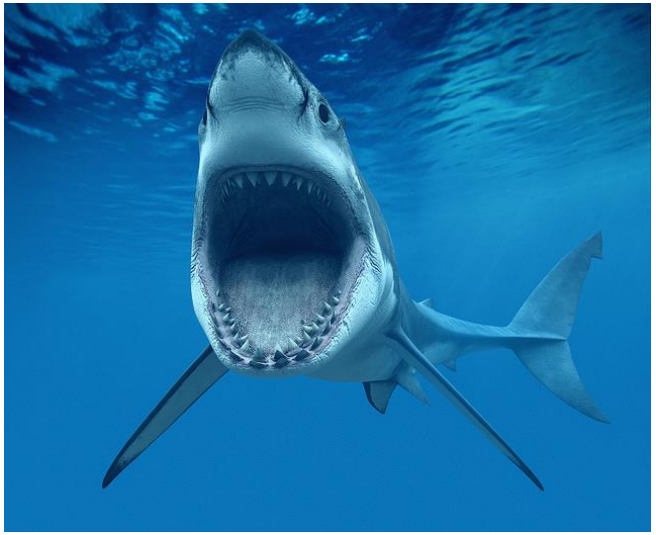
- I declare that I have no conflicts of interest
- The contents of this presentation reflect the opinions and views of the author.

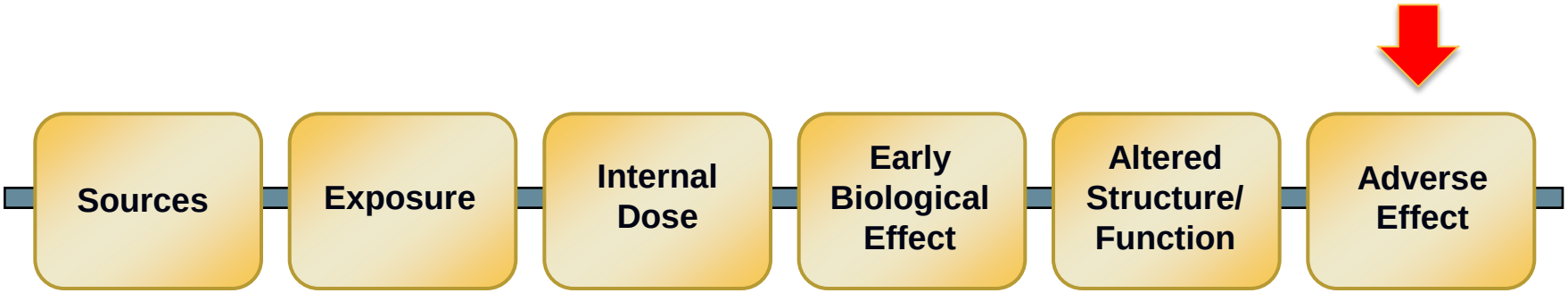
- Introduction
- NIEHS programs
  - Dioxin TEF R03 Program
  - Nano consortia
- CLARITY-BPA
- Lessons learned

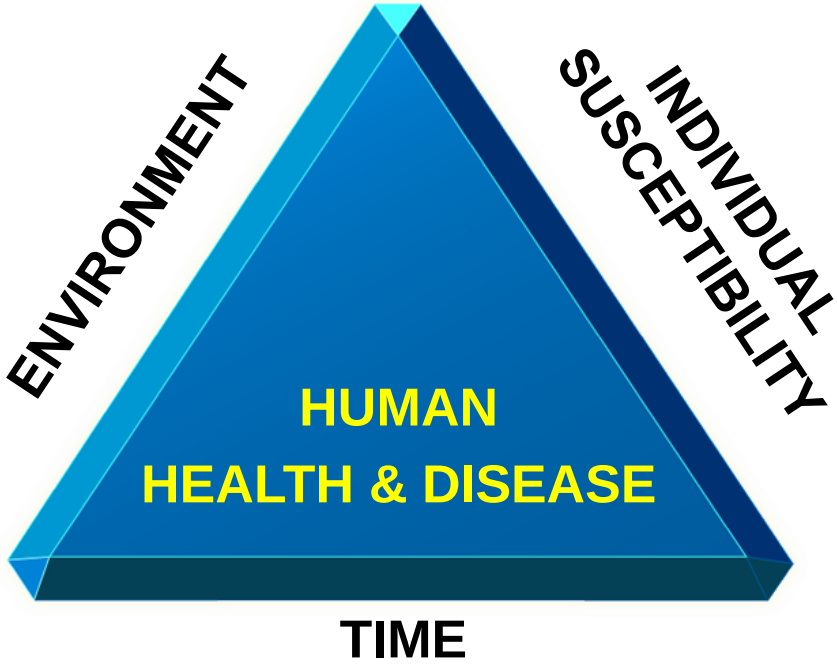


Risk = hazard x exposure

- Exposure assessment
- Hazard identification
- Hazard characterization
- Dose-response

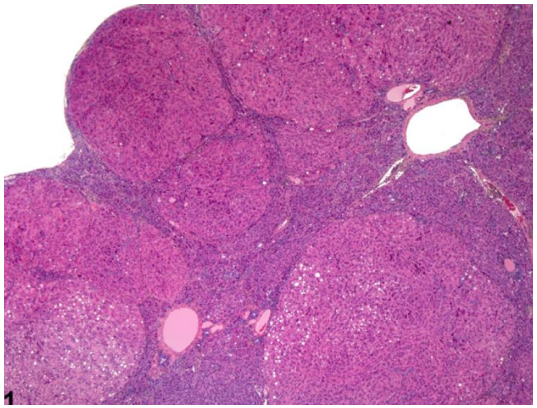


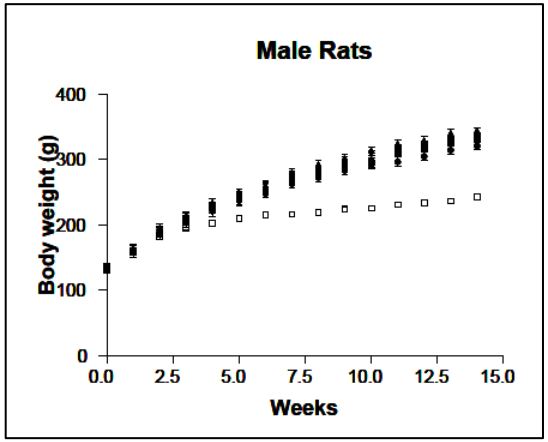

Sources
Exposure
Internal Dose
Early Biological Effect
Altered Structure/ Function
Adverse Effect


ENVIRONMENT
INDIVIDUAL SUSCEPTIBILITY
HUMAN
HEALTH & DISEASE
TIME

Biological levels of a hazard

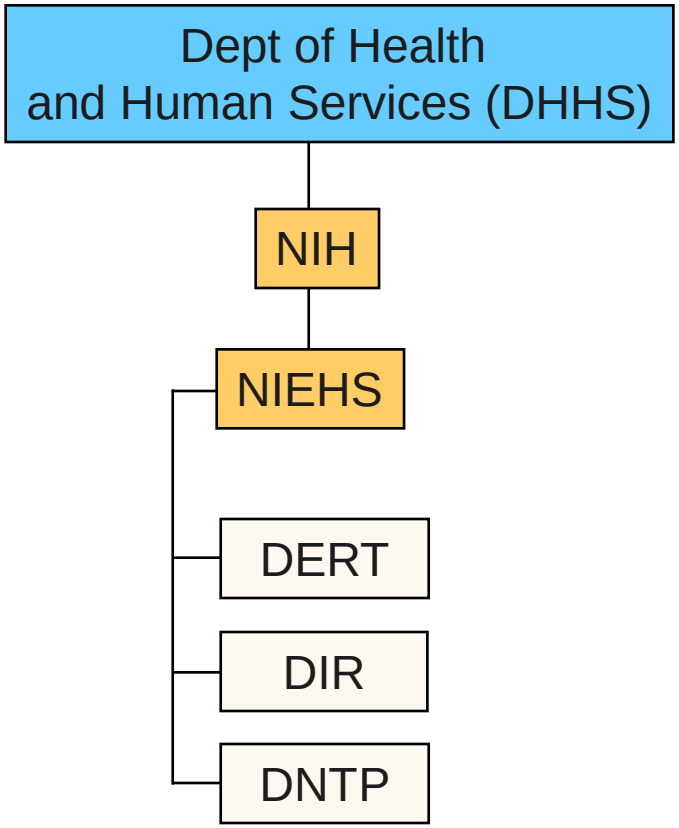
- Molecular
  - Eg cholinesterase inhibition
- Pathways
  - Eg oxidative stress
- Cellular
  - single cell necrosis
- Organ
  - Eg Neoplasia
- System
  - Eg disruption of thyroid hormone homeostasis
- Individual
  - Eg body weight, death
- Population
  - Eg Shifts in IQ distribution





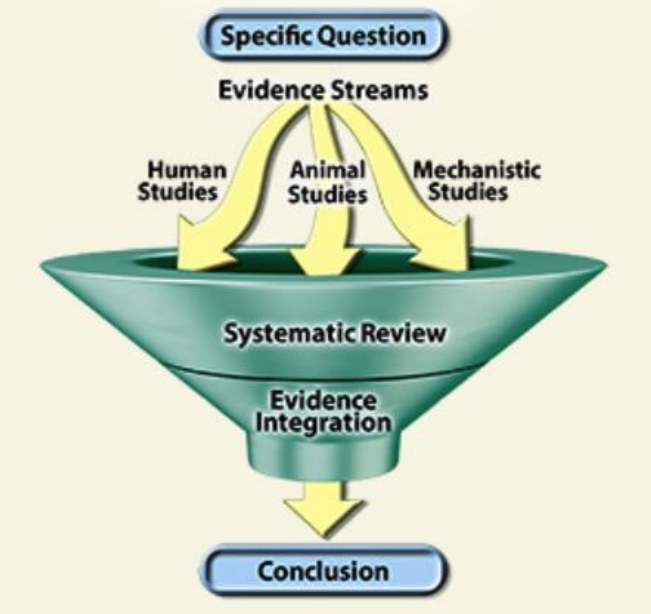
Overview of NIEHS research

- Funded by NIEHS
  - Division of Extramural Research and Training (DERT)
    - Grants
    - Superfund Research Program
    - Worker Education Training Program (WETP)
- Conducted by NIEHS
  - Intramural Research (DIR)
    - Investigator Initiated research
  - National Toxicology Program (DNTP)
    - Contract based research and testing



Integration of different data types

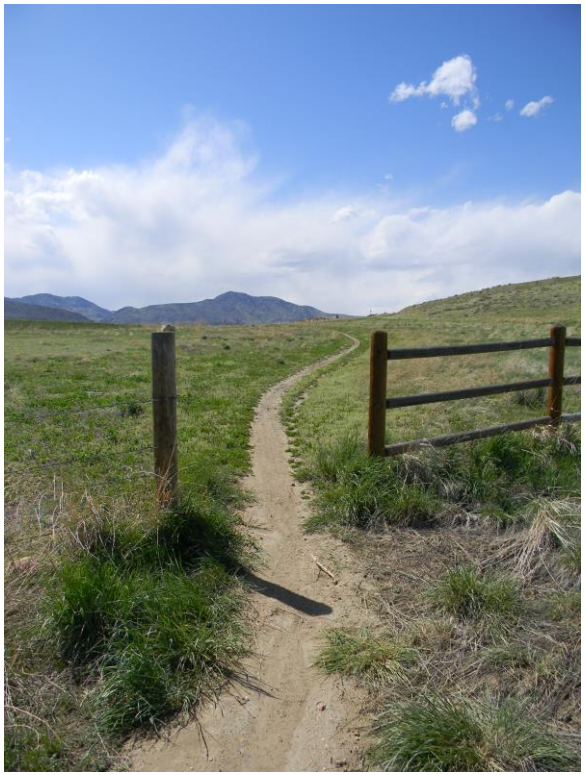
- Different “adverse” effects
  - Human, animal, mechanistic
- Different study types
  - Variety of designs
  - Different experimental models
- Differing levels of ”data trust”
  - Guidelines, GLP
  - Investigative
- Evidence integration as a critical step



Bridging the gap

- Most NIEHS funded research is “investigator initiated”
  - Innovation
  - Flexibility
- Regulatory Science
  - Consistency and “acceptance”
  - Applicability
- Design programs to enhance utility of NIEHS funded academic scientific research in a regulatory context

- Introduction
- NIEHS programs
  - Dioxin TEF R03 Program
  - Nano consortia
- CLARITY-BPA
- Lessons learned



Dioxin TEF program (1998-2004)

- Regulatory question
  - Dose additivity of action of dioxin-like chemicals (USEPA)
- Competitively funded academic grantees
  - “Small” R03 grants
  - Proposals to investigate specific endpoints samples for a series of seven NTP GLP chronic 2 yr rat bioassays
  - Individuals studies, ternary mixture and binary PCB mixtures
- Outcomes; Publications by R03 grantees
  - Hepatic Oxidative stress and DNA damage
  - Hepatic Transcriptomics
  - Intestinal hormone gene expression

Dioxin TEF program (1998-2004)

- Strengths
  - Controlled exposures and interim time points
  - Known targets and underlying mechanism
- Challenges
  - No coordination of grantee proposals
  - Endpoints driven by investigator interest, not regulatory need
  - No involvement of grantees in study design
  - No central collection of grantee data
  - Small R03 award limited extent of work

NIEHS Nano Consortium

- NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) (2010-2014)
  - To gain fundamental understanding of nanomaterial interactions with biological systems and translate observations from in vitro to in vivo
  - How diverse physical and chemical properties (PCPs) dictate these interactions
  - Aid development of risk assessment models to predict safety of ENMs based on PCPs
- Cooperative Agreement (U-mechanism)
  - Closer involvement of federal staff in direction of program
  - Sri Nadadur PhD (Program Administrator)

NIEHS Nano Consortium- composition

- Five U19 centers and Three U01 centers
- Three-prong approach per center
  - In vitro, in vivo, mathematical modeling
  - Grantee ENMs, Consortia-wide ENMs
    - Nanosilver, SWCNT, MWCNT, C60, MOx, Ceria, Qdots
- Selected Focus areas
  - PBPK-PD modeling: Ag, C60
  - Pulmonary dosimetry extrapolation in vitro to in vivo
  - Predictive pulmonary toxicity of metal oxides
  - Murine toxicity of nanoAg
  - Strain susceptibility to inhaled ENMs

NIEHS Nano Consortium-Lessons learned

- Strengths
  - Cooperative agreement funding (U) mechanism
  - Availability of well defined federal strategic plan with identified research needs and data gaps
  - Shared well characterized materials across consortium members
- Limitations
  - No involvement of regulators in selection of grantees
  - Loose connection between proposal and specific regulatory decision making needs
  - No centralized data repository or clear data sharing plan

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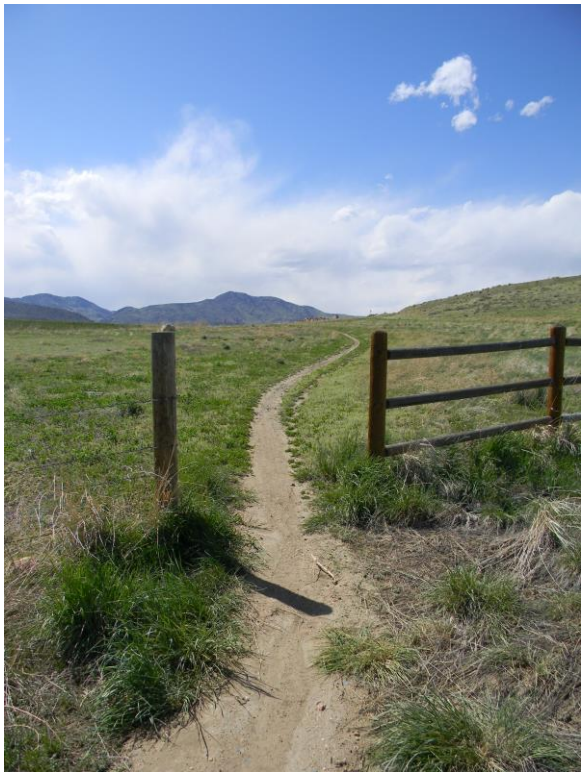
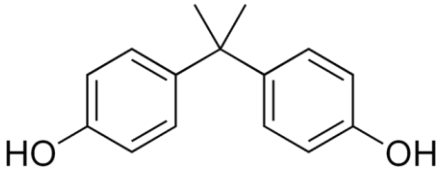


Bisphenol-A (BPA)

- 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



Cross Cutting Issues

- Bisphenols are an exemplar for multiple issues being addressed by NTP and NIEHS
  - What is “endocrine disruption”
  - How do we effectively assess hazards posed by compounds that cause “endocrine disruption”
  - What is low dose?
  - Shape of the dose response and evidence for non-monotonicity of effects across the dose range
  - How to integrate academic investigative research with regulatory guideline complaint research for decision making
  - How to assess hazards for classes of structurally/functionally related compounds
  - How to rapidly assess hazard of “replacements” for commodity chemicals that are shown to be toxic in model systems

CLARITY-BPA Inception

- Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA)
- Developed by NIEHS and FDA
- Goals
  - Address specific knowledge gaps and scientific uncertainties about BPA toxicity
  - Use a relevant compliant long-term oral dosing protocol that includes developmental exposure
  - Interrogate additional endpoints not typically assessed in guideline studies available for assessing BPA hazards
  - Evaluate collaborative approach that could become a new model for investigating complex or controversial chemical exposures.

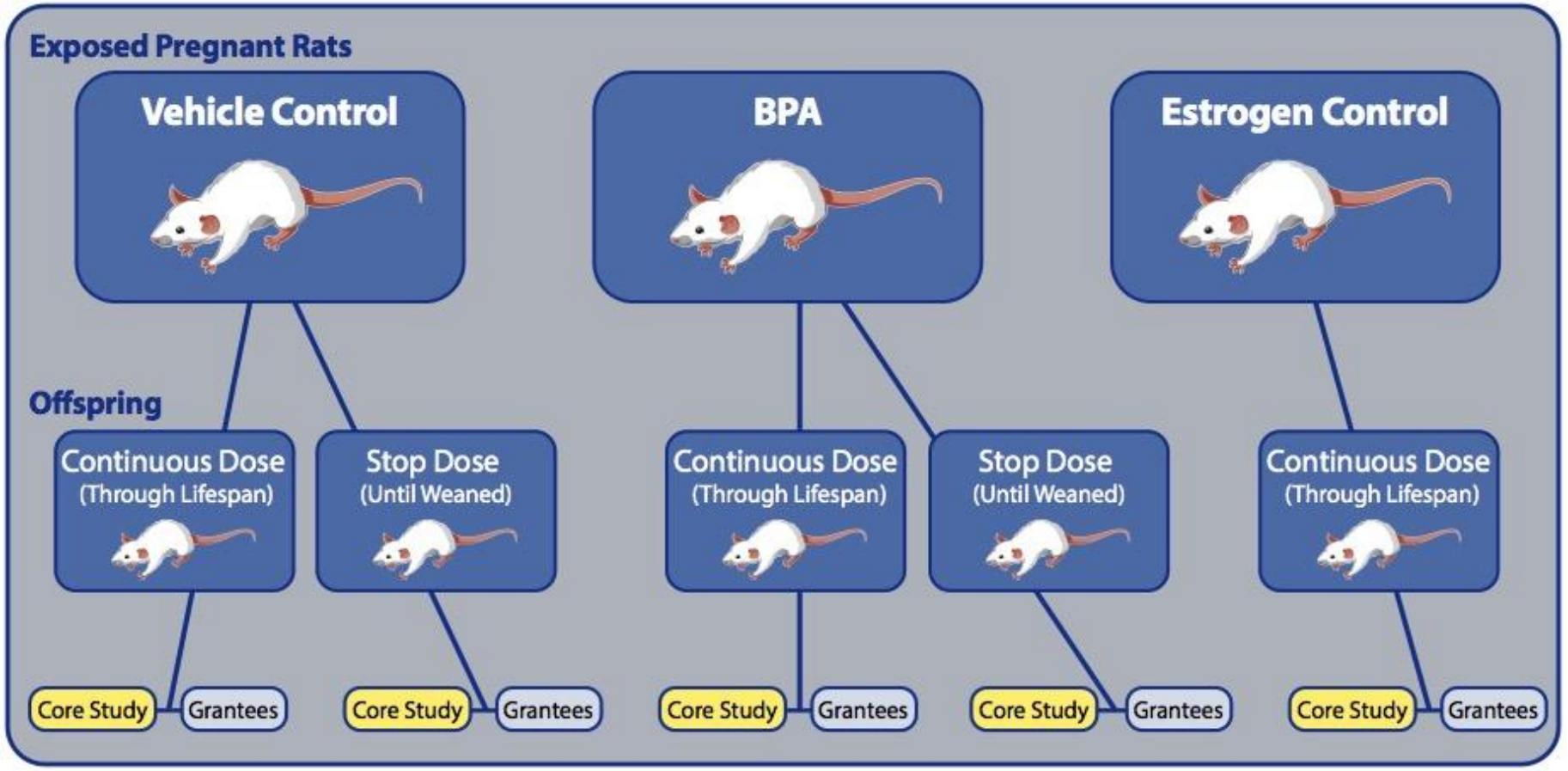
Consortium Development

- NIEHS Funding Opportunity Announcement (2010)
  - Develop a consortium of researchers to work with the NCTR and NTP in final design of chronic gavage toxicity study of BPA
  - Proposals solicited for hypothesis-driven mechanistic studies focusing on disease/dysfunction endpoints which can be added to the chronic study design
- Grantees selected via NIH scientific peer review (2011)
- Each grantee projects subsequently assessed for technical “feasibility” by NIEHS and NCTR for incorporation into the design
- Final Core Study design developed and agreed upon by all CLARITY-BPA consortium members

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
- "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 Program : Design Overview



NIEHS CLARITY-BPA Grantees

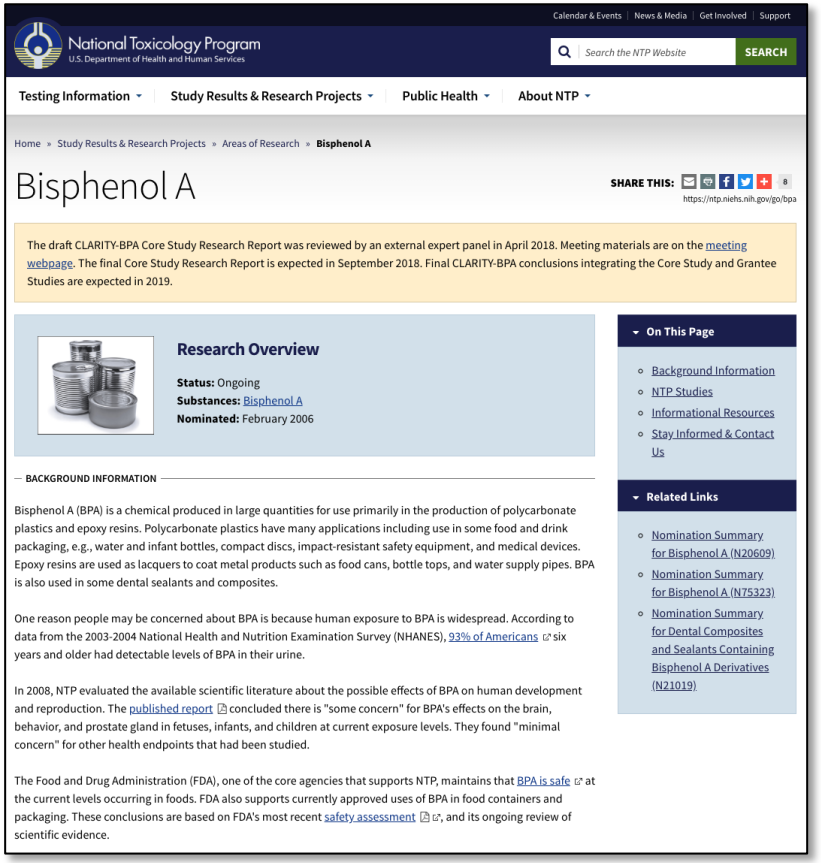
Principal Investigator	Institution	Health Endpoint
Scott Belcher	NC State University	Cardiovascular
Nira Ben-Jonathan	University of Cincinnati	Obesity/adipose tissue
Kim Boekelheide	Brown University	Testis function/sperm count
Jodi Flaws	University of Illinois	Ovarian function
Nestor Gonzalez-Cadavid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

- Scientific oversight
  - Steering committee: Representatives from NTP, NIEHS, NCTR, CFSAN, and researchers from the grantee institutions
- Guiding documents
  - Articles of Collaboration
  - CEBS database agreement
- Federal (NTP) database
- Core federal resources for making data publicly accessible

CLARITY Program Data Availability

- Program overview
- Links to Core Study report and data
- Links to Grantee primary raw data sets and publications



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

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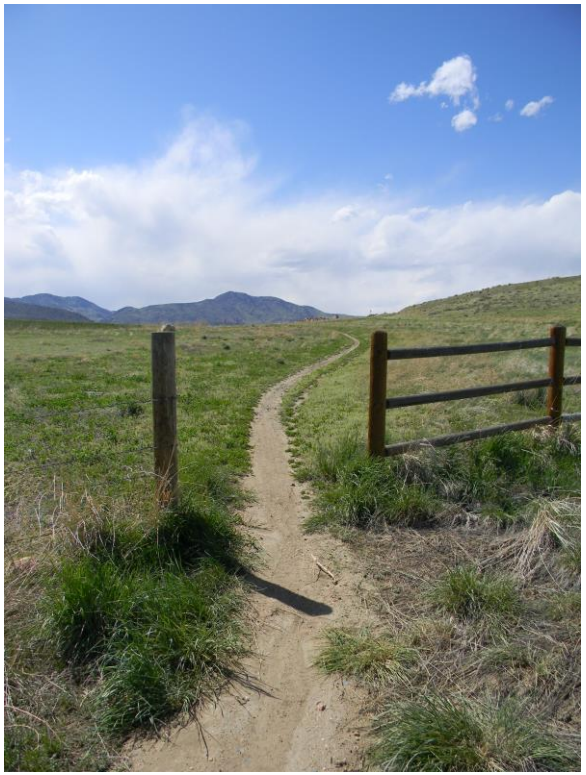

Limitations to the CLARITY approach

- Scheme for peer review and selection of grantee proposals followed traditional NIH peer review procedures
  - No involvement of end “regulatory” user
  - Not *specifically* aligned to address specific regulatory needs
- Academic investigators were limited to using a specific shared design and research model
  - Not necessarily optimal vs past experiences in other models
- Sample acquisition was centralized and coordinated
  - Specialized sample preparation or animal handling procedures required consierable coordination, training and resources.

Strengths of the CLARITY approach

- Identical BPA exposure conditions used for all investigations by the consortium
- Blinding of treatment for core study samples received by the academic grantees
- Development and communication of an a priori list of endpoints to be collected per study
- Requirement that all data planned to be collected be deposited in a private workspace in the NTP's database prior to decoding
- A priori intent to make all "primary" data available

Looking forward

- Need to maximize the utility of such collaborative programs
- Less resource intensive consortia
- Targeted and integrated problem formulation and consortia development phase
  - More direct and earlier communications between regulatory scientists and academic scientists
  - Closer alignment between the identified regulatory data gaps and the proposed studies
- More flexible funding schema after a consortia has been created
  - Flexibility to change directions, adjust goals

National Institute of Environmental Health Sciences

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National Toxicology Program
U.S. Department of Health and Human Services