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Review

A new approach to synergize academic and guideline-compliant research: The CLARITY-BPA research program

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ABSTRACT

Recently, medical research has seen a strong push toward translational research, or "bench to bedside" collaborations, that strive to enhance the utility of laboratory science for improving medical treatment. The success of that paradigm supports the potential application of the process to other fields, such as risk assessment. Close collaboration among academic, government, and industry scientists may enhance the translation of scientific findings to regulatory decision making. The National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), and U.S. Food and Drug Administration (FDA) developed a consortium-based research program to link more effectively academic and guideline-compliant research. An initial proof-of-concept collaboration, the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA), uses bisphenol A (BPA) as a test chemical. The CLARITY-BPA program combines a core perinatal guideline-compliant 2-year chronic toxicity study with mechanistic studies/endpoints conducted by academic investigators. Twelve extramural grantees were selected by NIEHS through an RFA-based initiative to participate in the overall study design and conduct disease-relevant investigations using tissues and animals from the core study. While the study is expected to contribute to our understanding of potential effects of BPA, it also has ramifications beyond this specific focus. Through CLARITY-BPA, NIEHS has established an unprecedented level of collaboration among extramural grantees and regulatory researchers. 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.

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1. Introduction

Translational or "bench-to-bedside" research has gained traction in recent years as a powerful paradigm for driving improvements in medical practice. By facilitating interchange and collaboration among basic biological researchers and clinical practitioners, clinicians are able to take advantage of new tools emerging from basic research and basic researchers are able to draw from real-world observations and needs when developing their investigations [1]. This translational model holds potential for other fields in which basic science is used to inform other practitioners, such as risk assessors. Building more effective connections between risk assessors and those who conduct basic hazard identification research could enhance the scientific basis of chemical risk assessments.

The current scientific paradigm for assessing the toxicity of chemicals is based on two main sources of information: academic research and guideline-compliant research (see Fig. 1). Academic research is generally initiated by independent investigators working in university settings who draw most of their research funding from federal grants. The culture and funding structures of academic research generally lend themselves to smaller-scale, hypothesis-driven studies that use a variety of experimental models to identify a chemical's effect on a variety of potential disease-related endpoints.

Guideline-compliant research, on the other hand, follows guideline procedures outlined for toxicity studies that are conducted to meet regulatory and statutory mandates. Often, such studies are conducted in accordance with guidance developed by a regulatory agency or an international organization. For example, some guideline studies follow FDA's "Redbook" [2] or the guidelines developed by the Organisation for Economic Co-operation and Development (OECD). Guideline studies can be conducted in accordance with Good Laboratory Practices (GLP), a set of internationally recognized quality assurance and quality control processes developed to ensure consistency and standardization in the conduct and reporting of chemical testing for regulatory purposes [3]. Because of the high level of rigor and resultant high level of investment needed to support guideline and GLP-compliant studies, these studies are generally conducted and financially supported as part of the intramural research activities of government agencies or by commercial interests, including bodies within the chemical industry or by contract laboratories as part of premarket or postmarket mandated toxicity testing.

Both guideline-compliant and academic investigator-initiated studies make valuable contributions to our understanding of the potential health effects of chemicals [4]. The strengths of academic research include a greater flexibility to respond to new scientific developments and experiment with new technologies, methods, or endpoints. Hypothesis-driven academic research is also often driven to explore fundamental mechanisms of biological phenomena, not just assessment of potential toxicity or risk. On the other hand, guideline studies conducted in accordance with GLP benefit from validated methods and established protocols, transparent data recording and reporting systems, and a level of standardization, quality control, statistical power, and consistency that allows results to be compared more easily across studies.

Evaluating the relative strengths and weaknesses of different and sometimes conflicting scientific findings is a challenge faced by risk assessors who must characterize risks based on the best available scientific evidence. FDA has confidence that guideline studies conducted according to GLP can provide statistically powerful, valuable, and reproducible results that can be used to identify and characterize chemical hazards as part of a risk assessment in support of regulatory decisions. However, academic research can also inform hazard identification and characterization. The CLARITY-BPA research program, initiated and funded by NIEHS through the NTP with the participation of FDA, represents a new model for research that draws upon the strengths of academic and regulatory expertise.

2. Assessing health effects of bisphenol A

Bisphenol A (BPA) is a common chemical that has been used to produce polycarbonate plastics and epoxy resins since the 1950s. The chemical is found in food cans, plastic food and beverage containers, toys, medical devices, thermal receipt papers, and many other metal and plastic products. BPA has been shown to migrate at low levels into foods and beverages from food packaging and reusable containers [5–7], and BPA and/or its metabolites have been reported in human serum, milk, saliva, urine, and amniotic fluid (summarized for example in Vandenberg, Chahoud [8,9]). The Food and Agriculture Organization of the United Nations and World Health Organization estimated that the average human exposure to BPA is between 0.4 and 1.4 μg/kg/day and assessed the available academic and guideline-compliant studies [10]. In 2008, an expert panel convened by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) examined BPA research related to human reproduction and development. Based largely on the panel's assessment [11], the NTP reported *negligible concern* for reproductive effects in non-occupationally exposed adults and *minimal concern* for occupationally exposed workers, but identified *some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current levels of human BPA exposure [12].

After weighing the available evidence, FDA has, for the most part, concluded that the evidence for BPA's toxicity is insufficient to warrant formal restrictions on the use of BPA in consumer products [13,14]. In a 2010 statement that was subsequently updated in 2012, FDA, in agreement with the NTP panel's 2008 findings, expressed "some concern" about the effects of BPA on the brain, behavior, and prostate gland of fetuses, infants, and children and encouraged consumers and industry to take reasonable steps to reduce human exposure to BPA, particularly among infants [13]. In 2012, FDA amended its food additive regulations to no longer provide for the use of polycarbonate resins in baby bottles and "sippy" cups in response to a food additive petition submitted by the American Chemistry Council proposing that FDA amend its regulations because manufacturers no longer use polycarbonate resins in these products [15]. FDA has called for further studies to clarify substantial uncertainties in BPA research, including: the routes of exposure employed, the lack of consistency among some of the measured endpoints or results between studies, the relevance of some animal models to human health, differences in the metabolism (and detoxification) of and responses to BPA both at different ages and in different species, and limited or absent dose response information for some studies [13].

Given the body of diverse and often difficult-to-interpret evidence on the health effects of BPA, NTP and NIEHS determined in 2010 that a new guideline-compliant study conducted in

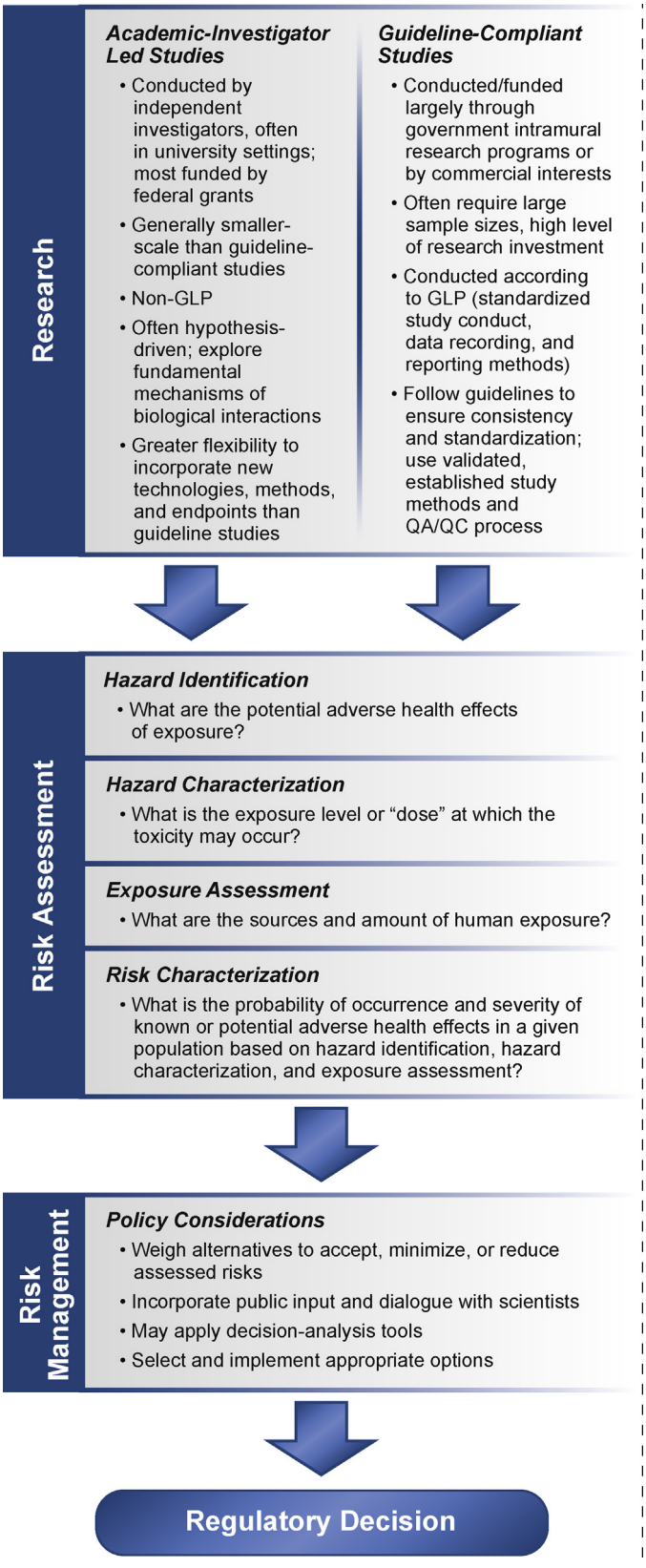

Fig. 1. Schematic of the current scientific paradigm for assesssing the toxicity of environment chemicals.

accordance with GLP was needed to reconcile uncertainties on the toxicity of BPA and offer risk assessors and risk managers a more comprehensive body of research to inform decision making. A previous chronic toxicity study of BPA [16] had not included developmental exposure, and many of the studies reporting effects following developmental exposures to low doses of BPA have not directly evaluated the potential long term consequences of the reported effects. Thus, a chronic toxicity study examining a wide dose range using a relevant long-term oral dosing protocol that includes developmental exposure and new endpoints not typically assessed in guideline studies was considered to be of value by NTP and NIEHS. In addition, FDA's ongoing review of BPA offered an opportunity to test a new, collaborative research model based on enhancing the links between academic and guideline-compliant research. These factors led to the genesis of the CLARITY-BPA research program.

3. CLARITY-BPA program

CLARITY-BPA is a collaborative effort between NTP and NIEHS with support from FDA to conduct a perinatal 2-year guideline chronic rodent toxicity study on BPA. In addition to the core elements of a guideline-compliant study, which include standard protocols and endpoints typically considered by regulatory agencies in risk assessment, the study involves extramural research partners and incorporates a wide range of doses and disease-relevant endpoints that have not been used in previous guideline-compliant BPA toxicity studies. By drawing on the strengths and rigor of a guideline-compliant study conducted in accordance with GLP and the expertise of the extramural scientists, the CLARITY-BPA consortium is designed to enhance risk assessment by resolving scientific uncertainties about BPA's health effects to better inform regulatory decision-making. The core guideline-compliant study is being conducted at FDA's National Center for Toxicological Research (NCTR). Study design and planning began in 2010; dosing began in September 2012, and the study is expected to conclude in early 2015.

3.1. Program organization

The CLARITY-BPA consortium is made up of NCTR staff, NIEHS and NTP staff, and 12 extramural grantees. NCTR staff led the design of the core chronic toxicity study and will perform the core study under GLP standards. NIEHS and NTP staff will manage consortium activities and facilitate grantee research. The 12 extramural grantees were chosen from applications submitted to a request for applications (RFA-ES-10-009) developed by NIEHS's Division of Extramural Research and Training. The RFA requested applications from researchers to add disease-focused endpoints that had been reported to be affected by BPA in academic research studies. Grantees were selected by NIEHS program staff based on the scientific merits of their proposals and their compatibility with the core study. Grantees have two main roles: (1) to inform the overall study design, and (2) to conduct additional mechanistic studies using dedicated tissues and animals from the core study.

The program is overseen by a Steering Committee, which sets consortium policies and resolves conflicts as needed. The Steering Committee is empowered to recommend adjustments to the study design to accommodate new knowledge and redirect the scientific focus of the grantee studies if necessary. The Steering Committee includes investigators representing each grant, the NCTR Principal Investigator responsible for the core study, a representative from NIEHS's Division of Extramural Research and Training, a NTP representative responsible for coordinating the project, a representative from FDA's Center for Food Safety and Applied Nutrition (CFSAN),

Table 1
Endpoints examined in the CLARITY-BPA research program.

a. Endpoints examined in the core guideline-compliant study.

Timeframe	Endpoints examined
Ongoing	• Body weight • Gestation time • Litter parameters (pup number, birth weight, sex ratio, etc.) • Time of vaginal opening • Estrous cyclicity and onset of aberrant cycles in aging animals • Palpable masses (beginning at 6 months of age, animals will be palpated weekly and any masses noted recorded with regard to approximate size and location)
Interim (1 year) necropsy	• *Complete necropsy*[a] In addition to the tissues listed in the NTP Specifications, fat pads (epididymal, ovarian/parametrial, and retroperitoneal) and penis will be taken at necropsy. • *Hematology*: including: hematocrit, hemoglobin concentration, erythrocyte, leukocyte, reticulocyte, and platelet counts, leukocyte differential count, mean corpuscular volume and mean corpuscular hemoglobin. • *Clinical chemistry* (*serum*): including: total protein, albumin, urea nitrogen, creatinine, alanine aminotransferase, gamma glutamyl transpeptidase, sorbitol dehydrogenase, aspartate aminotransferase, alkaline phosphatase, total bile acids, glucose, cholesterol, triglycerides, insulin, leptin, cardiac troponins T and I, T3, T4, and TSH. • *Sperm evaluation*: the left testis will be used for evaluation of testicular spermatid head counts. The left epididymis will be used for epididymal sperm counts, morphology, and motility evaluations. • *Tissue weights*: tissues to be weighed include: adrenals, brain, dorsolateral and ventral prostate (to be dissected and weighed after fixation), epididymides, heart, kidneys, liver, ovaries, pituitary (after fixation), seminal vesicles with coagulating gland, spleen, testes, thymus, thyroid (after fixation), epididymal, ovarian and parametrial (combined), retroperitoneal fat pads, uterus. • *Histopathology*: all organs taken at necropsy will be fixed and processed to paraffin block. The following tissues will be evaluated: adrenals, aorta (thoracic), bone marrow (femur), brain, right epididymis, heart, kidneys, liver, 5th left mammary gland (inguinal), ovaries, oviduct, pancreas, pituitary, prostate (dorsolateral and ventral), seminal vesicles with coagulating gland, spleen, right testis, thymus, thyroid, uterus, vagina. Any gross lesions will also undergo microscopic evaluation.
Terminal (2 year) necropsy	• Hematology, clinical chemistry, and organ weights will not be assessed. All other endpoints remain the same as those included in the interim necropsy.

b. Endpoints examined by NIEHS extramural grantees.

Area of focus	Description/endpoints	Principal investigator	Institution
Male reproductive development	Assessing BPA's effects on development of obstructive voiding disorder by examining: periurethral gland structure and epithelium/stroma function (in 1-day-old pups); bladder and periurethral gland structure and function (in adult); and gene expression/epigenetic changes (in both).	Frederick vom Saal	University of Missouri
Male reproduction	Evaluating testicular effects of BPA exposure through morphometric assessments of the testis, including quantitation of retained spermatid heads and the incidence of terminal dUTP nick end-labeling (TUNEL)-positive germ cells; identifying molecular biomarkers of effects in the testis and sperm.	Kim Boekelheide	Brown University
Male reproduction	Understanding the relationship between BPA exposure and erectile dysfunction by assessing: cellular and molecular damage; the roles of peripheral and central damage of the penile erectile response; and the compounding effects of low serum T and aging.	Nestor Gonzalez-Cadavid	Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Female reproduction and fertility	Understanding effects of BPA exposure on female fertility, specifically effects related to inhibition of follicle growth and inducement of atresia, potentially leading to low estradiol levels and infertility or premature ovarian failure.	Jodi Flaws	University of Illinois at Urbana-Champaign
Metabolism and heart disease	Assessing the effects of BPA exposure on development of metabolic syndrome by examining: gene expression; secretion of adipokines and cytokines; and adipose tissue cellularity.	Nira Ben-Jonathan	University of Cincinnati
Metabolic disease and diabetes	Understanding how BPA exposure influences gene expression and development of insulin resistance, type 2 diabetes, and obesity (males and females), and ovarian dysfunction (females).	Andrew Greenberg, Beverly Rubin	Tufts University
Uterine cancer	Identifying and assessing epigenetic markers for development of uterine cancer after BPA exposure.	Shuk-Mei Ho	University of Cincinnati
Prostate cancer	Investigating BPA's impacts on prostate cancer susceptibility by assessing: effects in the periurethral prostatic ducts; susceptibility of prostate to estrogen-driven carcinogenesis; methylation and gene expression; and changes in stem cells.	Gail Prins	University of Illinois at Chicago
Mammary cancer	Understanding influence of BPA exposure on development of mammary cancer by examining: epithelial organization; timing of the maturation of the fat pad; and collagen fiber organization and tissue density in periductal stroma.	Ana Soto	Tufts University
Neurobehavior	Evaluating effects of BPA on genetic and epigenetic expression related to sex specific developmental programming of the hippocampus and hypothalamus; assessing effects on anxiety, locomotor activity, spatial navigation, memory, sociosexual behavior, and cognitive behavior.	Heather Patisaul, Cheryl Rosenfeld	North Carolina State University, University of Missouri
Brain and thyroid function	Understanding how BPA affects thyroid hormone signaling; functioning of the hypothalamic-pituitary-thyroid axis; thyroid hormone actions in the brain, liver, pituitary, and heart; and gene expression.	R. Thomas Zoeller	University of Massachusetts, Amherst
Immunity	Evaluating the effects of BPA exposure on immune development and immune competence by investigating effects on: leukocyte composition, leukocyte estrogen receptors, and estrogen-sensitive genes involved in leukocyte function.	Norbert Kaminski	Michigan State University

[a] As defined in Section VII, 2 b. of the specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemical, biological, and physical agents in laboratory animals for the National Toxicology Program (NTP), January 2011.

and NTP and NCTR project officers responsible for administering the interagency agreement that supports the study. In addition, an External Scientific Panel of four scientists will provide overall programmatic guidance and offer advice in the management and technical performance of the research. Finally, a team of NIEHS/NTP project scientists with expertise in areas covered by the extramural research projects will provide input to the grantees and Steering Committee on the design and execution of extramural studies. Thus, the structure of the study and its oversight involve multiple levels of participation from both government agency representatives and academic researchers.

3.2. Study design

A 90-day subchronic toxicity study conducted under GLP at NCTR in 2010–2011 provided preliminary results to inform the design of the 2-year guideline-compliant chronic toxicity study. The subchronic study employed many of the same protocols as those that were planned for the chronic study, including the same animal model, housing conditions, and dosing route. In addition, a naïve (non-dosed) control and internal dosimetry was assessed in the subchronic study. In a series of meetings in 2011 and 2012, grantees and NCTR scientists reviewed results from the subchronic study and collaborated to outline the protocols of the chronic study and define how tissues and animals would be transferred to and handled by the extramural researchers. Because one of the main goals of the study is to fill knowledge gaps and address discrepancies between past academic and guideline-compliant research, the study design incorporates several elements that have not been included in past guideline-compliant BPA toxicity studies. The core study will also provide animals and tissues developed under conditions of analytical standardization often not included in academic research (e.g., internal dosimetry and analytical quantification and certification of dose, diet, and background of BPA and other sources of potential endocrine activity). Noteworthy study elements include the following:

- *Harmonization of protocols and data*: All aspects of the study (the guideline-compliant arm and the extramural arm) will follow a shared, robust protocol for animal housing and feeding, compound handling and dosing, measurement and evaluation, and sharing and storing of samples. This will provide a unified, standard framework for comparing and interpreting results for various endpoints. When possible, extramural testing will be centralized or coordinated for investigations that have common areas of focus, such as gene expression or epigenetics. Data analysis will also be conducted under a unified framework: NTP will advise on the statistical and pathological analyses for grantees' investigations. Data from the core GLP chronic study and grantee projects will be housed in a shared data repository where all final data will be publicly available (Chemical Effects in Biological Systems [CEBS] (http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm)). With few exceptions, extramural researchers will be blinded to the control status and BPA and ethinyl estradiol exposure levels of the animals and tissues; identifying treatment codes will be housed at NTP and researchers will receive this information after NTP receives grantees' raw data. In certain studies, information on specific doses or control animals will be provided to the grantees; unblinding was deemed necessary by these grantees for the specific methods and equipment used.
- *Endpoints*: The combined intramural and extramural studies will provide insights on a variety of specific endpoints, some of which have not been previously examined in a guideline GLP-compliant BPA toxicity study (see Table 1). Although all animals will be housed and dosed at the NCTR under tightly controlled conditions, grantees will have access to tissue samples and animals from the core study to investigate specific disease endpoints beyond those included in the core chronic study.
- *Dose range*: BPA will be orally administered in the following doses: 2.5, 25, 250, 2500, and 25,000 μg/kg body weight (bw)/day.
- *Dosing protocols*: Pregnant dams will be dosed using oral gavage beginning on gestation day 6 and continuing until the start of litter delivery. All dose solutions/suspensions will be prepared in an aqueous solution of 0.3% carboxymethylcellulose. In addition, pups will be dosed using oral gavage beginning on postnatal day 1 (day after birth), whereas previous studies have relied on lactational transfer for dosing pups, or started dosing at a later stage in development. At wean (postnatal day 21), some pups will continue the daily dosing (continuous dose arm), while others will not be dosed further (stop dose arm).
- *Reference estrogen controls*: To provide references for all studies, the design was adjusted to include two ethinyl estradiol control groups (0.05 and 0.5 μg/kg bw/day). For a subset of studies, a very high (250,000 μg/kg bw/day) BPA dose – a dose expected to have clear adverse systemic effects – was included. In addition, a propyl-2-thiouracil (PTU) control group was included for use in thyroid-specific studies.
- *Study length*: The core GLP chronic study will be conducted until the animals reach two years to examine the long term effects of perinatal exposure. The core GLP chronic study will include an interim evaluation at one year. Animals will be examined in the grantee studies at postnatal days 1, 15, 21, and 90 and at six months and one year.
- *Animal strain*: Sprague Dawley rats from the NCTR breeding colony will be used for all aspects of the study. Previous studies have documented this strain's sensitivity to ethinyl estradiol and other estrogens [17–19].
- *Reduction of confounds*: Potential sources of background BPA, including diet, cages, bedding, drinking water, and water bottle stoppers, will be measured and monitored. In addition, animals will be fed a diet low in soy, alfalfa, and other phytoestrogens, and several potential dietary estrogens and BPA levels will be measured in the chow regularly over the course of the study. The consideration of the base diet as a potential source of BPA is a unique and important aspect of the core chronic study.
- *Assessment of low-dose BPA and ethinyl estradiol blood levels*: The study will dose a subset of pups at postnatal days 4 and 21 with deuterated BPA (d-BPA) to measure both aglycone and conjugated BPA in blood for doses of 2.5, 25, and 250 μg/kg bw/day, 15 min after dosing (the approximate time of maximum concentration). In addition, ethinyl estradiol blood levels will be assessed 15 min after dosing of pups with 0.05 or 0.5 μg/kg bw/day ethinyl estradiol.

4. Conclusions

The CLARITY-BPA research program uses a unique collaborative approach to fill knowledge gaps and offer risk assessors a more comprehensive body of scientific information to better inform their risk assessments. Combining a core guideline-compliant chronic rodent toxicity study, conducted in accordance with GLP, with extramural investigations of specific disease endpoints, the study enhances the links between academic and guideline-compliant research. Although the program is still in its early stages, CLARITY-BPA represents an initial proof-of-concept collaboration that, if successful, may offer a new model for investigating complex or controversial chemical exposures. The model could prove particularly useful for investigating endocrine active agents by shedding light on doses, endpoints, and methods that may enhance the utility of traditional toxicology study designs for investigating

such chemicals. Just as translational research collaborations have increased the impact of basic research for improving medical practice, translational research collaborations can improve chemical risk assessments.

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