The Politics of Plastics: The Making and Unmaking of Bisphenol A "Safety"

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Bisphenol A (BPA), a synthetic chemical used in the production of plastics since the 1950s and a known endocrine disruptor, is a ubiquitous component of the material environment and human body. New research on very-low-dose exposure to BPA suggests an association with adverse health effects, including breast and prostate cancer, obesity, neurobehavioral problems, and reproductive abnormalities. These findings challenge the long-standing scientific and legal presumption of BPA's safety. The history of how BPA's safety was defined and defended provides critical insight into the questions now facing lawmakers and regulators: is BPA safe, and if not, what steps must be taken to protect the public's health? Answers to both questions involve reforms in chemical policy, with implications beyond BPA. (*Am J Public Health.* 2009;99:S559–S566. doi:10.2105/AJPH.2008.159228)

"US cites fears on chemical in plastics" was the headline of an April 14, 2008, front-page article in the *Washington Post*.[1] The chemical of concern was BPA, used in the production of plastics found in numerous commercial products, including laptops, cell phones, baby bottles, water main pipes, laboratory and hospital equipment, and food containers.

BPA made national headline news because of high economic, scientific, and political stakes involved in the debate about its safety. With over 6 billion pounds of BPA produced globally every year and continued growth expected in the coming years, the market for BPA is large and extensive.[2] Recent biomonitoring studies indicate that exposure to BPA is widespread,[3,4] and this ubiquity has raised concerns—or, as the April 2008 article noted, "fears"—regarding the health effects of exposure. A growing body of laboratory research on very low doses of BPA—levels that fall below the regulatory safety standard—reports associations with increased rates of breast and prostate cancer, chromosomal abnormalities, brain and behavioral abnormalities, and metabolic disorders.[5] In response to this new research on exposure to BPA and its health effects, state and federal lawmakers in the United States and around the world are faced with the critical question of whether BPA is safe.

In April 2008, the Canadian government took a precautionary approach, classifying BPA as "toxic" under the Canadian Environment Protection Act and is considering a limited ban.[6,7] By contrast, the European Food Safety Authority and the US Food and Drug Administration (FDA) declared BPA safe at estimated levels of human exposure.[8,9] Retailers, however, chose not to wait for a regulatory decision and began pulling plastic water and baby bottles made with BPA from the shelves in 2008. In early 2009, a bill banning BPA in children's food containers was introduced in Congress.[10] The safety and future of BPA remain resolutely uncertain.

There are two issues to be resolved in this current debate about BPA safety. First, what is the best available science for assessing the safety of BPA? And second, if BPA is unsafe, why was it presumed to be safe for the past 50 years and how did this understanding change? To answer these questions demands a critical examination of the historical process by which BPA's safety was defined and the ways this assumption was ultimately challenged by new scientific research.

Plastics and Estrogenicity

Although BPA was first synthesized in 1891, exploration of its commercial possibilities did not occur until the period between the two world wars. While in pursuit of a synthetic estrogen, Edward Charles Dodds, a British medical researcher at the University of London, identified the estrogenic properties of BPA in the mid-1930s.[11] For the next several years, Dodds continued testing chemical compounds in search of what he later referred to as the "mother substance," a powerful estrogenic substance that he identified as diethylstilbestrol (DES).[12]

DES was commercialized in the 1940s for the purported therapeutic treatment of numerous female "problems" related to menstruation, menopause, nausea during pregnancy, and for the prevention of miscarriages.[13] Meat producers injected animals with the synthetic estrogen to increase meat production. For 30 years, DES was prescribed to millions of pregnant women and injected into millions of animals despite persistent concerns about its carcinogenicity.[14] In 1971, the drug was finally banned for use in pregnant women after the first epidemiological studies reported rare vaginal cancers in young women exposed to DES while in their mothers' wombs.[15] After considerable debate and controversy, the FDA finally banned all forms of DES use in meat production in 1979.[14,16]

BPA never found use as a drug; its future was in plastics. Several years after Dodds published his research on synthetic estrogens, chemists in the United States and Switzerland synthesized the first epoxy resins using BPA, and commercial production began in the early 1950s.[17] Epoxy resins quickly found extensive use throughout industrial production as protective coatings on metal equipment, piping, steel drums, and the interior of food cans, as well as adhesives used to lay flooring and seal teeth. As a manager of Shell Chemical Company, one of the first producers of BPA and epoxy resins, noted in the mid-1970s, epoxy resins "now serve virtually every major US industry, either directly or indirectly."[18(p27)]

In 1957, chemists at Bayer and General Electric discovered another use for BPA—when polymerized (linked together in long chains) it forms a hard plastic called polycarbonate. This plastic is strong enough to replace steel and clear enough to replace glass. It found new uses in electronics, safety equipment, automobiles, and food containers. With markets for

both plastics booming over the subsequent two decades, the production of BPA in the United States reached half a billion pounds by the late 1970s.[2]

As BPA found more markets and major US producers (General Electric, Shell Chemical, Dow Chemicals, and Union Carbide in the first 20 years of production) added capacity, the chemical remade the material as well as the molecular environment. The ubiquity of BPA products meant there were more and more potential sources of exposure to this synthetic estrogen. And yet, although BPA's estrogenlike properties (or estrogenicity) were never completely forgotten, its safety was defined by its commercial use in plastics and, accordingly, by its toxic rather than hormonelike properties.

Defining Chemical Safety

How, then, was BPA's safety defined, scientifically and legally? For the past 50 years, BPA's safety, along with that of most chemicals, has been defined according to the scientific presumption that the dose–response relationship is monotonic—that is, with increasing dose the effect increases and vice versa. Thus, at some diminished level of dose, the effect is marginal. Legally, this is called the *de minimis* standard.

This legal interpretation of chemical safety as related to dose was included in the 1958 Federal Food, Drug and Cosmetics Act,[19] which directed the FDA to regulate chemicals in food. Prior to this law, hazards were prohibited from the food supply as dangerous per se, regardless of dose.[20] The 1958 law changed this by requiring that companies obtain FDA approval for the use of chemicals that directly or indirectly contaminated food during its production, processing, packaging, and distribution. This included thousands of chemicals, from preservatives and pesticide residues to chemicals used in packaging.

Because BPA migrates from epoxy resins and polycarbonates used in food packaging and production, the FDA considered the chemical to be an indirect food additive.[21] Early research demonstrating BPA's low general toxicity[22] and rapid metabolism in animals,[23] combined with the low levels at which it contaminates food, provided support for its approved use in food packaging. In other words, at very low or diminished levels, the FDA has long considered BPA in food to be safe. However, the agency established no regulatory standard for the chemical until 1988. (No regulatory standard was ever set for workplace exposure.)

But the 1958 law also included a separate standard for the safety of carcinogenic chemicals, the Delaney Clause, which stated that carcinogens were hazards per se regardless of dose.[24] The scientific principle at the time used to support dual standards for chemical safety—for carcinogens (hazards per se) and noncarcinogens (hazards defined by dose)—was the contention that carcinogens functioned differently than toxic compounds; a carcinogen, for example, could have low toxicity.[25] Although BPA's general toxicity was low, no examination of its carcinogenicity occurred until the late 1970s.

The Regulatory Toxicology of Bisphenol A

By the mid-1970s, the high-volume production of BPA and the large number of workers possibly exposed to the chemical captured the attention of researchers at the National Cancer Institute (NCI) responsible for coordinating the National Carcinogenesis Bioassay Program. In 1977, the NCI initiated the first carcinogenesis study of BPA. The carcinogenesis study followed the standard procedures for assessing cancer risk: it was a 2-year, adult rodent model experiment that exposed animals daily to high doses at and just below the toxic threshold on the assumption that if a carcinogenic effect was present it would more likely be seen at high doses.[26] The assumption that high-dose testing and adult animals could provide sufficient data for interpreting safety for a diverse population was a fundamental presumption of regulatory toxicity testing. Such a study design was not designed to investigate the transplacental effects (exposure effects on the offspring whose mother's had been exposed) of estrogenic compounds or hormonal carcinogenesis, areas of expanding research—particularly regarding DES carcinogenicity—in the 1970s.[27–29]

During the course of the BPA study, from 1977 to 1979, responsibility for the Carcinogenesis Bioassay Program passed from the NCI to the newly established National Toxicology Program (NTP), created to coordinate federal toxicological research. During this transfer, Congress asked the General Accounting Office (GAO) to investigate the quality of the private laboratories conducting research for the Carcinogenesis Bioassay Program. At the time, the quality of research and federal oversight of private laboratories were under considerable scrutiny; in 1976, the federal government conducted an extensive investigation of Industrial Bio-Test, one of the largest private research laboratories conducting chemical safety tests in the United States, and found extensive fraudulent practices.[30,31] Several years later, in 1979, the GAO's investigation found problems with several facilities working under contract for the NCI. The worst conditions were reported at Litton Biotechnics, where the investigators found maintenance problems, poor quality-control measures, and poor pathology practices, all of which, they concluded, could have affected the outcome of any research.[32] Litton Biotechnics was the laboratory hired to conduct the carcinogenesis bioassay of BPA in 1977.[26]

Despite the GAO's findings, neither the NCI nor the NTP required a reassessment of BPA's carcinogenicity, and in 1982, the NTP released the final report on the carcinogenesis study. With only 2 categories of evidence—"convincing evidence" or "no convincing evidence"—used to describe data at the time,[33] the report found "no convincing evidence" of carcinogenicity, with the following conditions added:

> [T]hat "bisphenol A is not carcinogenic" should be qualified to reflect the facts that leukemia in male rats showed a significant positive trend, that leukemia incidence in high-dose male rats was considered not significant only on the basis of the Bonferroni criteria, that leukemia incidence was also elevated in female rats and male mice, and that the significance of interstitial-cell tumors of the testes in rats was dismissed on the basis of historical control data.[26(ix)]

This study provided the basis for the first regulatory safety standard for BPA set by the Environmental Protection Agency (EPA) in 1988 and adopted by the FDA as a reference dose. Considering BPA to be a noncarcinogen, the EPA used the lowest dose from the carcinogenesis study as the "lowest observed adverse effect level" and divided this number by an uncertainty factor of 1000 to determine a reference dose of 50 μg/kg of body weight per day.[34] (The 1000-fold uncertainty factor was the safety margin between the lowest observed

adverse effect level in the carcinogenesis study and permitted daily exposure limits.) This remains the current safety standard. As for its long-overlooked estrogenic properties, the EPA noted that BPA's estrogenicity, more potent than that of o,p'-DDT, could explain evidence of impaired fertility in a small study in 1981[35]; however, the agency concluded that because of BPA's lack of bioaccumulation and short half-life, it did not present a likely threat or hazard.[36]

Bisphenol A as an Endocrine Disruptor

By the late 1980s, production of BPA in the United States soared to close to a billion pounds per year as polycarbonates found new markets in compact discs, digital versatile discs (DVDs), water and baby bottles, and laboratory and hospital equipment. Only a few years after the reference dose was set, the safety of BPA's estrogenicity, which was long presumed to be weak, came under the investigative lens of an expanding interdisciplinary field: the study of the hormonelike effects of synthetic chemicals.

In 1993, endocrinologists at Stanford University determined that BPA was leaching from polycarbonate flasks in their laboratory.[37] The researchers made this discovery while searching for an endogenous estrogen in yeast. What they originally thought was an endogenous estrogen, however, turned out to be BPA when tested with estrogen-responsive breast cancer cells. Their published findings brought BPA's estrogenicity to the attention of a number of researchers interested not only in synthetic estrogens but, more broadly, in what were referred to as endocrine disruptors.[38]

Endocrine disruption, the hypothesis that some chemicals could interfere with the production, processing, and transmission of hormones in the body and disrupt the normal functioning of the endocrine system, was a phrase coined at a meeting in 1991. The meeting, held at the Wingspread Conference Center in Racine, Wisconsin, was organized by Theo Colborn, then with the World Wildlife Fund, and J.P. "Pete" Myers, then director of an environmental grant-making foundation.[39] The outcome of the meeting, which brought together a diverse collection of researchers—wildlife biologists, endocrinologists, reproductive physiologists, and toxicologists—was a scientific consensus statement, "Chemically-Induced Alterations in Sexual Development," or the Wingspread Consensus Statement of 1991, that declared "with certainty" that some chemicals in the environment had the potential to disrupt the endocrine system of humans and wildlife.[40]

Although the term "endocrine disruption" was new at the time, the hypothesis built on decades of wildlife and laboratory research on synthetic and environmental estrogens. Beginning in 1979, researchers interested in the study of synthetic estrogenic compounds found in the environment, or "xenoestrogens," gathered every several years at the "Estrogens in the Environment" meeting, organized by John McLachlan at the National Institute of Environmental Health Sciences.[41] In the early 1980s, McLachlan published the first studies of transplacental effects of DES exposure that reproduced the carcinogenic and reproductive effects reported in epidemiological studies from the 1970s.[42,43]

McLachlan, along with Howard Bern, a comparative endocrinologist at the University of California, Berkeley, who studied in utero and neonatal exposure to DES in humans and animals in the early to mid-1970s, attended the 1991 Wingspread meeting. Many of the participants at that meeting, among them McLachlan, wildlife biologist Louis Guillette, molecular biologists Ana Soto and Carlos Sonnenschein, and biologist Frederick vom Saal, went on to become prominent leaders of the controversial and paradigm-shifting field of environmental endocrine disruption.[41]

Struck by the research presented at the meeting, vom Saal, who for years had studied the effects of in utero exposure to natural hormones on the developing organism, decided to test a number of synthetic estrogens. He chose BPA and octylphenol, also a chemical used in plastics and a synthetic estrogen. Unlike regulatory toxicity tests, this research exposed pregnant mice to levels of BPA determined to be physiologically active as synthetic estrogens. These were not toxic levels, and indeed fell below the safety standard of 50 μg/kg/day. In the first published studies on BPA from his laboratory in 1997, vom Saal's team reported increased prostate weights in the exposed mice and a higher than expected estrogenic response from BPA.[44] Other researchers published two additional papers on the low-dose effects of BPA: a 1997 report on the mammary gland[45] and a 1998 study of the female reproductive system.[46] Collectively, these new low-dose studies challenged the long-held presumption that BPA was a weak estrogen.

Low-Dose Safety of Bisphenol A

This new research on BPA fueled a heated debate about the safety of endocrine disruptors at a time when the EPA was struggling to establish a testing and screening program for such compounds. In 1996, Congress passed the Food Quality Protection Act, which amended the Federal Insecticide, Fungicide and Rodenticide Act,[47] and an amendment to the Safe Drinking Water Act.[48] Both amendments included language directing the EPA to establish a testing and screening program for endocrine disruptors.[41] The challenge faced by the EPA was to reach an agreement among a number of stakeholders, including representatives from industry and from environmental nongovernmental organizations, on a testing program. This meant agreeing on the definition of an endocrine disruptor and adverse health effects—for example, was a change in prostate size an adverse effect? Did binding to the estrogen receptor define a chemical as an endocrine disruptor? Should the agency change the testing protocol to include low doses and exposure during fetal and neonatal development, or were high-dose toxicity tests relevant for evaluating risks of endocrine disruptors? These all proved to be controversial topics, particularly the issue of testing at very low doses.[49]

In 2000, the EPA turned to the NTP and requested that the institute review the research on the effects of low doses of estrogenic compounds, including DES and BPA. The NTP's *Report of the Endocrine Disruptors Low Dose Peer Review*,[50] released in 2001, concluded that there was credible evidence for effects from BPA exposure at or below the safety standard, including vom Saal's studies and a replication of his findings by another laboratory.[51] The NTP report also included credible evidence of no effects reported by two studies[52,53] funded by the chemical industry. Further research on BPA was needed, the report concluded. As for low-dose effects generally, the NTP found

> that the current testing paradigm used for assessments of reproductive and developmental toxicity should be revisited to see if changes are needed regarding dose selection, animal model selection, age when animals are evaluated, and the end points being measured following exposure to endocrine-active agents.[50(vii)]

The call for a new testing paradigm recognized a growing consensus that low doses of endocrine-disrupting chemicals may not follow a monotonic dose–response relationship, an issue discussed in a National Academy of Sciences report, *Hormonally Active Agents in the Environment*,[54] published in 1999. In its discussion of dosing, the committee concluded:

> [I]f an underlying monotonic dose–response function (i.e., a function where response increases as dose increases or at least does not decrease) and a dose below which there is no effect (a threshold dose) are assumed when designing a toxicologic study, there is a risk of failing to understand or properly test a contaminant that does not display a monotonic dose-response function or threshold dose.[54(p82)]

The NTP's recommendation to reconsider the current testing paradigm and its failure to declare BPA safe set off alarm bells for the major industry trade groups. In a letter to the NTP in 2001, Steven Hentges, director of the Polycarbonate Business Unit of the American Plastics Council, wrote that the NTP's BPA panel "did not complete a weight-of-evidence assessment, which would have concluded that low-dose effects from BPA have not been demonstrated."[50(pC-52)] The American Plastics Council subsequently contracted with the Harvard Center for Risk Analysis—an organization that received financial support from the American Chemistry Council, the Society of the Plastics Industry, Dow Chemical Company, the Business Roundtable, Phillip Morris, and General Electric—to conduct a review.[55]

The Harvard Center report on BPA,[56] published in 2004, used a "weight of the evidence" assessment framework developed at a 2001 meeting sponsored by the Annapolis Center for Science and Policy,[57] an organization founded by the former vice president of the National Association of Manufacturers and funded by tobacco giant Phillip Morris[58,59] and ExxonMobil Foundation.[60] The framework assessed the published literature on BPA according to 7 categories used to evaluate the "relevance" and "reliability" of the data. ("Relevance" and "reliability" are also legal standards for assessing evidence in the courtroom.) The Harvard Center's review,[56] as well as an updated review released in 2006 by Gradient Corporation,[61] a private consulting firm specializing in risk science, concluded that two large multigenerational studies provided the most relevant and reliable data. These studies were funded by the American Plastics Council and the Society of the Plastics Industry.[62,63]

Both reports cited the same reasons for determining the relevance and reliability of these two studies: they used large number of animals, included a wide distribution of doses, measured a number of endpoints, and followed "Good Laboratory Practices" (regulatory standards for conducting research adopted in the mid-1970s[64] after the laboratory scandal discussed earlier in "The Regulatory Toxicology of Bisphenol A.") These larger studies, the Harvard Center's review concluded, "cast doubt on suggestions of significant physical or functional impairment."[56(p875)] Further, the report contended that inconsistent effects among different strains of animals, lack of a "single, biologically plausible explanation"[56(p877)] of effects due to differences in responses of BPA compared with estradiol or DES, and differences in the route of administered dose all reduced the reliability and relevance of low-dose studies.[56] These conclusions discounted evidence of significant effects presented in many of the low-dose studies, notably reports of nonlinear dose–response relationships, BPA binding to 2 estrogen receptors (α and β, as well as estrogen receptors on the cell membrane), the insensitivity of certain rodent strains to estrogen (specifically, those used in one of the multigenerational studies), and the critical significance of timing of exposure for determining endpoint.[65]

In 2005, after the release of the Harvard Center review, vom Saal, together with one of the original participants of the Harvard panel, published a response[66] to the Harvard Center's report that roundly criticized the work. They argued that the assessment failed to evaluate the body of research, given the current knowledge in endocrinology, developmental biology, and estrogen receptor research. Most alarmingly, they highlighted an apparent funding effect in the BPA research. Between 1997 and 2005, there were 115 studies on the effects of BPA at or below the safety standard, conducted by dozens of laboratories in the United States, Japan, and Europe. The reported effects of BPA included changes in fetal prostate and mammary gland development, disruption of chromosomal alignment in developing eggs in females, altered immune function, metabolic abnormalities, and changes in the brain and behavior. Of these 115 studies, 90% of those that were government funded reported some effects from exposures at or below the reference dose, whereas none of the 11 studies funded by industry reported any effects.[66]

This expanding field of research, the long list of reported effects at concentrations orders of magnitude below the safety standard, and charges of a funding effect drew the attention of the federal government in 2006.

Politics of Bisphenol A Safety Since 2005

Since the NTP's first assessment of BPA's low dose effects in 2001, five different reviews of the scientific literature have been conducted (Table 1). In 2006, the first of two government-sponsored assessments of the BPA literature was coordinated by the Division of Extramural Research and Training at the National Institute of Environmental Health Sciences. The meeting brought together 38 experts on endocrine disruptors and BPA in Chapel Hill, North Carolina. The meeting's final product, the Chapel Hill Consensus Statement, concluded with certainty, on the basis of several hundred studies, that BPA at concentrations found in the human body is associated with "organizational changes in the prostate, breast, testis, mammary glands, body size, brain structure and chemistry, and behavior of laboratory animals."[67(p134)]

On the heels of the Chapel Hill Statement, a second major government assessment was released. The Center for the Evaluation of Risks to Human Reproduction (CERHR),[68] located within the NTP, sponsored an assessment of the literature, the original draft of which was conducted by the private firm Sciences International. After a number of public meetings, an internal audit[69] to assess possible conflicts of interest by Sciences International, and a review by NTP staff, the CERHR released its final report on BPA in 2008. The report found "some concern for effects on the brain, behavior and prostate gland in fetuses, infants and children at current human exposures to BPA."[68(vii)]

TABLE 1—Reviews of Bisphenol A (BPA) Conducted in the United States

Sponsor	Title	Research Institution	Date Released	Key Findings
National Toxicology Program	*NTP Technical Report on the Carcinogenesis Bioassay of Bisphenol A (CAS No. 80-0507) in F344 Rats and B6c3fl Mice (Feed Study)*	Litton Biotechnics	1982	"[N]o convincing evidence of carcinogenicity"; "that 'bisphenol A is not carcinogenic' should be qualified to reflect the facts that leukemia in male rats showed a significant positive trend, that leukemia in high-dose male rats was considered not significant only on the basis on the Bonferroni criteria, that leukemia incidence was also elevated in female rats and male mice, and that the significance of interstitial-cell tumors of the testes in rats was dismissed on the basis on historical control data."[26(ix)]
National Institute of Environmental Health Sciences, Environmental Protection Agency	*National Toxicology Program's Report of the Endocrine Disruptor's Low Dose Peer Review*	National Toxicology Program	2001	"There is credible evidence that low doses of BPA [bisphenol A] can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA, and the consistency of these negative studies, the Subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general or reproducible finding."[50(vii)]
American Plastics Council	"Weight of the evidence evaluation of low-dose reproductive and developmental effects of bisphenol A"	Harvard Center for Risk Analysis	2004	"The panel found no consistent affirmative evidence of low-dose BPA effects for any endpoint. Inconsistent responses across rodent species and strain made generalizability of low-dose BPA effects questionable. Lack of adverse effects in two multiple generation reproductive and developmental studies casts doubt on suggestions of significant physiological or functional impairment."[56(p875)]
American Plastics Council	"An updated weight of the evidence evaluation of reproductive and developmental effects of low doses of bisphenol A"	Gradient Corporation	2006	"No effect is marked or consistent across species, doses and time points. Some mouse studies report morphological changes in testes and sperm and some non-oral mouse studies report morphological changes in the female reproductive organ. Owing to lack of first pass metabolism, results from non-oral studies are of limited relevance to oral human exposure."[61(p1)]
National Institute of Environmental Health Sciences, National Institutes of Health	"Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure"	National Institute of Environmental Health Sciences and invited BPA experts	2007	"We are confident that . . . human exposure to BPA is variable, and exposure levels cover a broad range [central tendency for unconjugated [active] BPA: 0.3-4.4 ng ml-1 (ppb)] in tissues and fluids in fetuses, children and adults. . . . Sensitivity to endocrine disruptors, including BPA, varies extensively with life stage, indicating that there are specific windows of increased sensitivity at multiple life stages. . . . BPA alters 'epigenetic programming' of genes in experimental animals and wildlife that results in persistent effects that are expressed later in life. . . . Specifically, prenatal and/or neonatal exposure to low doses of BPA results in organizational changes in the prostate, breast, testis, mammary gland, body size, brain structure and chemistry and behavior of laboratory animals."[67(p134)]
National Toxicology Program (NTP)	"NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol A"	Sciences International, Center for the Evaluation of Risks to Human Reproduction (CERHR)	2008	"[S]ome concern for effects on brain, behavior and prostate gland in fetuses, infants and children at current human exposures to bisphenol A."[68(vii)] "[T]he possibility that bisphenol A may alter human development cannot be dismissed."[68(p7)]

Because these conclusions drew on laboratory studies at levels "similar to those experienced by humans," the NTP–CERHR report declared that "the possibility that bisphenol A may alter human development cannot be dismissed."[68(p7)]

By the spring of 2008, BPA was making headlines in major national newspapers.[1,70] Within days of the NTP–CERHR report, the Canadian government announced its decision to declare BPA toxic, and retailers began scrambling to meet growing consumer demands for alternatives to BPA-based polycarbonate baby and water bottles. Environmental health advocates and researchers came before state legislatures in California, Maryland, Massachusetts, and Maine in support of a number of bills restricting BPA in children's products. Members

of Congress sent letters to the commissioner of the FDA demanding greater attention to the safety of BPA.[71,72] For its part, having authority to regulate BPA exposure in the food supply, the FDA could no longer sit on the sidelines of this debate.

In August 2008, the FDA released a draft assessment of the reproductive and developmental toxicity and carcinogenicity of BPA.[9] This latest assessment upheld the current safety standard based on the "no observed adverse effect level" reported in the two multigenerational studies funded by the major trade associations. As made apparent by this latest decision, if only these two multigenerational studies, which followed Good Laboratory Practice standards, are considered relevant and reliable for assessing human risk, the current safety standard is upheld. Indeed, the FDA cited the European decision and the Harvard Center and Gradient Corporation reviews to further substantiate their decision.

But the FDA Science Board Subcommittee on Bisphenol A, an external committee assigned to review the FDA's report, disagreed with the agency's decision to exclude the non–Good Laboratory Practice studies—the hundreds of papers on low-dose effects of BPA in the peer-reviewed literature—from its safety assessment. The subcommittee also concluded that the FDA failed to conduct a rigorous or extensive exposure assessment.[73] The FDA accepted the recommendations of the subcommittee, and in August 2009, they announced plans to conduct extensive toxicity tests of BPA at the National Center for Toxicological Research. In late September 2009, the EPA announced that the agency would conduct its own assessment.

Retailers and producers, however, continue to respond to mounting consumer concerns. In March 2009, six of the major baby bottle manufacturers announced the removal of BPA from their products,[74] and Sunoco, a BPA producer, in an unusual move that places it out of line with the major trade association's defense of the chemical's safety, is now requesting its business consumers to provide written confirmation that no BPA will be used in food containers intended for children younger than 3 years.[75]

Safety of Bisphenol A Contested

Although the retail market may be responding to concerns about BPA safety, the debate over the validity of the current BPA safety standard continues today. At the heart of this conflict is a struggle to determine what scientific research should be used to define chemical safety. The low-dose research on BPA represents part of a larger scientific paradigm shift in environmental health sciences, the result of extensive theoretical development in and replication of low-dose effects of endocrine-disrupting chemicals.[76] Building on research in epigenetics, the fetal basis of disease, endocrinology, and developmental biology, low-dose BPA studies explore new mechanisms of action and the relationship between timing of exposure and measured effect, and they measure organizational and functional changes as indicators of disease risk (e.g., mammary and prostate gland development, insulin regulation.)[5,65] This approach to studying the health effects of chemicals contrasts with the traditional safety tests used to define the BPA standard historically and currently. For example, the multigenerational studies used most recently by the FDA and the European Food Safety Authority to uphold BPA's safety did not measure microscopic precancerous lesions in the prostate and mammary glands, chromosomal abnormalities in female eggs, or neurobehavioral changes of concern to the NTP.

Defining the acceptability, reliability, and relevance of this low-dose BPA research in assessing risk and safety affects not only the future of this chemical; if there is consensus that the scientific paradigm informing safety testing has changed, the implications for reforming risk assessment and safety testing will be profound.

A decade ago, the NTP recommended that the testing paradigm for safety be revisited[50] and the National Academy of Sciences warned about the failure to detect effects of hormonally active agents if only threshold models of dose–response relationships are considered.[54(p82)] More recently, the National Academies of Sciences report on risk assessment, released in 2008, recommended moving away from threshold and nonthreshold dose–response models, noting that "noncancer effects do not necessarily have a threshold."[77(p8)] Over the past 8 years, the extensive body of scientific research on low-dose effects, the expansion of the number of scientists working on BPA and other endocrine disruptors, and recommendations from the FDA's Science Subcommittee, discussed in "Safety of Bisphenol A Contested," indicated that low-dose research is no longer on the margins of accepted scientific thought but is moving into the mainstream of accepted knowledge. And yet, although scientific understanding of BPA expanded dramatically over the past 10 years, its 20-year-old safety standard, based on a threshold-dose model, has remained fixed. ■

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This article was accepted May 23, 2009.

Acknowledgments

Funding for this research was provided by an American Council of Learned Societies and Andrew Mellon Dissertation Fellowship; a National Public Entity Risk Institute Dissertation Fellowship in Hazards, Risks and Disasters; a National Science Foundation Dissertation Research Improvement Grant (0724329); and a Chemical Heritage Foundation's John C. Haas Fellowship.

This research was part of larger dissertation project completed at Columbia University's Center for the History and Ethics of Public Health.

I thank the fellows at the Chemical Heritage Foundation for their comments and critical feedback on this article.

Human Participant Protection

No protocol approval was needed for this study.

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