Bisphenol A and Risk of Metabolic Disorders

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In this issue of *JAMA*, Lang and colleagues[1] report the results of the first major epidemiologic study to examine the health effects associated with the ubiquitous estrogenic chemical bisphenol A (BPA). This compound is the base chemical (monomer) used to make polycarbonate plastic food and beverage containers, the resin lining of cans, and dental sealants; it also is found in "carbonless" paper used for receipts as well as a wide range of other common household products. Based on their analysis of data from the National Health and Nutrition Examination Survey 2003-2004, Lang et al report a significant relationship between urine concentrations of BPA and cardiovascular disease, type 2 diabetes, and liver-enzyme abnormalities in a representative sample of the adult US population. This report, suggesting links between BPA and some of the most significant and economically burdensome human diseases, is based on a cross-sectional study and therefore cannot establish causality; follow-up longitudinal studies should thus be a high priority. Yet many peer-reviewed published studies report on related adverse effects of BPA in experimental animals,[2] and cell culture studies identify the molecular mechanisms mediating these responses.[3] These experimental findings add biological plausibility to the results reported by Lang et al.[1]

Based on this background information, the study by Lang et al,[1] while preliminary with regard to these diseases in humans, should spur US regulatory agencies to follow the recent action taken by Canadian regulatory agencies, which have declared BPA a "toxic chemical" requiring aggressive action to limit human and environmental exposures.[4] Alternatively, Congressional action could follow the precedent set with the recent passage of federal legislation designed to limit exposures to another family of compounds, phthalates, also used in plastic. Like BPA,[5] phthalates are detectable in virtually everyone in the United States.[6] This bill moves US policy closer to the European model, in which industry must provide data on the safety of a chemical before it can be used in products.

See also p 1303.

Subsequent to an unexpected observation in 1997, numerous laboratory animal studies[2] have identified low-dose drug-like effects of BPA at levels less than the dose used by the US Food and Drug Administration (FDA) and the Environmental Protection Agency to estimate the current human acceptable daily intake dose (ADI) deemed safe for humans. These studies have shown adverse effects of BPA on the brain, reproductive system, and—most relevant to the findings of Lang et al[1]—metabolic processes, including alterations in insulin homeostasis and liver enzymes.[2] However, no prior studies examining BPA for effects on cardiovascular function have been conducted in laboratory animals or humans.

Epidemiologists are informed by animal studies that identify potential human health hazards when the animal models and exposure levels are relevant and effects are mediated via response mechanisms present in humans. For example, when adult rats were fed a 0.2-μg/kg per day dose of BPA for 1 month (a dose 250 times lower than the current ADI), BPA significantly decreased the activities of antioxidant enzymes and increased lipid peroxidation, thereby increasing oxidative stress.[7] When adult mice were administered a 10-μg/kg dose of BPA once a day for 2 days (a dose 5 times lower than the ADI), BPA stimulated pancreatic β cells to release insulin. After administration of 100 μg/kg per day of BPA via injection or feeding for 4 days, mice developed insulin resistance and postprandial hyperinsulinemia. Follow-up studies showed that stimulation of mouse β-cell insulin production and secretion by between 0.1 to 1 nM of estradiol or BPA (23-230 pg/mL of BPA) is mediated by activation of the extracellular signal-related protein kinase 1/2 pathway by binding of BPA to estrogen receptor α and that via this nonclassical estrogen-response mechanism, BPA and estradiol have equal potency and efficacy.[8] BPA and estradiol are also equipotent at inhibiting adiponectin release from human adipocytes at 1 nM, further implicating BPA at current human exposure levels in insulin resistance and the metabolic syndrome.[9]

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The effects of BPA on β cells confirm that BPA acts as a potent estrogen via this recently discovered estrogen-response pathway, one also present in human tissues.[3] Importantly, while low doses of BPA and estradiol stimulated this response in β cells, 100-fold higher doses of BPA and estradiol did not stimulate β-cell insulin production in the mouse model[8] or adiponectin release from human adipocytes.[9] The biphasic or nonmonotonic dose-response curves observed in this and many other studies of BPA follow an inverted U shape, which is a common finding for endocrine-active chemicals and drugs, for which high doses inhibit (down-regulate) the low-dose response system while initiating a wide array of other adverse effects via different response mechanisms.[10] Despite decades of published observations by endocrinologists reporting nonmonotonic dose-response curves for hormonally active compounds, the core assumption used by the FDA, the Environmental Protection Agency, and the European Food Safety Authority in estimating ADIs for environmental chemicals is still based on a concept first articulated in the 16th century: "The dose makes the poison"[11]; ie, dose-response curves are assumed to be monotonic for environmental chemicals.

The FDA and the European Food Safety Authority have chosen to ignore warnings from expert panels[12] and other government agencies,[4,13] and have continued to declare BPA "safe."[14,15] The findings by Lang et al[1] that BPA is significantly related to serum markers of liver damage, such as increased γ-glutamyltransferase levels, that were predictive of metabolic disease, cardiovascular disease, and increased mortality in the Framingham longitudinal study,[16] challenge the safety of BPA. One factor that may be contributing to the refusal of regulatory agencies to take action on BPA in the face of overwhelming evidence of harm from animal studies reported in peer-reviewed publications by academic and government scientists is an aggressive disinformation campaign using techniques ("manufactured doubt") first developed by the lead, vinyl, and tobacco industries to challenge the reliability of findings published by independent scientists.[17,18]

Therefore, a marked discordance exists between the currently accepted ADI for BPA of 50 μg/kg per day and numerous adverse effects in animals occurring at levels far below this dosage in recent experiments using the tools of 21st-century biology.[2] A fundamental problem is that the current ADI for BPA is based on experiments conducted in the early 1980s using outdated methods (only very high doses were tested) and insensitive assays. More recent findings from independent scientists were rejected by the FDA, apparently because those investigators did not follow the outdated testing guidelines for environmental chemicals, whereas studies using the outdated, insensitive assays (predominantly involving studies funded by the chemical industry) are given more weight in arriving at the conclusion that BPA is not harmful at current exposure levels.[15]

If adults with increased levels of BPA are at greater risk for metabolic diseases, as is suggested by the findings reported by Lang et al,[1] follow-up longitudinal studies on infants, children, and adolescents, as well as pregnant women and fetuses, would be a high priority for 2 reasons. First, there is consensus from a National Institutes of Health–sponsored expert panel[12] and other government agency reports, including the US National Toxicology Program[13] and Canadian Ministry of Health,[4] that exposure to BPA during development poses the greatest risk for adverse effects; the fetus and infant are believed to be more susceptible to the estrogenic effects of BPA because of small body size and limited capacity to metabolize BPA.[19] Second, along with the exponential increase in the use of BPA in products during the last 30 years, there has been a dramatic increase in the incidence of obesity and type 2 diabetes in children.[20] Very low doses of BPA during fetal/neonatal life in rodents increase the rate of postnatal growth as well as advance puberty, with subsequent disruption of neuroendocrine function.[2] A causal role for BPA in these trends is plausible because BPA can alter the programming of genes during critical periods in cell differentiation during fetal and neonatal development. This process, referred to as "epigenetic programming," can result in the expression of metabolic disease and cancers during later life.[21,22] Examining developmental effects will require biomonitoring of BPA (and other endocrine-disrupting chemicals) in longitudinal studies that relate exposures during critical periods in development to subsequent disease. However, further evidence of harm should not be required for regulatory action to begin the process of reducing exposure to BPA.[4]

The report by Lang et al[1] should stimulate further studies and reevaluation of the basic assumptions in chemical risk assessments that led to FDA assurances that BPA is safe.[15] Their findings also heighten incentives for green chemistry (a new field based on collaboration between biologists and chemists to develop biologically inert chemicals for use in products) to find cost-effective replacements for BPA applications contributing to widespread human exposures.[23] Since worldwide BPA production has now reached approximately 7 billion pounds per year,[17] eliminating direct exposures from its use in food and beverage containers will prove far easier than finding solutions for the massive worldwide contamination by this chemical due its to disposal in landfills and the dumping into aquatic ecosystems of myriad other products containing BPA, which Canada has already declared to be a major environmental contaminant.[4]

The good news is that government action to reduce exposures may offer an effective intervention for improving health and reducing the burden of some of the most consequential human health problems. Thus, even while awaiting confirmation of the findings of Lang et al,[1] decreasing exposure to BPA and developing alternatives to its use are the logical next steps to minimize risk to public health.

Financial Disclosures: Dr vom Saal reported serving on the organizing committee of a National Institutes of Health (NIH)–sponsored conference on bisphenol A (BPA) held in Chapel Hill, North Carolina, in 2006; serving as an expert witness for the defendant in a trial in 2004 regarding the health effects of bisphenol; serving as a consultant for in-preparation litigation regarding BPA; serving as chief executive officer of XenoAnalytical LLC, which uses a variety of analytical techniques to measure estrogenic activity and BPA in tissues and leachates from products; and maintaining a Web site (http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html) that contains a document with references and abstracts for published articles on BPA. Dr Myers reported serving on the organizing committee of the NIH-sponsored conference on BPA held in Chapel Hill, North Carolina, in 2006; serving as chief executive officer/chief scientist of a nonprofit organization, Environmental Health Sciences, which aggregates and redistributes news about the environment and health from media sources around the world (EnvironmentalHealthNews.org; BPA coverage is included when it occurs, and no fees are charged for this service because it is supported by private foundations); publishing (with 2 coauthors) *Our Stolen Future*, a book that briefly mentions BPA (Dr Myers has received less than $10 000 in royalties for this book since publication); and publishing a companion non–revenue-generating Web site (OurStolenFuture.org) that summarizes emerging science about endocrine disruption, including findings on BPA.

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