

The Conflict between Regulatory Agencies over the 20,000-Fold Lowering of the Tolerable Daily Intake (TDI) for Bisphenol A (BPA) by the European Food Safety Authority (EFSA)

Frederick S. vom Saal,¹  Michael Antoniou,² Scott M. Belcher,³ Ake Bergman,⁴ Ramji K. Bhandari,¹ Linda S. Birnbaum,^{5,6} Aly Cohen,⁷ Terrence J. Collins,⁸ Barbara Demeneix,⁹ Anne Marie Fine,¹⁰ Jodi A. Flaws,¹¹ Veronique Gayrard,¹² William H. Goodson III,¹³ Andrea C. Gore,¹⁴ Jerrold J. Heindel,¹⁵ Patricia A. Hunt,¹⁶ Taisen Iguchi,¹⁷ Christopher D. Kassotis,^{18,19} Andreas Kortenkamp,²⁰ Robin Mesnage,²¹ Jane Muncke,²¹ John Peterson Myers,²² Angel Nadal,²³ Retha R. Newbold,²⁴ Vasantha Padmanabhan,^{25,26,27} Paola Palanza,²⁸ Zandra Palma,²⁹ Stefano Parmigiani,³⁰ Lyn Patrick,¹⁰ Gail S. Prins,³¹ Cheryl S. Rosenfeld,^{32,33} Niels E. Skakkebaek,³⁴ Carlos Sonnenschein,³⁵ Ana M. Soto,³⁵ Shanna H. Swan,³⁶ Julia A. Taylor,¹ Pierre-Louis Toutain,^{37,38} Frank A. von Hippel,³⁹ Wade V. Welshons,⁴⁰ Daniel Zalko,¹² and R. Thomas Zoeller⁴¹

¹Division of Biological Sciences, University of Missouri-Columbia, Columbia, Missouri, USA

²Department of Medical and Molecular Genetics, King's College London School of Medicine, London, UK

³Department of Biological Sciences, North Carolina State University, Raleigh, North Carolina, USA

⁴Department of Environmental Science (ACES), Stockholm University, Stockholm, Sweden

⁵Scientist Emeritus and Former Director, National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina, USA

⁶Scholar in Residence, Duke University, Durham, North Carolina, USA

⁷Integrative Rheumatology Associates, Princeton, New Jersey, USA

⁸Department of Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA

⁹Comparative Physiology Laboratory, Natural History Museum, Paris, France

¹⁰Environmental Medicine Education International, Mancos, Colorado, USA

¹¹Department of Comparative Biosciences, University of Illinois Urbana—Champaign, Urbana-Champaign, Illinois, USA

¹²ToxAlim (Research Centre in Food Toxicology), University of Toulouse, Toulouse, France

¹³California Pacific Medical Center Research Institute, San Francisco, California, USA

¹⁴Division of Pharmacology and Toxicology, University of Texas at Austin, Austin, Texas, USA

¹⁵Healthy Environment and Endocrine Disruptor Strategies, Raleigh, North Carolina, USA

¹⁶School of Molecular Biosciences, Center for Reproductive Biology, Washington State University, Pullman, Washington, USA

¹⁷Graduate School of Nanobioscience, Yokohama City University, Yokohama, Japan

¹⁸Institute of Environmental Health Sciences, Wayne State University, Detroit, Michigan, USA

¹⁹Department of Pharmacology, Wayne State University, Detroit, Michigan, USA

²⁰Centre for Pollution Research and Policy, Brunel University London, Uxbridge, UK

²¹Food Packaging Forum Foundation, Zurich, Switzerland

²²Environmental Health Sciences, Charlottesville, Virginia, USA

²³Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDIIBE) and CIBERDEM, Miguel Hernandez University of Elche, Elche, Alicante, Spain

²⁴Scientist Emeritus, NTP, NIEHS, Research Triangle Park, North Carolina, USA

²⁵Department of Pediatrics, Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan, USA

²⁶Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA

²⁷Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan, USA

²⁸Unit of Neuroscience, Department of Medicine and Surgery, University of Parma, Parma, Italy

²⁹PalmaMD, Miami, Florida, USA

³⁰Unit of Evolutionary and Functional Biology, Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

³¹Department of Urology, University of Illinois at Chicago, Chicago, Illinois, USA

³²Biomedical Sciences, Thompson Center for Autism and Neurobehavioral Disorders, University of Missouri—Columbia, Columbia, Missouri, USA

³³MU Institute of Data Science and Informatics, University of Missouri—Columbia, Columbia, Missouri, USA

³⁴Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

³⁵Department of Immunology, Tufts University School of Medicine, Boston, Massachusetts, USA

³⁶Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

³⁷Royal Veterinary College, University of London, London, UK

³⁸NTHERES, INRAE, ENVT, Université de Toulouse, Toulouse, France

³⁹Department of Community, Environment & Policy, University of Arizona, Tucson, Arizona, USA

⁴⁰Department of Biomedical Sciences, University of Missouri—Columbia, Columbia, Missouri, USA

⁴¹Department of Biology, University of Massachusetts, Amherst, Massachusetts, USA

BACKGROUND: The European Food Safety Authority (EFSA) recommended lowering their estimated tolerable daily intake (TDI) for bisphenol A (BPA) 20,000-fold to 0.2 ng/kg body weight (BW)/day. BPA is an extensively studied high production volume endocrine disrupting chemical (EDC) associated with a vast array of diseases. Prior risk assessments of BPA by EFSA as well as the US Food and Drug Administration (FDA) have relied on industry-funded studies conducted under good laboratory practice protocols (GLP) requiring guideline end points and detailed record keeping,

Address correspondence to Frederick S. vom Saal, Division of Biological Sciences, 105 Lefevre Hall, University of Missouri—Columbia, Columbia, MO 65211 USA. Telephone: (573) 356-9621. Email: vomsaalf@missouri.edu

J.P.M. and T.J.C. are on the board of a chemical company, Sudoc.com, but have given all shares to an irrevocable grantor trust so that they cannot benefit personally from the company's financial success. All other authors declare they have no actual or potential competing financial interests.

Conclusions and opinions are those of the individual authors and do not necessarily reflect the policies or views of EHP Publishing or the National Institute of Environmental Health Sciences.

Received 13 August 2023; Revised 5 March 2024; Accepted 5 March 2024; Published 9 April 2024.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to **508 standards** due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehpsubmissions@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

while also claiming to examine (but rejecting) thousands of published findings by academic scientists. Guideline protocols initially formalized in the mid-twentieth century are still used by many regulatory agencies. EFSA used a 21st century approach in its reassessment of BPA and conducted a transparent, but time-limited, systematic review that included both guideline and academic research. The German Federal Institute for Risk Assessment (BfR) opposed EFSA's revision of the TDI for BPA.

OBJECTIVES: We identify the flaws in the assumptions that the German BfR, as well as the FDA, have used to justify maintaining the TDI for BPA at levels above what a vast amount of academic research shows to cause harm. We argue that regulatory agencies need to incorporate 21st century science into chemical hazard identifications using the CLARITY-BPA (Consortium Linking Academic and Regulatory Insights on BPA Toxicity) non-guideline academic studies in a collaborative government–academic program model.

DISCUSSION: We strongly endorse EFSA's revised TDI for BPA and support the European Commission's (EC) apparent acceptance of this updated BPA risk assessment. We discuss challenges to current chemical risk assessment assumptions about EDCs that need to be addressed by regulatory agencies to, in our opinion, become truly protective of public health. Addressing these challenges will hopefully result in BPA, and eventually other structurally similar bisphenols (called “regrettable substitutions”) for which there are known adverse effects, being eliminated from all food-related and many other uses in the EU and elsewhere. <https://doi.org/10.1289/EHP13812>

Introduction

Bisphenol A (BPA) (CAS number 80-05-7) is worldwide one of the highest volume petroleum-based chemicals that is used in a wide range of products, including plastics, food and beverage packaging materials, as an additive in personal care products, and in thermal paper used in receipts.¹ BPA is classified as an endocrine disrupting chemical (EDC), which is defined as an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.²

As scientists and clinicians involved in studies of EDCs such as BPA, we strongly support the European Food Safety Authority's (EFSA's) recent recommendation to lower by 20,000-fold their prior temporary estimate of the daily human exposure to BPA that is safe, referred to in their reevaluation as the tolerable daily intake (TDI). The EFSA expert Panel on Food Contact Materials, Enzymes and Processing Aids (EFSA-CEP) stated “By comparing the new TDI with estimates of dietary exposure to BPA, our experts concluded that consumers with both average and high exposure to BPA in all age groups exceeded the new TDI, indicating health concerns.”³ The major change in approach by the EFSA-CEP in their BPA risk assessment included a review of independent academic research findings in addition to industry and government guideline research findings. This also was preceded by a process that was transparent and included publishing the review protocol and requesting comments prior to the initiation of the review.⁴

The inclusion of nonguideline studies by the EFSA-CEP to reach this decision has resulted in disagreement by other regulatory agencies. In particular, the German Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment) (BfR) considers that EFSA-CEP's chemical risk assessment methods are contrary to the traditional approach used in hazard characterization for risk assessments.^{5,6} The European Medicines Agency (EMA) also disputed the reevaluation methods used by the EFSA-CEP,⁷ which are reviewed in Zoeller et al.⁸ Interestingly, in the US, resistance to the EFSA-CEP systematic review approach may be changing⁹ due to the ongoing reorganization of the food safety division of the US Food and Drug Administration (FDA)¹⁰ after years of regulatory inaction,^{11–13} particularly for EDCs.^{2,14}

The European Commission (EC) in August 2023 published that it was planning to propose adopting the EFSA-CEP revision of the TDI for BPA, including a ban on its use in food packaging materials. Specifically, the EC published the following online: “This initiative will impose a ban on the use of BPA in food contact materials (FCMs), including plastic and coated packaging. This follows the publication of the European Food Safety Authority's opinion which indicates a concern for human health. The measure will also address the use of other bisphenols in FCMs to avoid replacing BPA with other harmful substances,” which has been updated as of

February 2024.^{15–18} This initial decision was also supported by the European Environment Agency (EEA) based on unsafe levels of BPA reported in biomonitoring studies in the EU.^{19,20}

Dozens of other bisphenols (BPA analogues) are currently used in products, many of which are labeled “BPA free.” This is a label that erroneously suggests to the public that the product does not contain a chemical (BPA) that has gained wide acceptance to pose a health hazard; these replacement bisphenols are referred to as “regrettable substitutions” (Table 1). In the case of bisphenols, many BPA analogues are structurally similar to BPA, although their EDC activity, potency, and pharmacokinetics can vary.^{62,63} For example, bisphenol S (BPS), bisphenol F (BPF), and other structurally similar bisphenols had previously been unregulated in the EU and thus have already become ubiquitous environmental contaminants.⁵⁶ Rat and mouse studies by academic scientists of some BPA analogues, particularly BPS and BPF, have revealed similar harm to that caused by BPA.⁵⁷ This problem applies to replacement chemicals for many classes of chemicals in addition to BPA⁶⁴ [e.g., polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), phthalates, per- and polyfluoroalkyl substances (PFAS), and organochlorine pesticides⁶⁵].

The first part of this commentary covers the hazards posed by BPA identified in academic hypothesis-driven studies. These peer-reviewed published findings from academic investigator studies have not been included by EFSA, the FDA, or German BfR in previous hazard identifications of BPA. This summary of selected published health effects of BPA emphasizes the importance that their inclusion in the recent EFSA-CEP systematic review had on the dramatic revision of the TDI for BPA. Second, we provide suggestions for using the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) collaborative project as a cost-effective model to bring chemical risk assessments into the 21st century.^{26,52} Third, we focus on the rationale for the revised TDI by the EFSA-CEP and the basis for our disagreement with the attempt by the German BfR to block its implementation. We also contrast the EFSA-CEP decision with the FDA declarations in both 2008 and 2018 that the public can be assured that BPA is safe. Fourth, we discuss the unique issues EDCs pose for traditional risk assessments that are directed at poisons. Our view is that the current approaches used in chemical risk assessments that were developed to test for poisons are not appropriate for determining the risks posed by BPA and other EDCs that interfere with hormones and that are not poisons.¹ This will require approaches that can be used to identify if a chemical is an EDC. For example, La Merrill et al. identified how ten key characteristics could be used to identify, organize, and utilize mechanistic data when evaluating whether chemicals could be classified as EDCs, and 9 of the 10 EDC key characteristics were met by BPA.⁶⁶

We provide suggestions to eliminate the current approaches used in chemical risk assessments for EDCs and to replace them

with risk assessment methods and assumptions based on 21st century endocrine science (Table 1). Statements of Principles from the Endocrine Society have emphasized the importance of testing low, human-relevant, levels of exposure rather than just very high doses in hazard assessments of EDCs, such as BPA.² Fifth, we identify a number of additional issues critical for sustainability (including “sustainable chemistry”) and for improving the assessment of hazards to the environment and public health posed by EDCs and other chemicals present in a myriad of products (Table 1). Our hope is that these critical improvements will happen in the near future in the EU, US, Asia, and elsewhere. We propose that while the approach used by the EFSA-CEP in revising the TDI for BPA is an initial step in the right direction, much more remains to be done.³

Adverse Effects of BPA Reported in Academic Studies

The decision by EFSA to lower by 20,000-fold the tolerable daily exposure to BPA is supported by research that hundreds of scientists around the world have conducted over the last 25 years showing that exceedingly small exposures to BPA are related to a wide range of disease in humans and by research with experimental animals demonstrating that low doses of BPA cause the same diseases.^{1,26} The list of adverse effects associated with exposure via different routes to BPA is truly vast based on examination of the totality of the published literature on BPA. These include studies of mechanisms involving cell culture and cell-free systems, environmental and wildlife/human biomonitoring, pharmacokinetics, and adverse effects in wildlife, laboratory animals, and humans. The total number of citations retrieved in PubMed when bisphenol A/BPA was the search term resulted in over 13,000 entries as of February 2024, indicating that BPA is a highly researched synthetic petroleum-based chemical. While it is beyond the scope of this paper to survey this vast published literature, we describe below evidence for some of the adverse health effects associated with developmental and adult exposure to environmentally relevant doses of BPA.

Exposure to BPA is related to neurological disorders such as ADHD,⁶⁷ autism,⁶⁸ other behavioral effects that are sex specific,²⁴ neuroendocrine disorders,^{69,70} and reduction of synaptic connections between neurons in the hippocampus impacting cognition and memory in both rats and monkeys.⁷¹ Neurobehavioral effects are not commonly examined in guideline studies conducted for risk assessments. BPA is also implicated in metabolic diseases such as obesity and fatty liver disease,⁷² stimulation of insulin secretion by the pancreas, disruption of glucose regulation, and increased risk of diabetes mellitus.⁷³ A prospective study reported that elevated BPA in human urine is also related to an increase in the future risk of cardiovascular disease, including heart attack and death.⁷⁴

A large portion of the literature relates BPA exposure to adverse reproductive effects involving all reproductive organs and functions in males and females. Considerable attention has been paid to the increase in male reproductive system disorders related to fetal exposure to EDCs, including BPA; these are referred to collectively as testicular dysgenesis syndrome,⁷⁵ which is associated with declining fertility. There is also evidence for an accelerating decrease in sperm count and quality in men during the first two decades of the 21st century (when BPA production increased dramatically) relative to the rate of sperm count and quality decline that had been documented during the 20th century.⁷⁶ BPA is one of the EDCs associated with genital defects in men when exposure occurs during the fetal period of sexual differentiation.⁷⁷ Research in mice showed that BPA negatively, and irreversibly, impacted the spermatogonial stem cell pool when exposure occurred

during development of the testes.⁷⁸ Developmental BPA exposure is also related to reduced adult sperm production in men.^{45,79} Developmental and adult BPA exposure is associated with decreased libido and disruption of the neuroendocrine control of testicular function in human^{80–83} and in animal⁸⁴ studies. Adult exposure to BPA also resulted in obstructive voiding disorder in male mice.⁸⁵ BPA exposure during development followed by an elevation in estrogen later in life, which happens in men as they age (a two-hit model), has been related to prostate cancer in male rats^{86,87} as well as benign prostatic hyperplasia (BPH), prostatitis, and obstructive voiding disorder in male mice.⁸⁸

The global decline in fertility also involves effects of BPA in women, including disruption of oocyte development,^{89,90} low fertility, and, if fertilization does occur, increased incidence of miscarriage.⁹¹ An extensive literature relates developmental^{92,93} or adult⁹⁴ exposure to BPA to mammary gland abnormalities in animals, and *in vitro* studies with human breast tissue demonstrates disrupted gene pathways using BPA doses relevant to current human exposures.⁹⁵ These findings have led to predictions that breast cancer in women is likely impacted by exposure to BPA as well as other EDCs with estrogenic activity.⁸⁶ Similarly, BPA impacts uterine glands in rats after exposure during development⁹⁶ or in adulthood,⁹⁷ leading to concern about its potential as a risk factor in cancer and other diseases of the uterus.

While BPA has primarily been studied for its estrogen-mimicking hormonal activity, it can activate or interfere with numerous other hormone receptors and enzymes,² thus accounting for the large number of diseases related to chronic exposure to BPA.^{1,36,98} We have not attempted to dissect each referenced study above to determine if it would meet the requirements demanded by risk assessors. However, most studies of BPA by academic scientists in the biomedical community are focused on hypothesis-driven experiments relating to diseases, unlike guideline studies. These very expensive academic studies are virtually always subjected to prior review by university, state, or government funding panels and then again by expert reviewers for journals in order to be accepted for publication. In contrast, many guideline studies used in risk assessments are funded by chemical corporations, are not published, the data are not available to the public, and sometimes not all data are provided to regulatory agencies⁹⁹ except through litigation, which we refer to as “regulation by litigation.”

In 1965, the importance of dealing with uncertainty in assessing cause and effect relationships was articulated by Austin Bradford Hill: “All scientific work is incomplete... That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.”¹⁰⁰ BPA is not just a threat to human health but to the global environment. The 1992 Rio Declaration on Environment and Development,¹⁰¹ which the US and EU signed, included the following: “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.” Our view is that the vast number of human, animal, and environmental adverse effects of BPA shown in multiple experiments by different independent academic investigators cannot continue to be ignored by risk assessors in Germany, the US, and elsewhere, who need to follow EFSA’s lead.

CLARITY-BPA: A New Approach to Assess Chemical Hazards and Dose Responses

The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) was a government-academia collaboration to link a guideline study (funded by the FDA) with hypothesis-driven, academic investigator studies, funded by the

Table 1. Issues that need to be addressed by regulatory agencies to bring 21st century endocrine and chemical science into the assessment of risks posed by EDCs to human health and the environment.

Issue	Rationale	Ref
Risk assessment methods	Risk assessment assumptions do not apply to EDCs.	Vom Saal and Vandenberg ¹ and Vandenberg et al. ²¹
Hazard identification: uses only high-doses to predict low-dose effects	Assessing hazard currently involves rejection of known receptor-mediated low-dose effects of EDCs.	Vom Saal and Vandenberg, ¹ Welshons et al., ²² and Vandenberg et al. ²¹
Group assessment: this is needed instead of testing individual chemicals	Regulate chemicals such as BPA and analogue bisphenols as a group prior to replacing BPA with other bisphenols in products.	ECHA ²³
Sex differences: expectation that EDCs act the same in males and females	Sex-differences in outcomes are a common feature of exposure to EDCs but are either ignored or if found are used to reject the findings.	Palanza et al., ²⁴ Williams et al., ²⁵ and Heindel et al. ²⁶
Epigenetics: need to be included in hazard identification	Endocrine disruptors can alter the epigenome and are implicated in the development of disease, but this is ignored in risk assessments.	Kundakovic et al. ²⁷
Transgenerational effects: need to be included in hazard identification	Adverse effects of BPA and other EDCs can be transmitted to future (even unexposed) generations, but this is ignored in risk assessments.	Jung et al. ²⁸ and Kundakovic et al. ²⁷
Dose-response assessment	NMDR mechanisms: low dose stimulation of a hormone's own and other receptors and high-dose inhibition of the hormone's own and other receptors is referred to as receptor up-regulation and down-regulation.	Vandenberg et al., ²¹ Vom Saal et al., ²⁹ Medlock et al., ³⁰ and Gupta ³¹
	Activation of expression of a regulated gene can be maximal at low doses while inhibition of expression of the same gene occurs at high doses. Entirely different genes can be activated at low vs. high doses.	Coser et al. ³² and Taylor et al. ³³
	BPA is a SERM that does not fully replicate the actions of endogenous estrogens, similar to the drug tamoxifen.	Vom Saal and Vandenberg ¹ and Jordan et al. ³⁴
	Low-dose BPA inhibits or induces enzymes (e.g., aromatase) increase results in an increase in intracellular estradiol.	Arase et al. ³⁵
Threshold hypothesis: regulators accept the validity of thresholds for EDCs	Opposing responses can be triggered through different estrogen receptors (such as ER α and ER β) or thyroid, androgen, and aryl hydrocarbon receptors.	Reif et al., ³⁶ Vom Saal and Vandenberg, ¹ Vandenberg et al., ²¹ and Villar-Pazos et al. ³⁷
Exposure assessment: route of administration that is relevant to humans needs to be assessed	Assumption of a threshold for EDCs is false if background hormone levels being disrupted are already above threshold.	Zoeller et al., ² Hoel, ³⁸ Blair et al., ³⁹ and Sheehan ⁴⁰
	Exposure to BPA via sublingual, respiratory, and transdermal routes can lead to higher levels of bioactive (free) BPA in blood compared with free BPA levels following gavage administration.	Gaynard et al. ⁴¹ and Hormann et al. ⁴²
Transparency: need to know chemicals in products	Corporations do not reveal all chemicals used in products, limiting biomonitoring.	van Deelen ⁴³ and Maffini et al. ⁴⁴
Human relevant mixtures: need to be examined	Chemicals in mixtures relevant to human exposures need to be examined, not individually (including chemicals not structurally related).	Kortenkamp et al. ⁴⁵ and Luijten et al. ⁴⁶
Risk characterization: based on the assumption of negligible exposure to BPA	Regulatory agencies have ignored the academic studies showing BPA hazards at low doses and have assumed human exposure is negligible.	Vom Saal and Vandenberg ¹ and Vandenberg et al. ⁴⁷
Risk management: cost-benefit analysis is not protective of the public health	“Cost-benefit analysis” has emphasized costs to industry, while ignoring the public health costs, which are over 10-fold higher.	Trasande et al., ⁴⁸ Attina et al., ⁴⁹ and Davenport ⁵⁰
Precautionary principle: accepted in the EU but rejected in the US	Chemical regulatory bodies should always err on the side of precaution. Risk managers in the US have rejected a precautionary approach to chemical safety.	Sachs ⁵¹
CLARITY-BPA: provides a cost-effective model for including 21st century science in hazard identification	CLARITY-BPA was designed to create a collaboration between government and academic scientists to bring 21st century science into the assessment of BPA (and other chemical) hazards.	Heindel et al., ²⁶ Schug et al., ⁵² Heindel et al., ⁵³ Vandenberg et al., ⁵⁴ and Howdeshell et al. ⁵⁵
Regrettable substitutions: regulatory agencies need to stop this from happening	Hazardous analogues are replacing BPA (e.g., BPS) that are more potent than BPA and are now ubiquitous human contaminants.	Chen et al., ⁵⁶ Ullah et al., ⁵⁷ Hormann et al., ⁴² and Gaynard et al. ⁵⁸
Sustainable chemistry: these critical issues need to be considered by regulatory agencies	Principles of sustainable chemistry should be added to the chemistry curriculum so that the chemists who synthesizing chemicals know the basics of biology and modern toxicology.	Collins ⁵⁹
	The sustainable option for BPA, that is contributing to all non-communicable diseases that are increasing in incidence, is to reduce production, use, and disposal, as BPA-based products are not recyclable.	Vom Saal and Vandenberg ¹
	Development of new approaches and techniques to remove BPA and other toxic chemicals from drinking water presents a global challenge.	Schug et al. ⁶⁰ and Collins ⁵⁹
	Remediation methods to remove EDCs from water that are not overwhelmingly expensive are being developed.	Onundi et al. ⁶¹

Note: BPA, bisphenol A; BPS, bisphenol S; CLARITY-BPA, Consortium Linking Academic and Regulatory Insights on BPA Toxicity; EDCs, endocrine disrupting chemicals; ER α , estrogen receptor alpha; ER β , estrogen receptor beta; NMDR, nonmonotonic dose responses; Ref, reference; SERM, selective estrogen receptor modulator.

National Institute of Environmental Health Sciences (NIEHS). CLARITY-BPA was a comprehensive industry-standard Good Laboratory Practice (GLP) guideline-compliant 2-year chronic exposure study of BPA toxicity (Table 1). GLP guideline studies follow prescribed protocols and record keeping requirements, and results using these protocols are accepted by risk assessors as valid (although this has been disputed).^{102,103} All tissues examined in CLARITY-BPA were from rats produced under GLP protocols by the FDA National Center for Toxicological Research (NCTR). The guideline studies conducted by NCTR scientists were supplemented by 14 hypothesis-driven independent investigator-initiated studies that involved observations of animal behavior or use of tissues provided to the academic researchers who were blinded to treatment. The NIEHS funded academic investigators, each with demonstrated expertise in studying different outcomes known to be caused by BPA, to participate in the unprecedented collaborative approach used in CLARITY-BPA.

One of the primary objectives of CLARITY-BPA was to greatly expand the range and sensitivity of outcomes examined in hazard identification studies for environmental chemicals and to examine whether academic scientists could replicate their prior findings using animals from a GLP government-controlled study.^{52,53} In a 2013 publication by representatives from all participating agencies and the academic investigators, they explained the reason for choosing BPA as the test chemical: “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 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.”⁵²

By providing researchers with blinded samples from rats produced under GLP protocols by the FDA-NCTR, the NIEHS/National Toxicology Program (NTP) sought to compare the guideline study findings with the academic research results using state-of-the-art methods, but in separate laboratories that in many cases involved using tissues from the same animals.²⁶ The findings were then going to be compared in a final integrated review with the results from a standard toxicological guideline study conducted by toxicologists at the FDA-NCTR that was contractually agreed to by all participants.⁵³ The Crl:CD-SD rats (the animal model used in FDA-NCTR research) were produced and exposed to a wide range of doses of BPA as well as two doses of the estrogenic positive control drug, ethinylestradiol. Most guideline studies do not include positive controls that provide information about the sensitivity of the research approach and ensure that a response to BPA could be detected by comparison with a drug with known effects in humans on many of the systems being examined and at the doses being used.¹⁰⁴

In compliance with the NIEHS/NTP/FDA CLARITY-BPA contract with the academic investigators,⁵³ most of the academic investigators participated in an integrated review of their BPA findings and compared them with results from the FDA’s guideline study findings.²⁶ A major finding from CLARITY-BPA was that at the lowest dose of BPA that was examined [2.5 µg/kg body weight (BW)/day], still considered safe by the FDA but now not the EFSA-CEP, the academic investigators reported statistically significant results for the brain, prostate, urinary tract, ovary, mammary gland, and heart. Nonmonotonic dose-response (NMDR) relationships were also found, with a breaking point between the 25 and 250 µg/kg BW/day doses.¹⁰⁵ Specifically, an integrated analysis of the independent data sets²⁶ revealed that in females, 2.5 µg/kg BW/day BPA affected white adipose tissue, behavior, ovarian follicles, heart, mammary gland, uterus, and peptide and steroid hormones analyzed by different

laboratories blind to treatment. In males, the 2.5 µg/kg BW/day dose also showed strong correlations with white adipose tissue, heart, prostate, and peptide hormones. These findings show that results from independent studies on tissues from the same animals are statistically significantly related to each other. We propose that since these CLARITY-BPA findings came from one large FDA-conducted experiment that followed GLP guidelines and involved sharing tissues (blinded) from the same treated animals with multiple academic investigators, the findings cannot be dismissed as spurious or random. However, this is a common criticism leveled at research published by independent scientists showing that low doses of BPA cause adverse effects on individual end points.²⁶

The academic investigator integrated analysis²⁶ demonstrated that many of the guideline study end points were less likely to reveal low-dose effects of BPA than were the academic end points that involved using the most sensitive approaches available. In addition, not all prior findings by the academic collaborators using other animal models were replicated in the NCTR CD-SD rat, revealing the importance of using an animal model that has been demonstrated to be sensitive to the chemical being examined.¹⁰⁶ For example, the NCTR CD-SD rats did not exhibit the expected response to low doses of thyroxine (T₄), showing this rat strain to lack utility for studying effects of thyroid-disrupting chemicals.²⁶ Crl:CD-SD rats, from which the NCTR CD-SD rats were derived (the NCTR purchased Crl:CD-SD rats in 1972 from Charles River), also show low sensitivity to estrogens compared with other experimental animal models.^{106,107} Delclos et al.¹⁰⁸ reported that in the NCTR CD-SD rat, Ethinylestradiol (EE2) administered by gavage at 5 µg EE2/kg BW/day resulted in an opposite effect on the timing of puberty (delay in both vaginal opening and first estrus) relative to other rat and mouse studies that show an advance in the onset of puberty with developmental exposure to estrogenic chemicals, such as low doses of BPA; examples include advanced age at first estrus in CF-1 mice¹⁰⁹ and advanced vaginal opening in Wistar rats.¹¹⁰

In contrast to the academic investigators,²⁶ the FDA did not participate in a contractual tripartite (NTP/FDA/academic investigator)-integrated review, and, instead, the FDA’s publication by Camacho et al.¹¹¹ was their only contribution after completion of CLARITY-BPA studies, as described by Heindel et al.²⁶ The NTP final report states¹¹²: “This report does not attempt to integrate the findings or offer interpretation of reported findings.” However, this integration of core guideline and academic hypothesis-driven findings was a primary reason NIEHS initiated CLARITY-BPA, and so it was up to the academic investigators, under the leadership of Dr. Jerrold Heindel,²⁶ to publish a “data integration” review; CLARITY-BPA has also been reviewed by others.^{54,55}

Importantly, there were statistically significant findings in the FDA’s guideline study for a number of parameters at the 2.5 µg/kg BW/day dose: significant effects on mammary gland adenocarcinoma and kidney pathology in females and prostate inflammation in males.^{54,111} However, the FDA rejected their own findings because the data regarding statistically significant low-dose effects did not conform to the toxicological model that effect level had to increase monotonically as dose increased.¹¹¹ In the CLARITY-BPA study, the dose range was 10,000-fold,¹¹¹ and the assumption that for a hormone-mimicking chemical this dose range would result in a monotonic response requires ignoring decades of research by endocrinologists.^{21,22} The FDA’s approach necessarily leads to the prediction that only very high levels of exposure to BPA and other EDCs are of concern. The FDA also has rejected data from research showing that males and females do not show a similar response to low-dose exposure to most EDCs,¹¹³ while sex differences in the response to exposure to EDCs are, in fact, expected,²⁴ due

to the difference in background hormone levels in males and females that are being disrupted by EDCs (Table 1).¹¹³

The ability to conduct integrative analyses of multiple data sets from CLARITY-BPA by Heindel et al.²⁶ revealed that the effects of low-dose BPA are not confined to a single tissue, organ, or system. Instead, complex changes occurred in several systems in male and female rats exposed to a 2.5 µg/kg BW/day dose of BPA that was below the TDI (at that time the temporary TDI for BPA was 4 µg/kg BW/day in the EU). Thus, the CLARITY-BPA paradigm of combining traditional guideline studies conducted by a GLP-certified laboratory with a consortium of expert academic investigators has the potential to move chemical risk assessments into the 21st century instead of just relying on guideline approaches that were being used over 50 years ago (Table 1).¹¹⁴

The German BfR Objection to the Revised TDI for BPA and the EFSA-CEP Response

BPA is related to disorders associated with chronic low-grade inflammation in men and women^{72,115} and also disrupts immune function in mice.^{115–117} The decision by the EFSA-CEP to use an increase in Th17 cells as the most sensitive outcome in revising the TDI,¹¹⁸ while acknowledging the wide range of harm associated with BPA exposure,¹¹⁹ led to an objection by the German BfR. Importantly, “BfR acknowledged that there is evidence that BPA can have this and other effects on the immune system.”⁶ Thus, while disputing the use by EFSA-CEP of an immune response to establish the revised TDI, the German BfR did not dispute that BPA disrupts normal immune function.

A main criticism by the German BfR of the EFSA-CEP’s decision was that the use of mechanistic data from an academic study reporting effects of BPA on Th17 cells was not based on strong enough direct evidence of a link to “an apical adverse outcome.”⁶ The position of the EFSA-CEP was that “The probability of an apical adverse effect occurring after triggering an intermediate end point is influenced by several factors, including other stressors, genetics and nutrition. Even though BPA is an extremely data-rich substance, current knowledge is insufficient to estimate the proportion of the population that may develop apical adverse immune effects from BPA exposure.”³ As was pointed out in the response by the EFSA-CEP,⁶ the German BfR cited as support for their concern studies that did not examine Th17 cells. The German BfR cited studies including a study¹²⁰ conducted as part of the CLARITY-BPA collaborative program (discussed further below) that did not examine Th17 cells and a study conducted by the FDA prior to CLARITY-BPA that did not examine Th17 cells but also reported that the negative control rats had been contaminated with BPA, negating the value of the study.¹⁰⁸

The EFSA-CEP also correctly stated that there is no requirement that to be adverse, an apical (disease) end point had to be used rather than an intermediate end point,⁶ such as stimulation of Th17 cells that release a potent inflammatory cytokine that is related to disease outcomes. Relevant to this controversy, a subsequent publication identified multiple adverse outcomes in adult men and women exposed to elevated levels of BPA, such as obesity and dysregulation of blood lipids.¹¹⁵ These adverse apical outcomes were shown to be related to increased secretion of the inflammatory cytokine interleukin-17A (IL17A), which is produced by Th17A cells. In addition, the multiple adverse outcomes in humans were consistent with extensive evidence of similar adverse effects of BPA related to inflammation and an increase in Th17 cells and IL17 in mice,^{115,117} negating the criticisms by the German BfR. Narrowly defining “adversity” has been commonly used as a basis for objecting to consideration of disruption of the endocrine system by EDCs as adverse, even during the most vulnerable period, fetal development, when effects are permanent and thus adverse.¹²¹

Kortenkamp et al.¹²² criticized EFSA-CEP for using a restricted time frame, which eliminated critical studies from their time-limited systematic review. The EFSA-CEP was thus criticized for not focusing on other health hazards due to exposure to BPA, particularly during pregnancy. Kortenkamp et al. emphasized the evidence for fetal BPA exposure effects on a decrease in adult testicular sperm production,⁷⁹ which, interestingly, was one of the first effects identified in adult male mice whose pregnant mothers had been exposed to an oral BPA dose of 20 µg/kg BW/day.¹²³ Kortenkamp et al. concluded that, if used by the EFSA-CEP, a decrease in testicular sperm count would have led to about a 10-fold higher TDI than the 0.2 ng/kg BW/day proposed by the EFSA-CEP based on Th17 data. However, the TDI based on testicular sperm effects calculated by Kortenkamp et al. would still have been far lower than the 1,000-fold higher TDI proposed by the German BfR relative to the EFSA-CEP-revised TDI. Interestingly, the German BfR-proposed TDI was also based on their analysis of effects of BPA on sperm count but only as a result of exposure to BPA in adulthood, not exposure during the most sensitive period during developmental,⁵ in contrast to Kortenkamp et al.⁷⁹

The German BfR expressed concern that there was a lack of the biological pathways by which BPA would lead to an adverse outcome (e.g., chronic inflammation), referred to as an adverse outcome pathway (AOP).⁶ An AOP is a conceptual model to describe the sequence of biological events that link a chemical’s interaction with a biological target to an adverse health outcome. There is nothing wrong with scientists seeking to understand the molecular pathways connecting EDCs with disease outcomes; in fact, this is a primary goal of much academic research. However, this argument is problematic when applied to risk assessments because there are multiple initial triggers (molecular initiating events) that have been identified for different pathways by which BPA can cause effects as a result of interacting with multiple receptors and enzymes.³⁶ In addition, a focus on mode of action does not take into account the multiple chemicals in a human-relevant mixture of chemicals, acting through different pathways, that can impact the same disease end point, such as a decline in testicular sperm production.¹²⁴ In its response to the German BfR, the EFSA-CEP emphasized that establishing a “causal link” between an “intermediate end point” and an “apical end point” is not required to make a regulatory decision.⁶

Disagreement over the EFSA-CEP Conservative Approach

The German BfR⁶ argued that “conservative worst-case assumptions are used in every step of the risk assessment process [by EFSA], . . . resulting in an over-conservative health based guidance value; HBGV” (i.e., the revised TDI). Kortenkamp et al.¹²² conducted a detailed analysis of the statistical approaches used by the EFSA-CEP and German BfR in their risk assessments of BPA and concluded: “Our deconstruction of the proposed alternative BfR TDI shows that this value is the result of a procedure in which less protective choices were made consistently at every possible turn.” What is unusual is that within the EU, the precautionary principle has already been applied by the European Commission to the regulation of BPA in specific products: “A prohibition for BPA in Food Contact Materials specifically for infants and young children also applies based on the precautionary principle.”¹⁶ However, the issue of a conservative (precautionary) approach by the EFSA-CEP is an important part of the dispute by the German BfR regarding the revised TDI by the EFSA-CEP. Importantly, the Endocrine Society, comprised of over 18,000 physicians and basic endocrine researchers, strongly endorses precaution when there is evidence that warrants it, which is certainly the case for BPA.¹²⁵

The mandate for regulatory agencies is to use the most sensitive outcome in the most sensitive animal model to arrive at an

estimation of the level of daily human exposure to a chemical that is protective for those who are the most sensitive to the effects, rather than just those at the median or the least sensitive individuals.¹²⁶ There is considerable variability in the sensitivity to hormonally active drugs and thus likely also to EDCs, and studies have revealed that pharmacokinetics of estrogenic drugs can vary considerably among individuals.¹²⁷

Relevant to the EFSA-CEP decision are data that the public health costs due to environmental EDCs, including BPA, have been estimated to be hundreds of billions of Euros per year just in the EU,⁴⁸ and much higher in the US.⁴⁹ The public health costs and environmental damage related to exposure to EDCs and other types of toxic chemicals have been evaluated using a process called “cost–benefit analysis” by Risk Managers (Table 1); attempts to change this in the USA are underway.^{128,129}

The Argument over BPA Pharmacokinetics

There was criticism by the German BfR published in the “Diverging Views” report⁶ regarding whether the pharmacokinetic studies used to compare metabolic processes in animals to estimate BPA disposition in humans were valid. We agree with some of the arguments made by the German BfR regarding comments about pharmacokinetics made by the EFSA-CEP (e.g., assertions that the study by Doerge et al.¹³⁰ was useful by the EFSA-CEP, while the German BfR pointed out that the Doerge et al. study only reported being able to measure BPA in very few of their samples and was thus not useful). There were other disagreements about BPA pharmacokinetics, such as whether serum BPA levels are linear with administered dose, which is the case as shown in mice by Taylor et al.,¹³¹ where internal dose of BPA was highly correlated ($R^2 = 0.98$; i.e., linear) following an oral administered dose between 2 and 100,000 μg BPA/kg BW. We agree with the BfR that biomonitoring is important, but there was previously a well-funded (74 million euro) biomonitoring program in the EU, the HBM4EU project 2016–2021, which was aimed at obtaining more data about environmental exposures.^{20,132} However, increased funding for additional global biomonitoring studies in the EU, US, and elsewhere is essential. Importantly, none of the disagreements over pharmacokinetics change the conclusion by the EFSA-CEP that BPA is a human health hazard at dramatically lower exposures than the TDIs estimated in prior risk assessments by EFSA,¹³³ the German BfR,¹³⁴ and the FDA¹³⁵ or the current approach to calculating the TDI by the German BfR.¹²²

Pharmacokinetics of BPA varies dramatically with route of administration, and thus bioactive BPA in humans cannot just be modeled by exposure in food, particularly if BPA is administered experimentally by intragastric gavage, which bypasses rapid sublingual absorption into the systemic circulation.⁴¹ Centers for Disease Control and Prevention (CDC) data have shown that there are multiple exposures to BPA throughout the day from unknown sources, some leading to unexpectedly high BPA levels in urine.¹³⁶ Thus, the use of one intragastric gavage administration per day in laboratory animal studies, a common practice in toxicological studies (and by the FDA in the CLARITY-BPA study), does not reflect the “real world” exposure of people to BPA.^{41,42,137}

Another important issue is that metabolic pathways have been shown to lead to the formation of several reactive oxidative metabolites/intermediates of BPA.^{138–140} In addition, one trace BPA metabolite, 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP), has been reported to be about 1,000-times more biologically active than BPA.¹⁴¹ Also not taken into account are findings that the current methods used to measure BPA in biomonitoring studies using surrogate standards result in markedly lower values for total BPA

relative to newer analytical methods that use authentic standards for conjugated (primarily glucuronidated) BPA.¹⁴²

Changes in the FDA Food Safety Division

The former FDA Center for Food Safety and Applied Nutrition (CFSAN), along with the EFSA, have in the past taken a very traditional approach in assessing the risks posed by BPA and other EDCs in food and cosmetics.^{11,55} In contrast to the EFSA-CEP approach in revising the TDI for BPA, the FDA-CFSAN chose to reject inclusion of nonguideline study findings in its assessment of the risks posed by BPA or any other chemical of concern in food, food packaging, or personal care products.^{111,135,143,144} As such, FDA-CFSAN rejected the use of all data generated through grants from the US National Institutes of Health (NIH) when the guideline portion of CLARITY-BPA was completed,¹⁴⁴ although NIH-funded research findings are heavily relied on by the FDA Center for Drug Evaluation and Research (FDA-CDER).

In 2022, the FDA commissioner requested an external evaluation of the food programs by the Reagan-Udall Foundation for the FDA.^{10,145–147} Our expectation is that the changes recommended by the Reagan-Udall Foundation, if implemented, would alleviate some of the FDA food safety agency’s administrative structural and functional problems. For example, the FDA-CDER accepts that hormonal drugs show nonmonotonic dose responses, examples being the breast cancer drug tamoxifen²¹ and leuprolide acetate, which is a GnRH agonist that stimulates testosterone production at low pulsatile doses but inhibits testosterone production at the continuous high therapeutic dose used to treat prostate cancer.¹⁴⁸ In sharp contrast, prior FDA-CFSAN leadership and scientists have rejected that nonmonotonic dose responses exist for hormonally active chemicals in food. FDA-CFSAN rejected as not biologically plausible any data that did not show a monotonic increase in response as dose increased.^{26,111} The expectation would be that all centers within the FDA would work together and continually assess an evolving scientific landscape and update assessment approaches to incorporate the latest research results and methodologies, but this has not been the case.¹¹

For example, the prior FDA-CFSAN first conducted a risk assessment for BPA in 2008 focusing on exposure from food-contact materials, updated by the FDA in 2010.¹³⁵ The FDA Science Board charged with reviewing the document in 2008 rejected the BPA risk assessment and stated that: “The draft FDA report does not articulate reasonable and appropriate scientific support for the criteria applied to select data for use in the assessment. Specifically, the Subcommittee does not agree that the large number of nonGLP studies should be excluded from use in the safety assessment.”¹⁴³

In spite of the FDA Science Board’s rebuke of the FDA’s 2008 BPA risk assessment, the day after completing the guideline portion of the NIEHS/NTP- and FDA-funded collaborative CLARITY-BPA study in 2018, the FDA Deputy Commissioner for Foods and Veterinary Medicine, Dr. Stephen Ostroff, issued a press release that, based only on the guideline studies, the FDA could assure the public that BPA was safe.¹⁴⁴ Ten years after being told that this rejection of nonguideline studies was unacceptable by their own Science Review Board, the FDA had not changed its position on rejecting all nonguideline findings, even from the collaborative CLARITY-BPA GLP study that used animals raised and treated by technicians and scientists at the FDA. At the time of Dr. Ostroff’s statement in 2018, there were almost 10,000 other published studies concerning the health effects of BPA that were not being used by the FDA.¹

The decision by the FDA to reject the use of academic investigator nonguideline studies in its 2018 assessment of BPA¹⁴⁴ is relevant to the EFSA decision because the EFSA-CEP waited for all

of the results from the NIEHS/NTP/FDA/investigator CLARITY-BPA study to be published before reaching a final decision regarding the TDI for BPA. Critically, the EFSA-CEP accepted findings from the academic arm of CLARITY-BPA while the FDA rejected those findings from their own research partners.^{111,119}

Assumptions in Chemical Risk Assessments That Cannot Be Applied to EDCs

Components of chemical risk assessment that require revision for evaluation of EDCs have been identified in multiple publications over the last 40 years. These include position statements from the Endocrine Society, from scientists at NIEHS, academic scientists, and even from scientists from the FDA-NCTR prior program on environmental estrogens, as described below. Components of chemical risk assessments are as follows: *a*) hazard identification, *b*) dose-response evaluation, *c*) exposure assessment, *d*) risk characterization, and *e*) risk management (Table 1).

Hazard Identification Has Required Use of Guideline Studies and GLP

Toxicological hazard identification for chemicals is the identification of intrinsic toxicological properties of a chemical and its capacity to interfere with normal biological processes in living organisms. The toxicological properties of a single chemical are investigated by conducting a set of internationally approved animal (normally rat) studies; the results of these studies are generally accepted by risk assessors as valid, regardless of whether the experimental design involved appropriate negative and positive controls.^{103,104,149} These are referred to as “guideline studies” that typically measure organ weights coupled with conventional (hematoxylin and eosin staining) rather than more sophisticated techniques, such as immunohistochemistry, to identify specific targets of interest. Also, guideline studies are not focused on disease outcomes, unlike most academic studies.

The discovery that many environmental chemicals could disrupt the endocrine system¹⁵⁰ should have resulted in a paradigm shift regarding the approaches used to assess the risks posed by EDCs.¹⁵¹ Yet, after three decades of compounding evidence, endocrine disruption is shockingly still not recognized as a unique problem by chemical risk assessment agencies in the US and Germany as well as in Asian countries. Regulatory toxicology approaches are geared toward detecting poisons, but EDCs are not poisons in the classic sense. The ability of regulatory agency toxicologists to protect the public from the harmful effects of EDCs requires knowledge of the mechanisms of hormone action and how the regulation of organ systems by hormones can be disrupted by EDCs, as described in statements of principles sponsored by the Endocrine Society.^{2,121}

We are concerned that commercial laboratories hired to conduct hazard identifications generally do not have the required expertise to conduct 21st century sophisticated research, which is thus absent from guideline protocols.^{55,152} It is also not practical for one contract lab to be expected to save all tissues for more detailed molecular analysis using the many techniques available today. This leads us to conclude that the collaborative program based on the CLARITY-BPA model should be accepted as the best approach to incorporate 21st century science into chemical hazard identification. Recruiting a number of individual academic investigators, each with extensive expertise studying a specific issue of interest, and many with an advanced knowledge of statistical approaches needed to analyze complex data sets,^{26,105} to conduct (blinded to treatment) one component of the hazard identification could greatly enhance both hazard and dose-response evaluation.^{26,55,103}

Incorporate Sex, Transgenerational, and Epigenetic Effects into Assessment of Chemical Hazards

Results from numerous experimental studies have not only demonstrated adverse effects of BPA on a wide array of organs, but also have provided evidence for sex-biased behavioral and physiological outcomes. Sex differences are a common feature of exposure to endocrine disruptors^{24,25} (Table 1).

There is also mounting evidence for effects of BPA and other EDCs (e.g., pesticides, phthalates, dioxin¹⁵³) that can be transmitted to subsequent generations—even if those descendants are not themselves exposed. These transgenerational effects include decreased fertility in subsequent generations. The transgenerational effects of BPA and other chemicals have been demonstrated in animal models (from fish to mammals^{28,154}) and thus need to be considered in assessing the impact that current exposures can have on future generations in humans. There is evidence that transgenerational effects of BPA are mediated through epigenetic mechanisms that are the subject of intensive investigation (Table 1).^{28,154} These findings also emphasize the need for a greater focus by regulatory agencies on exposures during developmental periods of heightened vulnerability during which epigenetic reprogramming is occurring. In addition, for the directly exposed generation, we recommend a greater awareness regarding long-latency disease expression after exposure during critical periods in development when organ systems are forming, which is referred to as the developmental origins of health and disease (DOHaD).¹⁵⁵

Dose–Response: Thresholds and Nonmonotonic Dose Responses

The dose–response core assumptions in risk assessments are as follows. *a*) The dose–response curve always increases (or decreases) monotonically, although this is false for hormones, hormonal drugs, and EDCs.²¹ *b*) High-dose testing predicts low-dose safety estimates because dose responses are always monotonic. The risk assessment community has refused to abandon the assumption that high-dose testing predicts low-dose safety estimates because dose responses are always monotonic, even though for EDCs such as BPA, testing only high doses does not predict receptor-mediated responses that occur at doses far below the doses predicted to be safe by risk assessors.²¹ *c*) “Safe” doses exist below a theoretical threshold. However, this has been shown to be false for any chemical that mimics an endogenous hormone that is already above any putative threshold.^{38–40} All of these current risk assessment assumptions are accepted as fact even though they contradict data from EDC, including BPA research,¹ and involve rejecting that the principles of hormone action and endocrinology apply to EDCs.^{2,121}

The issue of whether or not there is a threshold below which chemicals such as BPA will not cause an effect has been debated by risk assessors, but in 1982 an FDA panel advised the FDA: “Do not assume there is no hazard below an arbitrary threshold.”^{156,157} However, in 1995 the FDA rejected this expert panel’s advice and created the “Threshold of Regulation Rule,” which exempts substances used in food contact materials from regulation as food additives if the dietary concentration is below the arbitrary limit of 0.5 parts per billion (ppb)^{158,159}; concentrations of BPA over 1,000-fold lower than this arbitrary FDA threshold have significant effects in rat brain and pituitary cells.^{160,161}

In summary, we propose that the risk assessment assumptions related to the threshold and dose–response issues need to be abandoned. Specifically, *a*) there cannot be a threshold below which there are no adverse effects that exist for EDCs that alter the activity of endogenous hormones already causing effects and

are thus above any putative threshold. And, *b*) the belief that thresholds exist for EDCs is coupled to rejection of data that non-monotonic dose responses (NMDRs) are common for hormones, hormonal drugs, and EDCs (Table 1).²¹

In more detail, the prediction of a threshold assumes that all dose-response relationships are monotonic, which is required to use “safety factors” to estimate the TDI based only on data from guideline studies that typically only use a few very high doses, not relevant to human exposures.^{21,40} In addition, the calculated TDI [the FDA’s acceptable daily intake (ADI)] using these assumptions is not experimentally determined to cause no adverse effects.¹⁵¹ Experiments that show effects below the TDI have been rejected by the FDA, such as the FDA’s own statistically significant findings of effects at a dose below the TDI in CLARITY-BPA that were determined to be “not biologically plausible” and thus were not taken into account.¹¹¹

BPA disrupts endocrine systems that operate at very low concentrations in blood.¹ The actions of hormones, including the steroid hormone 17 β -estradiol, can be adversely altered by numerous EDCs, including BPA. Estrogenic endocrine disruptors were initially the most focused-on chemicals when scientists began studying EDCs.¹⁵⁰ Based on studies in mice²⁹ and human cells in culture,²² estradiol is active at levels below parts per trillion (pg/mL or ng/L) concentrations in blood. These very low concentrations are active because when a hormone, hormonal drug, or EDC binds to any of the multiple estrogen or other receptors in target cells (e.g., in the brain, breast, uterus, pancreas, adipose tissue, prostate, etc.), there is a massive signal amplification that occurs in the target cell, resulting in a large response.¹⁶² Receptor-mediated amplification of low-dose effects is not considered in studies examining the systemic effects of poisons.

The low-dose effects of BPA (that occur within the range of exposure in the general population) are not predicted by only testing a few high doses typically administered in guideline toxicological research used for risk assessments.^{1,22} The arguments of the German BfR against the proposed TDI for BPA by the EFSA-CEP focused on retaining traditional approaches used in guideline toxicity studies.^{5,6} This typically involves only examining a few very high doses starting at the maximum tolerated dose (MTD) and the application of safety factors to calculate a TDI, regardless of whether or not a no-effect dose is found, which just results in application of an additional safety factor.^{2,21} The Endocrine Society has applauded the decision by the EFSA-CEP to revise the TDI for BPA¹⁶³ and has also issued numerous position papers urging regulators to accept the basic principles of endocrinology in regulating EDCs.^{2,121,125}

Exposure Assessment

Methods to assess human exposure to chemicals are a very weak part of chemical risk assessments because all of the possible routes of exposure are not known for chemicals used in many products. A problem is that in the US corporations are not required to identify this information to the public or to the FDA, due to the Generally Recognized as Safe (GRAS) loophole in the law, discussed below.

We urge regulatory agencies in all countries to enforce the disclosure of chemicals in products. We also recommend adoption of a requirement that a corporation that makes a chemical provide the authentic standards required for government and independent scientists to accurately measure the chemical and its major metabolites in biomonitoring studies.¹⁴² This is essential for exposure assessment, since without knowledge of how and where chemicals are being used, regulators have to default to models rather than data. The regulatory system in the EU, as a result of the chemical regulation known as the Registration, Evaluation, Authorization,

and Restriction of Chemicals (REACH),¹⁶⁴ provides for more transparency regarding chemicals in products relative to the US, but REACH still needs additional safeguards.⁴³ For example, the use of intragastric gavage administration as a default method of exposing animals to chemicals, such as BPA, to assess exposure has been criticized because it is clearly a stressful procedure¹³⁷ and because gavage is not relevant to different routes of human exposure to BPA or many other chemicals (e.g., in cosmetics, building materials, and aerosols¹⁶⁵). This has also been shown by very high BPA exposure from holding a thermal receipt when coupled with the use of hand sanitizer,⁴² an issue that has been addressed in the EU but, as yet, not in the US.¹⁶⁶

We strongly support that in exposure assessments there is a determination of the mixture of chemicals to which various populations are exposed, which can then inform scientists regarding the testing of mixtures at human-relevant concentrations.⁴⁵ This issue is thus complex, as it involves more than examining chemicals that are just part of a class of structurally similar chemicals, such as the dozens of BPA analogues being marketed in different products as being “BPA free.”²³ Importantly, it has been identified that multiple chemicals that are not structurally similar occur within the mixture of chemicals to which human populations are exposed and can contribute to the same disease outcome.⁴⁵ This would require a dramatic change in approaches used by regulatory agencies that only currently examine one chemical at a time in hazard identifications. However, regulatory agencies, scientists, and the public are largely in the dark regarding the hundreds or even thousands of chemicals to which the public may be chronically exposed. We urge that the number of chemicals examined in the ongoing National Health and Nutrition Examination Survey (NHANES) conducted by the CDC be greatly expanded (this also needs to occur in the EU), but they need to have a better idea regarding what to look for, which requires transparency regarding chemicals being used in products (Table 1).

Risk Characterization

As described above, the assumptions used to identify a chemical’s hazards do not apply to EDCs (based on only testing high doses, assuming that the dose response is always monotonic, and that there should not be sex differences in response to exposure). Because these underlying assumptions in hazard assessments do not apply to EDCs, then the characterization of risk for EDCs, which is an estimation of the occurrence of known or potential adverse health effects, will be false. Risk is calculated as equal to hazard times exposure ($R = H \times E$). We have reviewed above that there are a vast number of human, experimental animal, and mechanistic studies using cell culture or other *in vitro* methods demonstrating that BPA is a hazardous EDC. It is clearly incorrect to conclude that BPA poses no risk based on the assumption of negligible exposure to BPA, regardless of the published hazards posed by BPA at human exposure levels.¹ For example, previously, the FDA predicted that all reports of detectable bioactive (free) BPA associated with adverse effects in human biomonitoring studies⁴⁷ were due to assay contamination, thus leading to rejection of many published findings,¹³⁰ which was shown to be false.^{167,168}

The toxicological model “the dose makes the poison,” results in only BPA at levels far above exposures of the general population being tested in hazard assessments, but this is not protective of the health of the general population. Sadly, levels of BPA in workers exposed occupationally to BPA are very high, but no regulatory agency in the US, such as the Occupational Safety and Health Administration (OSHA), has acknowledged and acted on these findings published by the National Institute for Occupational Safety and Health (NIOSH).^{169,170}

Risk Management

In the US, the White House Office of Information and Regulatory Affairs (OIRA), which is part of the Office of Management and Budget (OMB), has been the gatekeeper for all new federal rules and regulations. OIRA administrators have used “cost-benefit analysis,” along with other factors, in chemical regulation decisions, but there is an ongoing effort to prioritize the public health^{128,129} (Table 1). Regulatory agencies could spend years working on proposed regulatory changes, only to have them die in this office.

Need for Transparent and Sustainable Approaches to Protect the Environment and Public Health

There are critical issues that need to be addressed to result in a sustainable chemical enterprise and improve the approaches to evaluating chemicals for their potential to harm the environment and public health prior to their use in products. A summary of issues to achieve sustainability is presented in Table 1.

Regrettable Substitutions

The issue of replacing hazardous chemicals, such as BPA, with, in many cases, chemicals not subjected to prior testing for their hazards and that are later shown to be as bad or worse than the chemicals they replaced, is referred to as “regrettable substitutions” (Table 1).^{19,20} Little will be accomplished by banning BPA in products, such as thermal receipt paper in the EU,¹⁶⁶ although not in the US, if potentially even worse bisphenols, such as BPS, which is metabolized at a significantly slower rate than BPA,⁶³ are allowed to be used, and these products are then labeled “BPA free,” suggesting a safer product.

In October 2022 two German regulatory agencies, the Federal Office for Chemicals (BfC) in collaboration with the German Environment Agency (UBA), submitted a proposal to the European Chemicals Agency (ECHA) to restrict bisphenol A and some other bisphenol analogues, such as BPS, BPF, BPB (2,2-Bis(4-hydroxyphenyl)butane) and BPAF (4,4'-(1,1,1,3,3,3-Hexafluoropropane-2,2-diyl)diphenol) of similar concern for the environment.¹⁶⁴ In April 2022 ECHA had released a statement that they had examined 148 bisphenols and identified 34 bisphenols that would be covered under a “group restriction.”²³ But, in late August 2023, under heavy pressure from industry,⁴³ Germany withdrew its restriction proposal for bisphenols.¹⁶⁴

The Food Additives Amendment law was passed in the US in 1958. However, chemicals such as polycarbonate resins (e.g., BPA-based chemicals) used in food and beverage packaging were grandfathered in [labeled “generally recognized as safe” (GRAS)] as an indirect food additive in 1963 by the FDA.¹⁵⁹ However, this law stipulated that regulators should take into consideration “the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet.”¹⁷¹ However, since being tasked with assessing the impacts on human health of mixtures of chemicals used as direct and indirect food additives, the FDA has not faithfully implemented this law and has not considered structurally similar chemicals (such as bisphenol analogues) when conducting risk assessments.⁴⁴

We also recognize that there are not adequate hazard data for many of the bisphenol analogues currently being used in products, making such a ban on their use a matter of precautionary action, consistent with the 1958 law. There should also be a mandate for a requirement of proof of safety prior to allowing use, which is required for drugs in the US but not chemicals in food, food packaging, personal care products, or other common household products.

The Need for the FDA to Create a New Rule Governing GRAS

When the Food Additives Amendment was signed into law in 1958 by the US Congress, it included that “Safe means that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”¹⁷² But, there was a gaping loophole in the law that allowed for an exemption from the food additive requirements for substances “generally recognized as safe” by scientific experts in the field. The GRAS exemption was supposedly based on a long history of use before 1958 or based on scientific studies. However, it turns out that scientists who have been invited to serve on panels to determine whether a chemical can be deemed as GRAS are predominantly a small band of consultants who are being paid by corporations that make the chemical.¹⁵⁹ Using experts paid by industry on panels to make decisions about the safety of new chemicals is an opaque process that has prompted some skeptics to characterize GRAS as more appropriately referred to as “Generally Recognized as Secret.”¹⁷³

While the concept of GRAS was initially supposed to apply to chemicals such as table salt, the FDA now allows industry to declare a chemical as GRAS without even notifying the FDA.^{156,159} In the US, corporations can put chemicals into food without informing the FDA. Thus, a large number of the estimated 10,000 chemicals used as additives in food and food packaging materials are not only not being regulated by the FDA, but currently the FDA has no mechanism to require chemical corporations to inform them regarding what chemicals are in products the FDA is supposed to be regulating.⁴⁴

We strongly urge the FDA to initiate regulatory action to close the GRAS loophole by corporations because we believe that without action by the FDA, the food supply in the US will remain unsafe,¹⁷² regardless of the administrative changes currently underway in the food safety division of the FDA. The agency’s lack of systematic pre- and post-market oversight continues to create health risks, as companies determine that their new chemicals are safe while keeping the FDA in the dark.^{44,172,173} We strongly support premarket testing of chemicals in products and in food and food packaging materials in the EU and propose that this needs to be required in the US. In the EU, we believe that issues specific to endocrine disruption that were on the initial agenda need to be addressed in revising REACH.⁴³

Apply the Principles of Sustainable Chemistry into Designing the Next Generation of Chemicals

An important need is to add to the chemistry curriculum the principles of safe and sustainable chemistry,⁵⁹ so that the chemists who are responsible for synthesizing chemicals have included in their training the basics of biology and modern toxicology. This information is critical in determining which products should or should not be commercialized (Table 1). For example, BPA [di-(p-hydroxyphenyl)dimethyl methane] was reported in the journal *Nature* in 1936 to be 100% effective in a rat vaginal epithelium cornification bioassay for estrogenic activity in a study whose authors were looking for chemicals that could be used as fertility drugs.¹⁷⁴ However, in the 1950s, chemists synthesized polycarbonate from BPA, which was then used to make baby bottles, in the resin lining of metal cans, and in other food and beverage packaging. Organic chemistry textbooks cover that ester bonds linking BPA molecules in polycarbonate (consisting of chains of BPA molecules) would be subject to hydrolysis that would release free (bioactive) BPA under normal conditions of use (heating or an increase or decrease in pH), but this did not deter the

use in food and beverage packaging of BPA with known estrogenic activity (Table 1).

The consequence is that staggering amounts of BPA have been produced over the past 70 years, and much is still present in the environment.¹⁷⁵ BPA is considered a nonpersistent chemical, but BPA is actually persistent when it settles into a low-oxygen environment (e.g., in river sediment).¹⁷⁶ While reducing the production and use of hazardous chemicals such as BPA is essential, there is also a need to develop remediation methods that are not overwhelmingly expensive. Techniques are being developed to remove BPA and other toxic chemicals from drinking water,⁶¹ which is a tremendous global challenge, since BPA is a ubiquitous contaminant.

Conclusions

From the perspective of both clinicians and scientists involved in EDC research, we strongly support the EFSA-CEP proposed 20,000-fold reduction of the TDI for BPA to 0.2 ng/kg BW/day.^{26,54} The overwhelming scientific evidence points to the fact that BPA is a hazardous chemical with endocrine disrupting properties that adversely impacts the health of humans and wildlife, as well as the environment, at exceedingly low concentrations, far below prior estimates of safety based on the sole use by risk assessors of guideline study results. In its recent scientific opinion, the EFSA-CEP correctly concluded that exposure to BPA at present levels is of concern for the public health.³ The proposed 20,000-fold reduction in the TDI for BPA by the EFSA-CEP is consistent with the conclusion reached based on the findings from the collaborative CLARITY-BPA study (based on current risk assessment methods),^{26,54} although we reject the current risk assessment assumption that creates the illusion that there is a threshold dose below which any BPA exposure is safe. The EFSA-CEP revised TDI is so low that it requires a ban of BPA use in food and food contact materials, which we support.

The EFSA-CEP revised TDI resulted from the decision to take into account data of academic origin as well as data generated using systematic review guideline protocols, but the EFSA-CEP limited the time period of their systematic review. We predict that the EFSA-CEP would have reached a much stronger conclusion about other BPA hazards if their risk assessment had not been limited to only less than a 6-year time period (1 January 2013 to 15 October 2018). The EFSA-CEP's rationale was that they had already reviewed earlier findings in their 2015 risk assessment of BPA.¹⁷⁷ Critically, this prior 2015 risk assessment had not used the systematic review protocol and had limited the literature review to only include studies with oral exposure. EFSA had also previously dismissed numerous important academic findings, particularly developmental effects on the mammary gland, male reproductive system, metabolic syndrome, and brain and behavior, which could have led to stronger conclusions about BPA hazards to other organs by the EFSA-CEP.^{122,178} Use of a transparent systematic review of *all* of the data (not just data from a restricted time period) is a conceptually revolutionary approach that we recommend be used by government agencies in future chemical risk assessments.¹⁷⁸

The EFSA-CEP recognized the value of the combined guideline and academic investigator findings from the CLARITY-BPA project, which unequivocally demonstrated statistically significant adverse effects at levels of BPA below the previous TDI.^{26,54,55} Critically, the FDA rejected the nonguideline findings from CLARITY-BPA.¹¹¹ Our proposal is that CLARITY-BPA should serve as a model for integrating 21st century academic research into a hybrid and pluralistic regulatory assessment process for identifying hazards posed by chemicals, as initially envisioned by administrators at the NIEHS and NTP.^{52,53,55} This will allow regulatory agencies to quickly integrate state-of-the-art research

approaches into chemical risk assessments instead of just relying on rigid guideline protocols, some of which are obviously obsolete (e.g., weighing the brain to assess neurological effects).

Our advice is that while the CLARITY-BPA paradigm should be the future for regulatory toxicology studies, there need to be clear rules of governance to ensure adherence to unbreakable rules and complete transparency. This was actually expected to happen in CLARITY-BPA. Heindel et al.,⁵³ with authors representing NIEHS, NTP, FDA, and independent investigators, stated: "For CLARITY-BPA, we developed a set of articles of collaboration, confidentiality statements, publication agreements, memos describing transfer of data to the CEBS database, and an SOP for decoding of all data, which have been critical to the functioning of the program." However, the FDA withdrew from this contractual agreement, and the expected formal NTP report containing an integrated review of guideline and academic findings never happened.^{26,55,112} One possibility would be to include involvement of an independent third entity that would curate all of the data (while blinded to the source and treatment) to ensure that rules governing the analysis and presentation of all data are adhered to.

In the EU, REACH became law in 2007 and was supposed to be revised in the fall of 2023 as part of the Green Deal in the EU,¹⁷⁹ but this was met with intense resistance from industry.⁴³ In spite of the resistance, the European Commission Draft published for public comment restricts BPA from food contact materials and also requires bisphenol analogues used to replace BPA to undergo a full risk assessment and authorization prior to use.^{15–18} In the US, the new Deputy Commissioner for Human Foods in the FDA has proposed that one of the three core missions he has established is "safeguarding the food supply through the safe use of chemicals and dietary supplements."¹⁴⁷

In summary, the EFSA decision on BPA is a significant step in the right direction at a time when additional giant steps are needed to completely redesign the methods used to regulate exposure to tens-of-thousands of untested chemicals in food, beverages, and household products (summarized in Table 1). We hope the EFSA-CEP's new risk assessment for BPA using systematic review of the literature encourages the FDA, UK Environment Agency, the German BfR, as well as other regulatory agencies, such as in Japan and other countries in Asia, to rethink their approaches and assumptions used to regulate chemicals and bring rational, science-based chemical regulation into the 21st century.

We are optimistic that modern science will finally be used to inform the assessment of risks posed by chemicals being used in common household products leading to ubiquitous exposure, with BPA being just one of a large number of examples. Now it is up to regulators in Europe, the US, and the rest of the world to implement effective regulations that truly protect human and environmental health.

Acknowledgments

We acknowledge the wisdom and expertise of Daniel M. Sheehan (1944–2012) who made significant contributions to the issues covered in this commentary.

References

1. Vom Saal FS, Vandenberg LN. 2021. Update on the health effects of bisphenol A: overwhelming evidence of harm. *Endocrinology* 162(3):bqaa171, <https://doi.org/10.1210/endocr/bqaa171>.
2. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. *Endocrinology* 153(9):4097–4110, PMID: 22733974, <https://doi.org/10.1210/en.2012-1422>.
3. EFSA (European Food Safety Authority). 2023. *Re-evaluation of the Risks to Public Health Related to the Presence of Bisphenol A (BPA) in*

Foodstuffs - Immunotoxicity. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2023.6857> [accessed 16 November 2023].

4. EFSA. 2017. *Bisphenol A (BPA) Hazard Assessment Protocol*. <https://www.efsa.europa.eu/en/supporting/pub/en-1354> [accessed 19 July 2023].
5. BfR (German Federal Institute for Risk Assessment). 2023. *Bisphenol A: BfR Proposes Health Based Guidance Value, Current Exposure Data are Needed for a Full Risk Assessment*. German BfR Opinion No 018/2023. <https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.bfr.bund.de%2Fcm%2F349%2Fbisphenol-a-bfr-proposes-health-based-guidance-value-current-exposure-data-are-needed-for-a-full-risk-assessment.pdf&data=0%5C0%7Cvomsaalf%40missouri.edu%7C00668889a7cd2499cc36408dbcfcba374%7Ce3fefdbef7e9401ba51a355e01b05a89%7C0%7C0%7C638328056232386145%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzliLCJBTi6lk1haWwILCJXCI6Mn0%3D%7C3000%7C%7C%7C&sdata=oZN%2FOHogWMS9UDxpmly13nUEQ9SL2P4wXKNACqeb9Y%3D&reserved=0> [accessed 12 November 2023].
6. EFSA/BfR. 2023. *Report on Diverging Views Between EFSA and BfR on EFSA Updated Bisphenol A Assessment*. <https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.efsa.europa.eu%2Fsites%2Fdefault%2Ffiles%2F2023-04%2Fbfr-efsa-art-30.pdf&data=0%5C0%7Cvomsaalf%40missouri.edu%7C00668889a7cd2499cc36408dbcfcba374%7Ce3fefdbef7e9401ba51a355e01b05a89%7C0%7C0%7C638328056232386145%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzliLCJBTi6lk1haWwILCJXCI6Mn0%3D%7C3000%7C%7C%7C&sdata=TbYMZdly6DULCNBK0koxyU7mif%2Fwu00XvobC78BNJx0%3D&reserved=0> [accessed 12 November 2023].
7. EFSA/EMA (European Medicines Agency). 2022. *Report on Divergent Opinion Between EFSA and EMA on Bisphenol-A_Final Adopted*. https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.ema.europa.eu%2Fen%2Fdocuments%2Freport%2Freport-divergent-opinion-between-efsa-ema-bisphenol_en.pdf&data=0%5C0%7Cvomsaalf%40missouri.edu%7C00668889a7cd2499cc36408dbcfcba374%7Ce3fefdbef7e9401ba51a355e01b05a89%7C0%7C0%7C638328056232386145%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzliLCJBTi6lk1haWwILCJXCI6Mn0%3D%7C3000%7C%7C%7C&sdata=iamfT0oM1EfHb1QbjgL%2BkUE8fxwcnLA8UXKBhcoK4U%3D&reserved=0 [accessed 12 November 2023].
8. Zoeller RT, Birnbaum LS, Collins TJ, Heindel J, Hunt PA, Iguchi T, et al. 2023. European medicines agency conflicts with the European food safety authority (EFSA) on bisphenol a regulation. *J Endocr Soc* 7(9):bvad107, PMID: 37873497, <https://doi.org/10.1210/jendso/bvad107>.
9. Covington. 2023. FDA updates on food and color additives. Covington Alert, online edition. 3 November 2023. <https://www.cov.com/en/news-and-insights/insights/2023/11/fda-updates-on-food-and-color-additives> [accessed 2 February 2024].
10. FDA (Food and Drug Administration). 2023. *FDA Provides Update on Proposal for Unified Human Foods Program, including New Model for the Office of Regulatory Affairs*. <https://www.fda.gov/news-events/press-announcements/fda-provides-update-proposal-unified-human-foods-program-including-new-model-office-regulatory> [accessed 14 November 2023].
11. Birnbaum LS. 2022. Op-Ed: FDA fails to protect the public from chemical health risks. *Environmental Health News*, online edition. 21 April 2022. <https://www.ehn.org/fda-chemical-regulation-2657184101.html> [accessed 31 July 2023].
12. Evich HB. 2022. The FDA's food failure. *Politico*. 8 April 2022. <https://www.politico.com/interactives/2022/fda-fails-regulate-food-health-safety-hazards/> [accessed 15 November 2023].
13. Maffini M, Nettner T. 2023. *European Commission plans to ban food uses of BPA. We ask again: where is FDA?* Washington DC: Environmental Defense Fund. <https://blogs.edf.org/health/2023/06/09/european-commission-plans-to-ban-food-uses-of-bpa-we-ask-again-where-is-fda/> [accessed 15 November 2023].
14. Duh-Leong C, Maffini MV, Kassotis CD, Vandenberg LN, Trasande L. 2023. The regulation of endocrine-disrupting chemicals to minimize their impact on health. *Nat Rev Endocrinol* 19(10):600–614, PMID: 37553404, <https://doi.org/10.1038/s41574-023-00872-x>.
15. EC (European Commission). 2023. *Food Safety – Restrictions on Bisphenol A and Other Bisphenols in Food Contact Materials*. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13832-Food-safety-restrictions-on-bisphenol-A-BPA-and-other-bisphenols-in-food-contact-materials_en [accessed 15 November 2023].
16. EC. 2023. *Questions and Answers (Q&A) Concerning the Risk Management Approach for Bisphenol A (BPA) and Other Bisphenols in Food Contact Materials (FCMs)*. https://food.ec.europa.eu/system/files/2023-08/cs_fcm_wg_20230804_qandas.pdf [accessed 15 November 2023].
17. EC. 2024. *Food Safety: Commission Launches 4-Week Feedback Period on Ban of BPA in Food Contact Materials*. <https://ec.europa.eu/newsroom/sante/newsletter-archives/50834> [accessed 9 February 2024].
18. EC. 2024. *Food safety – Restrictions on Bisphenol A (BPA) and Other Bisphenols in Food Contact Materials*. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13832-Food-safety-restrictions-on-bisphenol-A-BPA-and-other-bisphenols-in-food-contact-materials_en [accessed 9 February 2024].
19. EEA (European Environment Agency). 2023. *Public Exposure to Widely Used Bisphenol A Exceeds Acceptable Health Safety Levels*. <https://www.eea.europa.eu/en/newsroom/news/public-exposure-to-bisphenol-a#:~:text=In%20the%20countries%20that%20participated,constitutes%20a%20potential%20health%20concern> [accessed 16 November 2023].
20. European Human Biomonitoring Initiative. 2022. *Policy Brief - Bisphenols*. <https://www.hbm4eu.eu/wp-content/uploads/2022/05/Policy-Brief-Bisphenols.pdf> [accessed 16 November 2023].
21. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, et al. 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev* 33(3):378–455, PMID: 22419778, <https://doi.org/10.1210/er.2011-1050>.
22. Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, Vom Saal FS. 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environ Health Perspect* 111(8):994–1006, PMID: 12826473, <https://doi.org/10.1289/ehp.5494>.
23. ECHA (European Chemicals Agency). 2022. *Group Assessment of Bisphenols Identifies Need for Restriction*. <https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fecha.europa.eu%2Fgroup-assessment-of-bisphenols-identifies-need-for-restriction&data=0%5C0%7Cvomsaalf%40missouri.edu%7C00668889a7cd2499cc36408dbcfcba374%7Ce3fefdbef7e9401ba51a355e01b05a89%7C0%7C0%7C638328056232386145%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzliLCJBTi6lk1haWwILCJXCI6Mn0%3D%7C3000%7C%7C%7C&sdata=2f0HogWMS9UDxpmly13nUEQ9SL2P4wXKNACqeb9Y%3D&reserved=0> [accessed 14 November 2023].
24. Palanza P, Paterlini S, Brambilla MM, Ramundo G, Caviola G, Gioiosa L, et al. 2021. Sex-biased impact of endocrine disrupting chemicals on behavioral development and vulnerability to disease: of mice and children. *Neurosci Biobehav Rev* 121:29–46, PMID: 33248148, <https://doi.org/10.1016/j.neubiorev.2020.11.015>.
25. Williams SA, Jasarevic E, Vandas GM, Warzak DA, Geary DC, Ellersiek MR, et al. 2013. Effects of developmental bisphenol A exposure on reproductive-related behaviors in California mice (*Peromyscus californicus*): a monogamous animal model. *PLoS One* 8(2):e55698, PMID: 23405200, <https://doi.org/10.1371/journal.pone.0055698>.
26. Heindel JJ, Belcher S, Flaws JA, Prins GS, Ho SM, Mao J, et al. 2020. Data integration, analysis, and interpretation of eight academic CLARITY-BPA studies. *Reprod Toxicol* 98:29–60, PMID: 32682780, <https://doi.org/10.1016/j.reprotox.2020.05.014>.
27. Kundakovic M, Gudsnuik K, Franks B, Madrid J, Miller RL, Perera FP, et al. 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. *Proc Natl Acad Sci USA* 110(24):9956–9961, PMID: 23716699, <https://doi.org/10.1073/pnas.1214056110>.
28. Jung YH, Wang HV, Ruiz D, Bixler BJ, Linsenbaum H, Xiang JF, et al. 2022. Recruitment of CTCF to an Fto enhancer is responsible for transgenerational inheritance of BPA-induced obesity. *Proc Natl Acad Sci USA* 119(50):e2214988119, PMID: 36469784, <https://doi.org/10.1073/pnas.2214988119>.
29. Vom Saal FS, Timms BG, Montano MM, Palanza P, Thayer KA, Nagel SC, et al. 1997. Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. *Proc Natl Acad Sci USA* 94(5):2056–2061, PMID: 9050904, <https://doi.org/10.1073/pnas.94.5.2056>.
30. Medlock KL, Lytle CR, Kelepouris N, Newman ED, Sheehan DM. 1991. Estradiol down-regulation of the rat uterine estrogen receptor. *Proc Soc Exp Biol Med* 196(3):293–300, PMID: 1998006, <https://doi.org/10.3181/00379727-196-4319>.
31. Gupta C. 2000. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. *Proc Soc Exp Biol Med* 224(2):61–68, PMID: 10806412, <https://doi.org/10.1046/j.1525-1373.2000.22402x>.
32. Coser KR, Chesnes J, Hur J, Ray S, Isselbacher KJ, Shioda T. 2003. Global analysis of ligand sensitivity of estrogen inducible and suppressible genes in MCF7/BUS breast cancer cells by DNA microarray. *Proc Natl Acad Sci USA* 100(24):13994–13999, PMID: 14610279, <https://doi.org/10.1073/pnas.2235866100>.
33. Taylor JA, Richter CA, Suzuki A, Watanabe H, Iguchi T, Coser KR, et al. 2012. Dose-related estrogen effects on gene expression in fetal mouse prostate mesenchymal cells. *PLoS One* 7(10):e48311, PMID: 23144751, <https://doi.org/10.1371/journal.pone.0048311>.
34. Jordan VC. 2019. The SERM Saga, something from nothing: American Cancer Society/SSO basic science lecture. *Ann Surg Oncol* 26(7):1981–1990, PMID: 30911948, <https://doi.org/10.1245/s10434-019-07291-1>.
35. Arase S, Ishii K, Igarashi K, Aisaki K, Yoshio Y, Matsushima A, et al. 2011. Endocrine disrupter bisphenol A increases in situ estrogen production in the mouse urogenital sinus. *Biol Reprod* 84(4):734–742, PMID: 21123812, <https://doi.org/10.1095/biolreprod.110.087502>.

36. Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, et al. 2010. Endocrine profiling and prioritization of environmental chemicals using ToxCast data. *Environ Health Perspect* 118(12):1714–1720, PMID: [20826373](https://doi.org/10.1289/ehp.1002180), <https://doi.org/10.1289/ehp.1002180>.

37. Villar-Pazos S, Martinez-Pinna J, Castellano-Munoz M, Alonso-Magdalena P, Marroqui L, Quesada I, et al. 2017. Molecular mechanisms involved in the non-monotonic effect of bisphenol-A on Ca^{2+} entry in mouse pancreatic beta-cells. *Sci Rep* 7(1):11770, PMID: [28924161](https://doi.org/10.1038/s41598-017-11995-3), <https://doi.org/10.1038/s41598-017-11995-3>.

38. Hoel DG. 1980. Incorporation of background in dose-response models. *Fed Proc* 39(1):73–75, PMID: [7351247](https://doi.org/10.1161/01.090303.x).

39. Blair RM, Fang H, Gaylord D, Sheehan DM. 2001. Threshold analysis of selected dose-response data for endocrine active chemicals. *Appl. Environ. Res.* 109(3):198–208, PMID: [11430497](https://doi.org/10.1034/j.1600-0463.2001.090303.x), <https://doi.org/10.1034/j.1600-0463.2001.090303.x>.

40. Sheehan DM. 2006. No-threshold dose-response curves for nongenotoxic chemicals: findings and applications for risk assessment. *Environ. Res.* 100(1):93–99, PMID: [16256101](https://doi.org/10.1016/j.envres.2005.09.002), <https://doi.org/10.1016/j.envres.2005.09.002>.

41. Gaynard V, Lacroix MZ, Collet SH, Viguerie C, Bousquet-Melou A, Toutain PL, et al. 2013. High bioavailability of bisphenol A from sublingual exposure. *Environ. Health Perspect.* 121(8):951–956, PMID: [23761051](https://doi.org/10.1289/ehp.1206339), <https://doi.org/10.1289/ehp.1206339>.

42. Hormann AM, Vom Saal FS, Nagel SC, Stahlhut RW, Moyer CL, Ellersiek MR, et al. 2014. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). *PLoS One* 9(10):e110509, PMID: [25337790](https://doi.org/10.1371/journal.pone.0110509), <https://doi.org/10.1371/journal.pone.0110509>.

43. van Deelen G. 2023. The chemical industry may have killed a landmark EU chemical policy. Here's what that means for the US. *Environmental Health News*. 9 November 2023. <https://www.ehn.org/eu-reach-chemical-policy-266066709.html> [accessed 2 February 2024].

44. Maffini MV, Neltner TG, Vogel S. 2017. We are what we eat: regulatory gaps in the United States that put our health at risk. *PLoS Biol* 15(12):e2003578, PMID: [29261673](https://doi.org/10.1371/journal.pbio.2003578), <https://doi.org/10.1371/journal.pbio.2003578>.

45. Kortenkamp A, Scholze M, Ermrl S, Priskorn L, Jorgensen N, Andersson AM, et al. 2022. Combined exposures to bisphenols, polychlorinated dioxins, paracetamol, and phthalates as drivers of deteriorating semen quality. *Environ. Int.* 165:107322, PMID: [35691715](https://doi.org/10.1016/j.envint.2022.107322), <https://doi.org/10.1016/j.envint.2022.107322>.

46. Luijten M, Vlaanderen J, Kortenkamp A, Antignac JP, Barouki R, Bil W, et al. 2023. Mixture risk assessment and human biomonitoring: lessons learnt from HBM4EU. *Int J Hyg Environ Health* 249:114135, PMID: [36758443](https://doi.org/10.1016/j.ijeh.2023.114135), <https://doi.org/10.1016/j.ijeh.2023.114135>.

47. Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Environ. Health Perspect.* 118(8):1055–1070, PMID: [20338858](https://doi.org/10.1289/ehp.0901716), <https://doi.org/10.1289/ehp.0901716>.

48. Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, et al. 2016. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European union: an updated analysis. *Andrology* 4(4):565–572, PMID: [27003928](https://doi.org/10.1111/andr.12178), <https://doi.org/10.1111/andr.12178>.

49. Attina TM, Hauser R, Sathyarayana S, Hunt PA, Bourguignon JP, Myers JP, et al. 2016. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes Endocrinol.* 4(12):996–1003, PMID: [27765541](https://doi.org/10.1016/S2213-8587(16)30275-3), [https://doi.org/10.1016/S2213-8587\(16\)30275-3](https://doi.org/10.1016/S2213-8587(16)30275-3).

50. Davenport C. 2023. You've never heard of him, but he's remaking the pollution fight. *New York Times*. 28 May 2023. https://www.nytimes.com/2023/05/28/climate/ricky-revesz-oira-regulation-bidenhtml?campaign_id=2&emc=edit_th_20230529&instance_id=93715&nl=todayshead [accessed 29 May 2023].

51. Sachs NM. 2011. Rescuing the strong precautionary principle from its critics. *University of Illinois Law Review* 2011:1285–1338, <https://doi.org/10.31228/osf.io/4xgv8>.

52. Schug TT, Heindel JJ, Camacho L, Delclos KB, Howard P, Johnson AF, et al. 2013. A new approach to synergize academic and guideline-compliant research: the CLARITY-BPA research program. *Reprod. Toxicol.* 40:35–40, PMID: [23747832](https://doi.org/10.1016/j.reprotox.2013.05.010), <https://doi.org/10.1016/j.reprotox.2013.05.010>.

53. Heindel JJ, Newbold RR, Bucher JR, Camacho L, Delclos KB, Lewis SM, et al. 2015. NIEHS/FDA CLARITY-BPA research program update. *Reprod. Toxicol.* 58:33–44, PMID: [26232693](https://doi.org/10.1016/j.reprotox.2015.07.075), <https://doi.org/10.1016/j.reprotox.2015.07.075>.

54. Vandenberg LN, Hunt PA, Gore AC. 2019. Endocrine disruptors and the future of toxicology testing - lessons from CLARITY-BPA. *Nat Rev Endocrinol.* 15(6):366–374, PMID: [30842650](https://doi.org/10.1038/s41574-019-0173-y), <https://doi.org/10.1038/s41574-019-0173-y>.

55. Howdeshell KL, Beverly BEJ, Blain RB, Goldstone AE, Hartman PA, Lemersis CR, et al. 2023. Evaluating endocrine disrupting chemicals: a perspective on the novel assessments in CLARITY-BPA. *Birth Defects Res.* 115(15):1345–1397, PMID: [37646438](https://doi.org/10.1002/bdr2.2238), <https://doi.org/10.1002/bdr2.2238>.

56. Chen D, Kannan K, Tan H, Zheng Z, Feng YL, Wu Y, et al. 2016. Bisphenol analogues other than BPA: environmental occurrence, human exposure, and toxicity—a review. *Environ. Sci. Technol.* 50(11):5438–5453, PMID: [27143250](https://doi.org/10.1021/acs.est.5b05387), <https://doi.org/10.1021/acs.est.5b05387>.

57. Ullah A, Pirzada M, Jahan S, Ullah H, Razak S, Rauf N, et al. 2019. Prenatal BPA and its analogs BPB, BPF, and BPS exposure and reproductive axis function in the male offspring of Sprague Dawley rats. *Hum. Exp. Toxicol.* 38(12):1344–1365, PMID: [31514588](https://doi.org/10.1177/0960327119862335), <https://doi.org/10.1177/0960327119862335>.

58. Gaynard V, Viguerie C, Cabaton N, Person E, Zalko D, Grandin F, et al. 2023. Importance of relative binding of bisphenol A and bisphenol S to plasma proteins for predicting their in vivo potencies. *Toxicol. Appl. Pharmacol.* 466:116477, PMID: [36940861](https://doi.org/10.1016/j.taap.2023.116477), <https://doi.org/10.1016/j.taap.2023.116477>.

59. Collins TJ. 2023. Building a safe and sustainable chemical enterprise. *Environmental Health News*. <http://ehn.org/european-union-chemical-regulation-strategy-2659442374.html> [accessed 30 June 2023].

60. Schug TT, Abagyan R, Blumberg B, Collins T, Crews D, DeFur P, et al. 2013. Designing endocrine disruption out of the next generation of chemicals. *Green Chem.* 15(1):181–198, PMID: [25110461](https://doi.org/10.1039/C2GC35055F), <https://doi.org/10.1039/C2GC35055F>.

61. Onundi N, Drake BA, Malecky RT, DeNardo MA, Mills MR, Kundu S, et al. 2017. A multidisciplinary investigation of the technical and environmental performances of TAML/peroxide elimination of bisphenol a compounds from water. *Green Chem.* 19(18):4234–4262, <https://doi.org/10.1039/C7GC01415E>.

62. Lin J, Deng L, Sun M, Wang Y, Lee S, Choi K, et al. 2021. An in vitro investigation of endocrine disrupting potentials of ten bisphenol analogues. *Steroids* 169:108826, PMID: [33753083](https://doi.org/10.1016/j.steroids.2021.108826), <https://doi.org/10.1016/j.steroids.2021.108826>.

63. Gely CA, Lacroix MZ, Roques BB, Toutain PL, Gaynard V, Picard-Hagen N. 2023. Comparison of toxicokinetic properties of eleven analogues of bisphenol A in pig after intravenous and oral administrations. *Environ. Int.* 171:107722, PMID: [36584424](https://doi.org/10.1016/j.envint.2022.107722), <https://doi.org/10.1016/j.envint.2022.107722>.

64. Scherer LD, Maynard A, Dolinoy DC, Fagerlin A, Zikmund-Fisher BJ. 2014. The psychology of 'regrettable substitutions': examining consumer judgements of bisphenol a and its alternatives. *Health Risk Soc.* 16(7–8):649–666, PMID: [29386966](https://doi.org/10.1080/13698575.2014.969687), <https://doi.org/10.1080/13698575.2014.969687>.

65. Maertens A, Golden E, Hartung T. 2021. Avoiding regrettable substitutions: green toxicology for sustainable chemistry. *ACS Sustain. Chem. Eng.* 9(23):7749–7758, PMID: [36051558](https://doi.org/10.1021/acssuschemeng.0c09435), <https://doi.org/10.1021/acssuschemeng.0c09435>.

66. La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, et al. 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol.* 16(1):45–57, PMID: [31719706](https://doi.org/10.1038/s41574-019-0273-8), <https://doi.org/10.1038/s41574-019-0273-8>.

67. Tewar S, Auinger P, Braun JM, Lanphear B, Yolton K, Epstein JN, et al. 2016. Association of bisphenol A exposure and attention-deficit/hyperactivity disorder in a national sample of U.S. children. *Environ. Res.* 150:112–118, PMID: [27281688](https://doi.org/10.1016/j.envres.2016.05.040), <https://doi.org/10.1016/j.envres.2016.05.040>.

68. Hansen JB, Bilenberg N, Timmermann CAG, Jensen RC, Frederiksen H, Andersson AM, et al. 2021. Prenatal exposure to bisphenol A and autistic- and ADHD-related symptoms in children aged 2 and 5 years from the Odense child cohort. *Environ. Health.* 20(1):24, PMID: [33712018](https://doi.org/10.1186/s12940-021-00709-y), <https://doi.org/10.1186/s12940-021-00709-y>.

69. Rosenfeld CS. 2017. Neuroendocrine disruption in animal models due to exposure to bisphenol A analogues. *Front. Neuroendocrinol.* 47:123–133, PMID: [28081100](https://doi.org/10.1016/j.yfrne.2017.08.001), <https://doi.org/10.1016/j.yfrne.2017.08.001>.

70. Patisaul HB. 2020. Achieving CLARITY on bisphenol A, brain and behaviour. *J. Neuroendocrinol.* 32(1):e12730, PMID: [31063678](https://doi.org/10.1111/jne.12730), <https://doi.org/10.1111/jne.12730>.

71. Elsworth JD, Jentsch JD, Groman SM, Roth RH, Redmond ED Jr, Leranth C. 2015. Low circulating levels of bisphenol-A induce cognitive deficits and loss of asymmetric spine synapses in dorsolateral prefrontal cortex and hippocampus of adult male monkeys. *J. Comp. Neurol.* 523(8):1248–1257, PMID: [25557059](https://doi.org/10.1002/cne.23735), <https://doi.org/10.1002/cne.23735>.

72. Heindel JJ, Howard S, Agay-Shay K, Arreola JP, Audouze K, Babin PJ, et al. 2022. Obesity II: establishing causal links between chemical exposures and obesity. *Biochem. Pharmacol.* 199:115015, PMID: [35395240](https://doi.org/10.1016/j.bcp.2022.115015), <https://doi.org/10.1016/j.bcp.2022.115015>.

73. Martinez-Pinna J, Sempere-Navarro R, Medina-Gali RM, Fuentes E, Quesada I, Sargis RM, et al. 2023. Endocrine disruptors in plastics alter beta-cell physiology and increase the risk of diabetes mellitus. *Am. J. Physiol. Endocrinol. Metab.* 324(6):E488–E505, PMID: [37134142](https://doi.org/10.1152/ajpendo.00068.2023), <https://doi.org/10.1152/ajpendo.00068.2023>.

74. Melzer D, Osborne NJ, Henley WE, Cipelli R, Young A, Money C, et al. 2012. Urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. *Circulation.* 125(12):1482–1490, PMID: [22354940](https://doi.org/10.1161/CIRCULATIONAHA.111.069153), <https://doi.org/10.1161/CIRCULATIONAHA.111.069153>.

75. Skakkebaek NE, Lindahl-Jacobsen R, Levine H, Andersson A-M, Jørgensen N, Main KM, et al. 2022. Environmental factors in declining human fertility. *Nat. Rev. Endocrinol.* 18(3):139–157, PMID: [34912078](https://doi.org/10.1038/s41574-021-00598-8), <https://doi.org/10.1038/s41574-021-00598-8>.

76. Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Jolles M, et al. 2023. Temporal trends in sperm count: a systematic review

and meta-regression analysis of samples collected globally in the 20th and 21st centuries. *Hum Reprod Update* 29(2):157–176, PMID: 36377604, <https://doi.org/10.1093/humupd/dmac035>.

77. Fernandez MF, Arreola JP, Jimenez-Diaz I, Saenz JM, Molina-Molina JM, Ballesteros O, et al. 2016. Bisphenol A and other phenols in human placenta from children with cryptorchidism or hypospadias. *Reprod Toxicol* 59:89–95, PMID: 26602963, <https://doi.org/10.1016/j.reprotox.2015.11.002>.
78. Vrooman LA, Oatley JM, Griswold JE, Hassold TJ, Hunt PA. 2015. Estrogenic exposure alters the spermatogonial stem cells in the developing testis, permanently reducing crossover levels in the adult. *PLoS Genet* 11(1):e1004949, PMID: 25615633, <https://doi.org/10.1371/journal.pgen.1004949>.
79. Kortenkamp A, Martin O, Ermel S, Baig A, Scholze M. 2022. Bisphenol A and declining semen quality: a systematic review to support the derivation of a reference dose for mixture risk assessments. *Int J Hyg Environ Health* 241:113942, PMID: 35168014, <https://doi.org/10.1016/j.ijeh.2022.113942>.
80. Fisher BG, Thankamony A, Mendiola J, Petry CJ, Frederiksen H, Andersson AM, et al. 2020. Maternal serum concentrations of bisphenol A and propyl paraben in early pregnancy are associated with male infant genital development. *Hum Reprod* 35(4):913–928, PMID: 32325494, <https://doi.org/10.1093/humrep/deaa045>.
81. Lärkeholm Müller M, Busch AS, Ljubicic ML, Upniers EN, Fischer MB, Hagen CP, et al. 2023. Urinary concentration of phthalates and bisphenol A during minipuberty is associated with reproductive hormone concentrations in infant boys. *Int J Hyg Environ Health* 250:114166, PMID: 37058994, <https://doi.org/10.1016/j.ijeh.2023.114166>.
82. Li D, Zhou Z, Qing D, He Y, Wu T, Miao M, et al. 2010. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. *Hum Reprod* 25(2):519–527, PMID: 19906654, <https://doi.org/10.1093/humrep/dep381>.
83. Li DK, Zhou Z, Miao M, He Y, Qing D, Wu T, et al. 2010. Relationship between urine bisphenol-A level and declining male sexual function. *J Androl* 31(5):500–506, PMID: 20467048, <https://doi.org/10.2164/jandrol.110.010413>.
84. Akingbemi BT, Sottas CM, Koulouva AI, Klinefelter GR, Hardy MP. 2004. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. *Endocrinology* 145(2):592–603, PMID: 14605012, <https://doi.org/10.1210/en.2003-1174>.
85. Nicholson TM, Nguyen JL, Leverson GE, Taylor JA, Vom Saal FS, Wood RW, et al. 2018. Endocrine disruptor bisphenol A is implicated in urinary voiding dysfunction in male mice. *Am J Physiol Renal Physiol* 315(5):F1208–F1216, PMID: 30019933, <https://doi.org/10.1152/ajprenal.00582.2017>.
86. Seachrist DD, Bonk KW, Ho SM, Prins GS, Soto AM, Keri RA. 2016. A review of the carcinogenic potential of bisphenol A. *Reprod Toxicol* 59:167–182, PMID: 26493093, <https://doi.org/10.1016/j.reprotox.2015.09.006>.
87. Prins GS, Hu WY, Xie L, Shi GB, Hu DP, Birch L, et al. 2018. Evaluation of bisphenol A (BPA) exposures on prostate stem cell homeostasis and prostate cancer risk in the NCTR-Sprague-dawley rat: an NIEHS/FDA CLARITY-BPA consortium study. *Environ Health Perspect* 126(11):117001, PMID: 30387366, <https://doi.org/10.1289/EHP3953>.
88. Taylor JA, Jones MB, Besch-Williford CL, Berendzen AF, Ricke WA, Vom Saal FS. 2020. Interactive effects of perinatal BPA or DES and adult testosterone and estradiol exposure on adult urethral obstruction and bladder, kidney, and prostate pathology in male mice. *Int J Mol Sci* 21(11):3902, PMID: 32486162, <https://doi.org/10.3390/ijms21113902>.
89. Susiarjo M, Hassold TJ, Freeman E, Hunt PA. 2007. Bisphenol A exposure in utero disrupts early oogenesis in the mouse. *PLoS Genet* 3(1):e5, PMID: 17222059, <https://doi.org/10.1371/journal.pgen.0030005>.
90. Patel S, Brehm E, Gao L, Rattan S, Ziv-Gal A, Flaws JA. 2017. Bisphenol A exposure, ovarian follicle numbers, and female sex steroid hormone levels: results from a CLARITY-BPA study. *Endocrinology* 158(6):1727–1738, PMID: 28324068, <https://doi.org/10.1210/en.2016-1887>.
91. Chavarro JE, Minguez-Alarcon L, Chiu YH, Gaskins AJ, Souter I, Williams PL, et al. 2016. Soy intake modifies the relation between urinary bisphenol A concentrations and pregnancy outcomes among women undergoing assisted reproduction. *J Clin Endocrinol Metab* 101(3):1082–1090, PMID: 26815879, <https://doi.org/10.1210/jc.2015-3473>.
92. Vandenberg LN, Maffini MV, Schaeberle CM, Ucci AA, Sonnenschein C, Rubin BS, et al. 2008. Perinatal exposure to the xenoestrogen bisphenol-A induces mammary intraductal hyperplasias in adult CD-1 mice. *Reprod Toxicol* 26(3–4):210–219, PMID: 18938238, <https://doi.org/10.1016/j.reprotox.2008.09.015>.
93. Paulose T, Speroni L, Sonnenschein C, Soto AM. 2015. Estrogens in the wrong place at the wrong time: Fetal BPA exposure and mammary cancer. *Reprod Toxicol* 54:58–65, PMID: 25277313, <https://doi.org/10.1016/j.reprotox.2014.09.012>.
94. Dairkee SH, Seok J, Champion S, Sayeed A, Mindrinos M, Xiao W, et al. 2008. Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. *Cancer Res* 68(7):2076–2080, PMID: 18381411, <https://doi.org/10.1158/0008-5472.CAN-07-6526>.
95. Goodson WH III, Luciani MG, Sayeed SA, Jaffee IM, Moore DH II, Dairkee SH. 2011. Activation of the mTOR pathway by low levels of xenoestrogens in breast epithelial cells from high-risk women. *Carcinogenesis* 32(11):1724–1733, PMID: 21890461, <https://doi.org/10.1093/carcin/bgr196>.
96. Vigezzi L, Bosquiazzo VL, Kass L, Ramos JG, Munoz-de-Toro M, Luque EH. 2015. Developmental exposure to bisphenol A alters the differentiation and functional response of the adult rat uterus to estrogen treatment. *Reprod Toxicol* 52:83–92, PMID: 25666754, <https://doi.org/10.1016/j.reprotox.2015.01.011>.
97. Neff AM, Blanco SC, Flaws JA, Bagchi IC, Bagchi MK. 2019. Chronic exposure of mice to bisphenol-A alters uterine fibroblast growth factor signaling and leads to aberrant epithelial proliferation. *Endocrinology* 160(5):1234–1246, PMID: 30892605, <https://doi.org/10.1210/en.2018-00872>.
98. Welshons WV, Nagel SC, Vom Saal FS. 2006. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. *Endocrinol* 147(Suppl 6):S56–S69, PMID: 16690810, <https://doi.org/10.1210/en.2005-1159>.
99. Mie A, Ruden C. 2023. Non-disclosure of developmental neurotoxicity studies obstructs the safety assessment of pesticides in the European union. *Environ Health* 22(1):44, PMID: 37259092, <https://doi.org/10.1186/s12940-023-00994-9>.
100. Hill AB. 1965. The environment and disease: association or causation? *Proc R Soc Med* 58(5):295–300, <https://doi.org/10.1177/003591576505800503>.
101. RIO. 1992. *Rio Declaration on Environment and Development*. https://culturalrights.net/descargas/drets_culturals411.pdf [accessed 3 December 2023].
102. Myers JP, Vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, et al. 2009. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. *Environ Health Perspect* 117(3):309–315, PMID: 19337501, <https://doi.org/10.1289/ehp.0800173>.
103. Vandenberg LN, Prins GS, Patisaul HB, Zoeller RT. 2020. The use and misuse of historical controls in regulatory toxicology: lessons from the CLARITY-BPA study. *Endocrinology* 161(5):bqz014, PMID: 31690949, <https://doi.org/10.1210/endocr/bqz014>.
104. Vom Saal FS, Welshons WV. 2006. Large effects from small exposures. II. The importance of positive controls in low-dose research on bisphenol A. *Environ Res* 100(1):50–76, PMID: 16256977, <https://doi.org/10.1016/j.envres.2005.09.001>.
105. Montevil M, Acevedo N, Schaeberle CM, Bharadwaj M, Fenton SE, Soto AM. 2020. A combined morphometric and statistical approach to assess nonmonotonicity in the developing mammary gland of rats in the CLARITY-BPA study. *Environ Health Perspect* 128(5):57001, PMID: 32438830, <https://doi.org/10.1289/EHP6301>.
106. Vom Saal FS, Hughes C. 2005. An extensive new literature concerning low-dose effects of bisphenol a shows the need for a new risk assessment. *Environ Health Perspect* 113(8):926–933, PMID: 16079060, <https://doi.org/10.1289/ehp.7713>.
107. Spearow JL. 2004. *Reviewer's Appendix to the EPA White Paper on Species/Stock/Strain in Endocrine Disruptor Assays*. https://www.researchgate.net/publication/333639096_Reviewer's_Appendix_to_the_White_Paper_on_SpeciesStockStrain_in_Endocrine_Disruptor_Assays_Prepared_for_US_EPA_Endocrine_Disruptor_Screening_Program_Washington_DC_Work_Assignment_No_4-5_Task_No_16 [accessed 18 July 2023].
108. Delclos KB, Camacho L, Lewis SM, Vanlandingham MM, Latendresse JR, Olson GR, et al. 2014. Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90. *Toxicol Sci* 139(1):174–197, PMID: 24496637, <https://doi.org/10.1093/toxsci/kfu022>.
109. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenberghe JG, Vom Saal FS. 1999. Exposure to bisphenol A advances puberty. *Nature* 401(6755):763–764, PMID: 10548101, <https://doi.org/10.1038/44517>.
110. Durando M, Kass L, Piva J, Sonnenschein C, Soto AM, Luque EH, et al. 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. *Environ Health Perspect* 115(1):80–86, PMID: 17366824, <https://doi.org/10.1289/ehp.9282>.
111. Camacho L, Lewis SM, Vanlandingham MM, Olson GR, Davis KJ, Patton RE, et al. 2019. A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results. *Food Chem Toxicol* 132:110728, PMID: 31365888, <https://doi.org/10.1016/j.fct.2019.110728>.
112. CLARITY-BPA Research Program. 2021. *NTP Research Report on the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA): A Compendium of Published Findings*. *NTP Research Report 18*. <https://pubmed.ncbi.nlm.nih.gov/34910417/> [accessed 18 November 2023].
113. FDA-CFSAN (Center for Food Safety and Applied Nutrition). 2019. *Listing of Color Additives Exempt From Certification; Soy Leghemoglobin*. <https://www.federalregister.gov/documents/2019/12/19/2019-27173/listing-of-color-additives-exempt-from-certification-soy-leghemoglobin> [accessed 6 June 2023].
114. Muncke J, Mahinka SP. 2009. 21st Century Toxicology and its Implications for FDA Regulation of Food-Contact Substances. *Food and Drug Law Institute*. https://www.morganlewis.com/~media/files/publication/outsid%20publication/article/fdli_21stcenturytoxicology_nov-dec2009.ashx [accessed 6 June 2023].

115. Hong X, Zhou Y, Zhu Z, Li Y, Li Z, Zhang Y, et al. 2023. Environmental endocrine disruptor bisphenol A induces metabolic derailment and obesity via upregulating IL-17A in adipocytes. *Environ Int* 172:107759, PMID: 36696794, <https://doi.org/10.1016/j.envint.2023.107759>.

116. Yanagisawa R, Koike E, Win-Shwe TT, Takano H. 2019. Oral exposure to low dose bisphenol A aggravates allergic airway inflammation in mice. *Toxicol Rep* 6:1253–1262, PMID: 31788436, <https://doi.org/10.1016/j.toxrep.2019.11.012>.

117. Gao L, Dong Y, Lin R, Meng Y, Wu F, Jia L. 2020. The imbalance of treg/Th17 cells induced by perinatal bisphenol A exposure is associated with activation of the PI3K/akt/mTOR signaling pathway in male offspring mice. *Food Chem Toxicol* 137:111177, PMID: 32028014, <https://doi.org/10.1016/j.fct.2020.111177>.

118. Luo S, Li Y, Li Y, Zhu Q, Jiang J, Wu C, et al. 2016. Gestational and lactational exposure to low-dose bisphenol A increases Th17 cells in mice offspring. *Environ Toxicol Pharmacol* 47:149–158, PMID: 27693988, <https://doi.org/10.1016/j.etap.2016.09.017>.

119. EFSA. 2023. *Bisphenol A in Food is a Health Risk*. <https://www.efsa.europa.eu/en/news/bisphenol-food-health-risk> [accessed 10 July 2023].

120. Li J, Bach A, Crawford RB, Phadnis-Moghe AS, Chen W, D'Ingiilo S, et al. 2018. CLARITY-BPA: effects of chronic bisphenol A exposure on the immune system: part 2 - characterization of lymphoproliferative and immune effector responses by splenic leukocytes. *Toxicology* 396–397:54–67, PMID: 29427786, <https://doi.org/10.1016/j.tox.2018.02.004>.

121. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. 2015. EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev* 36(6):E1–E150, PMID: 26544531, <https://doi.org/10.1210/er.2015-1010>.

122. Kortenkamp A, Martin O, Iacovidou E, Scholze M. 2024. Drivers of divergent assessments of bisphenol-A hazards to semen quality by various European agencies, regulators and scientists. *Int J Hyg Environ Health* 255:114293, PMID: 37976583, <https://doi.org/10.1016/j.ijeh.2023.114293>.

123. Vom Saal FS, Cooke PS, Buchanan DL, Palanza P, Thayer KA, Nagel SC, et al. 1998. A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior. *Toxicol Ind Health* 14(1–2):239–260, PMID: 9460178, <https://doi.org/10.1177/074823379801400115>.

124. Kortenkamp A. 2022. Invited perspective: how relevant are mode-of-action considerations for the assessment and prediction of mixture effects? *Environ Health Perspect* 130(4):41302, PMID: 35394810, <https://doi.org/10.1289/EHP11051>.

125. Endocrine Society. 2019. *Where We Stand on EDCs*. <https://www.endocrine.org/topics/edc/where-we-stand> [accessed 10 July 2023].

126. Koman PD, Singla V, Lam J, Woodruff TJ. 2019. Population susceptibility: a vital consideration in chemical risk evaluation under the Lautenberg toxic substances control act. *PLoS Biol* 17(8):e3000372, PMID: 31465433, <https://doi.org/10.1371/journal.pbio.3000372>.

127. Goldzieher JW, Stanczyk FZ. 2008. Oral contraceptives and individual variability of circulating levels of ethinyl estradiol and progestins. *Contraception* 78(1):4–9, PMID: 18555811, <https://doi.org/10.1016/j.contraception.2008.02.020>.

128. Axelrad D. 2023. *OMB's Draft Circular A-4 Falls Short on Equity*. San Francisco, CA: PRHE (Program on Reproductive Health and the Environment). <https://prheucsf.blog/2023/06/20/omb-s-draft-circular-a-4-falls-short-on-equity/> [accessed 16 November 2023].

129. Chemnick J. 2023. White House overhaul paves way for stricter regulations. *Politico*. 10 November 2023. <https://subscriber.politicopro.com/article/eenews/2023/11/10/white-house-makes-regulations-look-less-expensive-in-major-overhaul-00126477> [accessed 16 November 2023].

130. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. 2011. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. *Toxicol Lett* 207(3):298–305, PMID: 21983029, <https://doi.org/10.1016/j.toxlet.2011.09.020>.

131. Taylor JA, Vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, et al. 2011. Similarity of bisphenol a pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. *Environ Health Perspect* 119(4):422–430, PMID: 20855240, <https://doi.org/10.1289/ehp.1002514>.

132. OECD (Organisation for Economics Co-operation and Development). 2018. *Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals, Series on Testing and Assessment No. 296*. <https://www.oecd.org/chemicalsafety/risk-assessment/considerations-for-assessing-the-risks-of-combined-exposure-to-multiple-chemicals.pdf> [accessed 18 November 2023].

133. EFSA. 2015. Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA J* 13(1):3978, <https://doi.org/10.2903/j.efsa.2015.3978>.

134. Gies A, Heinzel B, Dieter HH, Heindel J. 2009. Bisphenol A workshop of the German federal environment agency - March 30–31, 2009 work group report: public health issues of bisphenol A. *Int J Hyg Environ Health* 212(6):693–696, PMID: 19879190, <https://doi.org/10.1016/j.ijheh.2009.09.006>.

135. FDA. 2010. *FDA Response to the Scientific Peer Review of FDA's Draft Assessment of Bisphenol A for Use in Food Contact Applications, June 15, 2010*. <https://www.fda.gov/media/85554/download> [accessed 21 March 2024].

136. Ye X, Wong LY, Bishop AM, Calafat AM. 2011. Variability of urinary concentrations of bisphenol a in spot samples, first morning voids, and 24-hour collections. *Environ Health Perspect* 119(7):983–988, PMID: 21406337, <https://doi.org/10.1289/ehp.1002701>.

137. Vandenberg LN, Welshons WV, Vom Saal FS, Toutain PL, Myers JP. 2014. Should oral gavage be abandoned in toxicity testing of endocrine disruptors? *Environ Health* 13(1):46, PMID: 24961440, <https://doi.org/10.1186/1476-069X-13-46>.

138. Zalko D, Soto AM, Dolo L, Dorio C, Rathahao E, Debrauwer L, et al. 2003. Biotransformations of bisphenol A in a mammalian model: answers and new questions raised by low-dose metabolic fate studies in pregnant CD1 mice. *Environ Health Perspect* 111(3):309–319, PMID: 12611660, <https://doi.org/10.1289/ehp.5603>.

139. Jaeg JP, Perdu E, Dolo L, Debrauwer L, Cravedi JP, Zalko D. 2004. Characterization of new bisphenol metabolites produced by CD1 mice liver microsomes and S9 fractions. *J Agric Food Chem* 52(15):4935–4942, PMID: 15264938, <https://doi.org/10.1021/jf049762u>.

140. Nakamura S, Tezuka Y, Ushiyama A, Kawashima C, Kitagawara Y, Takahashi K, et al. 2011. Ipso substitution of bisphenol A catalyzed by microsomal cytochrome P450 and enhancement of estrogenic activity. *Toxicol Lett* 203(1):92–95, PMID: 21402134, <https://doi.org/10.1016/j.toxlet.2011.03.010>.

141. Baker ME, Chandsawangbhuwana C. 2012. 3D models of MBP, a biologically active metabolite of bisphenol A, in human estrogen receptor alpha and estrogen receptor beta. *PLoS One* 7(10):e46078, PMID: 23056236, <https://doi.org/10.1371/journal.pone.0046078>.

142. Gerona RR, Vom Saal FS, Hunt PA. 2020. BPA: have flawed analytical techniques compromised risk assessments? *Lancet Diabetes Endocrinol* 8(1):11–13, PMID: 31813841, [https://doi.org/10.1016/S2213-8587\(19\)30381-X](https://doi.org/10.1016/S2213-8587(19)30381-X).

143. FDA. 2008. *FDA Science Board Subcommittee Report on Bisphenol A*. <https://graphics8.nytimes.com/packages/pdf/health/29bpa.pdf> [accessed 12 July 2023].

144. FDA. 2018. *Statement from Stephen Ostroff M.D., Deputy Commissioner for Foods and Veterinary Medicine, on National Toxicology Program Draft Report on Bisphenol A*. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm598100.htm> [accessed 12 July 2023].

145. Reagan-Udall. 2022. *Reagan-Udall Foundation Evaluation of FDA's Human Foods Program: Independent Expert Panel submitted report to FDA Commissioner*. <https://reaganudall.org/operational-evaluation-fdas-human-foods-programs> [accessed 20 November 2023].

146. Calif R. 2023. *FDA Proposes Redesign of Human Foods Program to Enhance Coordinated Prevention and Response Activities*. Silver Spring, MD: Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-proposes-redesign-human-foods-program-enhance-coordinated-prevention-and-response-activities> [accessed 22 November 2023].

147. Jones J. 2023. *FDA Deputy Commissioner for Human Foods Commits to Fulfilling Vision of Proposed Program. Statement From: James Jones, Deputy Commissioner for Human Foods*. Silver Spring, MD: Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-deputy-commissioner-human-foods-commits-fulfilling-vision-proposed-program> [accessed 4 December 2023].

148. Hoda MR, Kramer MW, Merserburger AS, Cronauer MV. 2017. Androgen deprivation therapy with leuprolide acetate for treatment of advanced prostate cancer. *Expert Opin Pharmacother* 18(1):105–113, PMID: 27826989, <https://doi.org/10.1080/14656566.2016.1258058>.

149. Vom Saal FS. 2019. Flaws in design, execution and interpretation limit CLARITY-BPA's value for risk assessments of bisphenol A. *Basic Clin Pharmacol Toxicol* 125(Suppl 3):32–43, PMID: 30589220, <https://doi.org/10.1111/bcpt.13195>.

150. Colborn T, Vom Saal FS, Soto AM. 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ Health Perspect* 101(5):378–384, PMID: 8080506, <https://doi.org/10.1289/ehp.93101378>.

151. Vom Saal FS, Sheehan DM. 1998. Challenging risk assessment. *Forum Appl Res Public Pol* 13:11–18.

152. Borrell B. 2010. Toxicology: the big test for bisphenol A. *Nature* 464(7292):1122–1124, PMID: 20414285, <https://doi.org/10.1038/4641122a>.

153. Skinner MK, Manikkam M, Guerrero-Bosagna C. 2010. Epigenetic transgenerational actions of environmental factors in disease etiology. *Trends Endocrinol Metab* 21(4):214–222, PMID: 20074974, <https://doi.org/10.1016/j.tem.2009.12.007>.

154. Thayil AJ, Wang X, Bhandari P, Vom Saal FS, Tillitt DE, Bhandari RK. 2020. Bisphenol A and 17alpha-ethynodiol-induced transgenerational gene expression differences in the brain-pituitary-testis axis of medaka, *Oryzias latipesdagger*. *Biol Reprod* 103(6):1324–1335, PMID: 32940650, <https://doi.org/10.1093/biolre/ioaa169>.

155. Heindel JJ, Skalla LA, Joubert BR, Dilworth CH, Gray KA. 2016. Review of developmental origins of health and disease publications in environmental epidemiology. *Reprod Toxicol* 68:34–48, PMID: 27871864, <https://doi.org/10.1016/j.reprotox.2016.11.011>.

156. SCOGS (Select Committee on GRAS Substances). 1982. *Insights on Food Safety Evaluation*. Life Sciences Research Office, Federation of American Societies for Experimental Biology. Food and Drug Administration. Bureau of Foods. <https://search.worldcat.org/title/9287474> [accessed 3 March 2024].

157. Senti FR. 1983. Insights on food safety evaluation: a synopsis. *Regul Toxicol Pharmacol* 3(2):133–138, PMID: 6612009, [https://doi.org/10.1016/0273-2300\(83\)90037-5](https://doi.org/10.1016/0273-2300(83)90037-5).

158. Munro IC, Renwick AG, Danielewska-Nikiel B. 2008. The threshold of toxicological concern (TTC) in risk assessment. *Toxicol Lett* 180(2):151–156, PMID: 18573621, <https://doi.org/10.1016/j.toxlet.2008.05.006>.

159. Maffini MV, Alger HM, Olson ED, Neltner TG. 2013. Looking back to look forward: a review of FDA's food additives safety assessment and recommendations for modernizing its program. *Compr Rev Food Sci Food Saf* 12(4):439–453, PMID: 33412683, <https://doi.org/10.1111/1541-4337.12020>.

160. Zsarnovszky A, Le HH, Wang HS, Belcher SM. 2005. Ontogeny of rapid estrogen-mediated extracellular signal-regulated kinase signaling in the rat cerebellar cortex: potent nongenomic agonist and endocrine disrupting activity of the xenoestrogen bisphenol A. *Endocrinology* 146(12):5388–5396, PMID: 16123166, <https://doi.org/10.1210/en.2005-0565>.

161. Jeng YJ, Watson CS. 2011. Combinations of physiologic estrogens with xenoestrogens alter ERK phosphorylation profiles in rat pituitary cells. *Environ Health Perspect* 119(1):104–112, PMID: 20870566, <https://doi.org/10.1289/ehp.1002512>.

162. Cinciristov S, Ellisdon AM, Suderman R, Pon CK, Evans BA, Kleifeld O, et al. 2018. Preassembled GPCR signaling complexes mediate distinct cellular responses to ultralow ligand concentrations. *Sci Signal* 11(551):eaan1188, PMID: 30301787, <https://doi.org/10.1126/scisignal.aan1188>.

163. Endocrine Society. 2023. Endocrine society experts applaud proposed EU limits on BPA in food. *Endocrine News*. April 2023. <https://www.endocrine.org/news-and-advocacy/news-room/2023/endocrine-society-experts-applaud-proposed-eu-limits-on-bpa-in-food#:~:text=The%20Endocrine%20Society%20praised%20the,through%20plastics%20and%20other%20packaging> [accessed 21 March 2024].

164. REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals). 2023. *Restriction on Bisphenol A and Related Bisphenols of Similar Concern for the Environment*. https://www.reach-clp-biozid-helpdesk.de/EN/Home/German_proposal_restriction/BPA/BPA.html [accessed 15 November 2023].

165. Xue J, Wan Y, Kannan K. 2016. Occurrence of bisphenols, bisphenol A diglycidyl ethers (BADGEs), and novolac glycidyl ethers (NOGEs) in indoor air from Albany, New York, USA, and its implications for inhalation exposure. *Chemosphere* 151:1–8, PMID: 26923236, <https://doi.org/10.1016/j.chemosphere.2016.02.038>.

166. Demierre AL, Reinhard H, Zeltner S, Frey S. 2024. Evaluating the efficiency of the 2020 ban of BPA and BPS in thermal papers in Switzerland. *Regul Toxicol Pharmacol* 146:105526, PMID: 37995898, <https://doi.org/10.1016/j.yrtph.2023.105526>.

167. Vandenberg LN, Gerona RR, Kannan K, Taylor JA, van Breemen RB, Dickenson CA, et al. 2014. A round robin approach to the analysis of bisphenol A (BPA) in human blood samples. *Environ Health* 13(1):25, PMID: 24690217, <https://doi.org/10.1186/1476-069X-13-25>.

168. vom Saal FS, Welshons WV. 2014. Evidence that bisphenol A (BPA) can be accurately measured without contamination in human serum and urine, and that BPA causes numerous hazards from multiple routes of exposure. *Mol Cell Endocrinol* 398(1–2):101–113, PMID: 25304273, <https://doi.org/10.1016/j.mce.2014.09.028>.

169. Hines CJ, Jackson MV, Christianson AL, Clark JC, Arnold JE, Pretty JR, et al. 2017. Air, hand wipe, and surface wipe sampling for bisphenol A (BPA) among workers in industries that manufacture and use BPA in the United States. *J Occup Environ Hyg* 14(11):882–897, PMID: 28650732, <https://doi.org/10.1080/15459624.2017.1339164>.

170. Hines CJ, Jackson MV, Deddens JA, Clark JC, Ye X, Christianson AL, et al. 2017. Urinary bisphenol A (BPA) concentrations among workers in industries that manufacture and use BPA in the USA. *Ann Work Expo Health* 61(2):164–182, PMID: 28395354, <https://doi.org/10.1093/annweh/wwx021>.

171. Nettner T, Maffini MV. 2020. *FDA's Failure on Food Chemical Safety Leaves Diseases*. New York, NY: Environmental Defense Fund. <https://uscode.house.gov/view.xhtml?hl=false&edition=prelim&path=&req=granuleid%3AUSC-prelim-title21-section348> [accessed 3 March 2024].

172. Matouskova K, Neltner TG, Maffini MV. 2023. Out of balance: conflicts of interest persist in food chemicals determined to be generally recognized as safe. *Environ Health* 22(1):59, PMID: 37670318, <https://doi.org/10.1186/s12940-023-01004-8>.

173. Nettner TG, Maffini MV. 2014. *Generally Recognized as Secret: Chemicals Added to Food in the United States*. New York, NY: National Resources Defense Council. <https://www.nrdc.org/sites/default/files/safety-loophole-for-chemicals-in-food-report.pdf> [accessed 25 November 2023].

174. Dodds EC, Lawson W. 1936. Synthetic strogenic agents without the phenanthrene nucleus. *Nature* 137(3476):996, <https://doi.org/10.1038/137996a0>.

175. Masoner JR, Kolpin DW, Furlong ET, Cozzarelli IM, Gray JL, Schwab EA. 2014. Contaminants of emerging concern in fresh leachate from landfills in the conterminous United States. *Environ Sci Process Impacts* 16(10):2335–2354, PMID: 25111596, <https://doi.org/10.1039/c4em00124a>.

176. Environment Canada, Health Canada. 2008. *Screening Assessment for The Challenge Phenol, 4,4'-(1-methylethylidene)bis- (Bisphenol A) Chemical Abstracts Service Registry Number 80-05-7*. Ottawa, Canada: Environment Canada and Health Canada. <https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=3c756383-1> [accessed 4 December 2023].

177. EFSA. 2015. *European Food Safety Authority Scientific Opinion on Bisphenol A*. https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/factsheetbpa150121.pdf [accessed 30 November 2023].

178. Vandenberg LN, Pelch KE. 2022. Systematic review methodologies and endocrine disrupting chemicals: improving evaluations of the plastic monomer bisphenol A. *Endocr Metab Immune Disord Drug Targets* 22(7):748–764, PMID: 34610783, <https://doi.org/10.2174/1871530321666211005163614>.

179. European Council. 2019. *European Green Deal*. Brussels, Belgium: European Council. <https://www.consilium.europa.eu/en/policies/green-deal/> [accessed 26 November 2023].