REPORT 5 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-11)
Bisphenol A
(Resolution 408-A-10)
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. To evaluate and summarize existing data on the biological mechanisms of bisphenol A (BPA), in vitro and in vivo effects of low doses of BPA, its metabolic disposition, and the extent of population exposures. In addition, results obtained from epidemiologic surveys on BPA exposure and human health are briefly noted.

Methods. English-language reports on studies using animals and human subjects were selected from a PubMed search of the literature from 1990 to March 2011 using the substance terms "bisphenol A/phenols/estrogens, nonsteroidal/endocrine disruptors," in combination with the MeSH terms "risk assessment," "toxicity," "environmental exposure," "environmental monitoring," "blood/urine," "food contamination," "food packaging," "pregnancy," "fetus/drug effects," "prenatal exposure," and "pathophysiology." When high-quality systematic reviews and meta-analyses were identified, they formed the basis for summary statements. Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the US Environmental Protection Agency, US Food and Drug Administration, National Institute of Environmental Health Sciences, and Safer States.

Results. More than 2 billion pounds of BPA enter US commerce annually, entering the food chain and water stream from various sources. Most human exposure is thought to be based on dietary intake. BPA is firmly established as an endocrine disruptor, interacting with various estrogen-related cellular pathways with a high sensitivity, and demonstrating epigenetic influences. Biomonitoring studies of urine and blood samples reveal nearly ubiquitous human exposure; free concentrations of BPA are in the range associated with cellular effects. These results are at odds with most formal government-sponsored risk assessments, which deem BPA to be safe and devoid of harm at current exposure levels. Nevertheless, several states and municipalities in the US have banned the sale of BPA-containing baby bottles and cups. Recently, the FDA concluded that some concern exists for the potential of BPA to cause harmful effects on the brain, behavior, and prostate gland in fetuses, infants, and young children.

Conclusion. Better understanding of the routes and extent of human exposure to BPA are needed. Additionally, confirmation of animal models that are relevant for modeling human exposure and for establishing valid endpoints for risk assessment of low doses is needed. This will assist in addressing uncertainties surrounding the spectrum of BPA's mechanisms of action, the tissue-specific impacts of exposures, and the critical windows of susceptibility during which target tissues are sensitive to BPA. In the meantime, measures should be taken to reduce BPA dietary exposures and industry should pursue safe alternatives to BPA. Consumers can voluntarily take action to reduce dietary exposures.

It is important that the FDA actively incorporate current science into the regulation of food and beverage BPA-containing products, and such incorporation should be transparent. In addition, a critical need exists for the EPA to make the risk assessment of environmental chemicals more efficient and responsive to emerging data. The development of new technologies and a strengthened legislative platform for action will assist in this endeavor.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 5-A-11

Subject: Bisphenol A

Presented by: Al Osbahr III, MD, Chair

Referred to: Reference Committee E
(Robyn F. Chatman, MD, Chair)

Resolution 408-A-10 "Restricting Bisphenol A Use" introduced by the Illinois Delegation and referred by the House of Delegates asked:

> That our American Medical Association support federal legislation to restrict bisphenol A from children's products.

BACKGROUND

Originally synthesized in 1891, bisphenol A {2,2-bis(4-hydroxyphenyl)propane} or BPA was discovered to possess estrogenic activity in the 1930s. Its potential use as a synthetic estrogen was abandoned with the development of more potent synthetic estrogens such as diethylstilbesterol (DES). In the 1950s, BPA's value as an additive and component in the chemical industry was established and it became widely used in the manufacture of polycarbonate plastics and epoxy resins. These substances are used in many products across the food and beverage industry including bottles, packaging and metal can linings, other containers, and tableware. Biologically active monomers of BPA can hydrolyze and leach from these products, contaminating the contents; this process is substantially accelerated by increased temperature or changes in pH.[1-4]

BPA also is used in other products that consumers use or come into contact with, such as lightweight eyeglass lenses, compact discs, cigarette filters, dental sealants, certain medical devices, and the coating of thermal and carbonless papers, including cash register receipts. The use of BPA-containing resins in foundry castings and for lining water and waste water pipes, combined with leaching of BPA from products that are not recycled and deposited in landfills, contributes to the presence of BPA in sewage effluents and groundwater sources, streams, and rivers and the eventual exposure of various aquatic species (as well as humans) to BPA.[5-10]

Endocrine Disruptors

Based on observations of adverse health outcomes of vertebrates living in the Great Lakes, a group of diverse scientists convened in 1991 (the Wingspread Meeting) to address the topic of chemically-induced alterations in wildlife development, including problems related to sexual differentiation and reproductive function in mammals and fish. A consensus statement from the conference resulted in the term "endocrine disruptor" being introduced into the scientific community.[11] In contemporary usage, endocrine disruptors are exogenous compounds that have the potential to interfere with hormonal regulation and the normal endocrine system and

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consequently cause health effects in animals and humans. BPA is regarded by the Endocrine Society and Environmental Protection Agency (EPA) as an endocrine-disrupting agent.[12] The questions surrounding the use and safety of BPA are part of a much broader concern about the regulation of potentially toxic chemicals. The AMA supports centralized regulatory oversight of endocrine disrupting chemicals based on comprehensive data addressing both low-level and high-level exposures. Public policies should be developed and revised under the direction of a collaborative group comprising endocrinologists, toxicologists, occupational/environmental medicine specialists, epidemiologists, and policymakers (Policy D-135.982, Regulation of Endocrine Disrupting Chemicals, AMA Policy Database). The AMA also supports restructuring the Toxic Substances Control Act (TSCA) to help federal and state agencies more efficiently assess human and environmental health hazards of industrial chemicals and reduce or eliminate the use of the most harmful substances (Policy H-135.942, Modern Chemicals Policies). The National Academy of Sciences recently released a report addressing both the technical analysis that supports risk assessment of environmental chemicals and improving its utility. The report concluded that a number of improvements are needed to streamline EPA's risk assessment process to ensure that they make better use of appropriate available science and that such information is more relevant to decision making.[13] A special need exists to evaluate that effects of chemicals, including endocrine disruptors, on vulnerable windows of exposure such as occur during pregnancy, infancy, and childhood.

The published literature on BPA is voluminous. Research-based studies have shown adverse reproductive, developmental, and metabolic effects in animal models and aquatic species from BPA. New data about in vitro and in vivo effects of low doses of BPA, the metabolic disposition of oral doses and extent of population exposures, and results from epidemiologic surveys have broadened the debate on BPA and also raised new questions. This report will summarize some of the main areas of agreement, identify relevant new findings, address some research gaps, and recommend appropriate AMA actions.

This report does not address dental exposures to BPA or ecological effects in birds, aquatic, or other invertebrate species. See the recent review by Fleisch and co-authors for information on bisphenol A and related compounds in dental materials.[14] Several recent reviews have examined the potential ecological impacts of BPA.[15-19] In general, studies have shown that BPA can "affect the growth, reproduction and development in aquatic organisms."[20] The potential for adverse ecological effects from BPA and other endocrine disruptors lends further credence to the need for careful examination of current practices.

METHODS

English-language reports on studies using animals and human subjects were selected from a PubMed search of the literature from 1990 to March 2011 using the substance terms "bisphenol A," "phenols," "estrogens, nonsteroidal," and "endocrine disruptors," in combination with the MeSH terms "risk assessment," "toxicity," "environmental exposure," "environmental monitoring," "blood/urine," "food contamination," "food packaging," "pregnancy," "fetus/drug effects," "prenatal exposure," and "pathophysiology." When high-quality systematic reviews and meta-analyses were identified, they formed the basis for summary statements. Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the US Environmental Protection Agency, US Food and Drug Administration, National Institute of Environmental Health Sciences, and Safer States.

REGULATION OF BPA

The majority (85% to 90%) of BPA manufactured and used in the US falls under the jurisdiction of the EPA and TSCA, a federal law passed in 1976 designed to regulate industrial chemicals. BPA was one of 62,000 chemicals "grandfathered" as a safe substance by TSCA; thousands of additional chemicals have subsequently entered into commerce. The FDA has jurisdiction over the use of BPA in food and beverage packaging (and medical devices), which accounts for less than 5% of the BPA produced annually. The EPA published a bisphenol A action plan in March 2010, but does not intend to initiate regulatory action under TSCA (at this time) on the basis of human health effects.[20]

Reference Dose

For risk assessment, a reference dose (RfD), typically 100-fold less than the no observed effect level (NOAEL) is calculated as an acceptable daily human intake. The current EPA RfD for BPA was set at 50 μg/kg/day in 1988. This value was established by using the lowest observable adverse effect level (LOAEL), which was based on the lowest dose studied (50 mg/kg/day), and imposing a 1000-fold safety factor because a NOAEL had not been determined. This RfD was last reviewed in 1993; the critical effect that was used as the basis for the RfD was reduced mean body weight in adult rats. The uncertainty factor of 1000 is the highest uncertainty factor given by EPA to an RfD calculation and incorporates a 10-fold factor for animal to human extrapolation, 10-fold for protecting sensitive individuals, and an additional 10-fold safety factor for uncertainty in the importance of "duration" when extrapolating from subchronic to chronic exposure. So-called "low dose" effects for BPA are defined as those that occur at daily doses lower than 50 mg/kg/day or at environmentally relevant exposure levels.

BPA MECHANISMS OF ACTION

Multiple cellular sites and pathways have been identified as targets of BPA action.

Classical (Nuclear) Estrogen Receptors

BPA interacts with classical estrogen nuclear receptors (ERα and ERβ) that function in the nucleus as transcription factors regulating gene expression in response to hormone binding. Hormone-bound estrogen receptor binds to specific DNA sequences termed estrogen response elements activating gene expression. BPA binds to ERα and ERβ with a somewhat higher affinity for ERβ. However, BPA's potency is 1000 to 10,000-fold lower than estrogens such as 17β-estradiol or DES.[21,22] Therefore, BPA has typically been viewed as a weak environmental estrogen. Although the biological significance is uncertain, BPA also interacts with androgen and thyroid hormone receptors at higher concentrations and also has been described as a weak agonist for the glucocorticoid receptor.[23,24]

Rapid Signaling Estrogen Receptors

Although BPA is substantially weaker than native estrogens in activating ERα and ERβ, it is now established that BPA can stimulate various other estrogen-mediated cellular responses at very low concentrations in an equipotent fashion; some cell functions are affected at concentrations between 1pM (0.23 pg/ml; 1 part per trillion) and 1nM (0.23 ng/ml; 1 part per billion).[24-35] 17β-estadiol (estradiol) can modify the activities of various intracellular signaling networks (e.g., calcium mobilization, kinase activity) within seconds to minutes via membrane-associated or intracellular receptor systems, independent of nuclear hormone receptors. BPA is able to activate these

pathways at very low concentrations and similar to estradiol, may exhibit a loss of efficacy at higher concentrations generating a non-monotonic or inverted-U shaped[#] dose response curve.[24] BPA also binds to a G-protein coupled estrogen receptor (GPER) that may mediate some of estrogen's other membrane-based rapid signaling events.[36,37] GPER has been implicated in the function of pancreatic islet cells, bone growth, and immune and cardiovascular function.[38]

Estrogen-Related Receptors

Compared with its affinity for ERα or ERβ, BPA is 100 times more potent at the so-called estrogen-related receptor γ (ERRγ), an orphan receptor that shares a sequence homology with nuclear estrogen receptors but does not respond to estradiol.[39,40] ERRγ may play a role in the differentiation and maturation of the fetal brain, and has been implicated in regulating mitochondrial function.[41,42] This receptor exhibits high baseline activity and can interact with its own, as well as native estrogen response elements. When BPA is bound to ERRγ, it preserves the receptor's basal activity and prevents inactivation by antiestrogens. By virtue of its ability to interact with ERα, ERβ, and ERRγ, BPA has access to a cellular platform that may affect the overall estrogenic responses in a particular cell type.

Epigenetic/Molecular Mechanisms

Epigenetic effects are DNA structural modifications that result in heritable changes in gene expression that do not involve changes in the DNA sequence (e.g., DNA methylation). Exposure to BPA in utero has been shown to affect the methylation status of several genes suggesting a role for epigenetic mechanisms in BPA's effects.[43-45]

BPA also is included in the Comparative Toxicogenomics Database (http://ctd.mdbil.org/), a public resource on environmental chemicals that describes cross-species chemical-gene/protein interaction and chemical- and gene-disease relationships. Several potential gene targets for BPA are identified in this database; the top ten based on published gene interactions are listed in Table 1.

Genes affected by treatment with BPA or positive control estrogens also are compiled in the NextBio Enterprise repository (www.nextbio/com/b/nextbio.nb). In essence, the number of "overlapping genes" or genes in common affected by BPA and estradiol ranges from 7% to 36%, lending further support to the notion that BPA is not simply an estrogen-like substance or estrogen receptor modulator. The data compiled in the Comparative Toxicogenomics Database found that BPA and estradiol had a 19% overlap in comparable sets of interacting genes.

Other Biochemical/Molecular Data on BPA

To help address the formidable challenge of characterizing toxicity pathways and prioritizing the testing of the huge array of environmental chemicals in existence today, the EPA developed the *ToxCast* program and a high throughput screening system (*Tox21*). Phase 1 of this program evaluated 309 chemicals (including BPA) in 467 cellular assays with 9 different technology platforms using a prioritization scheme for detecting endocrine activity (www.epa.gov/ncct/toxcast). BPA was the 3rd most active chemical based on reactivity deemed relevant to endocrine signaling and related gene targets.[38]

[#]This relatively novel dose response curve is not well-modeled or captured by the NOAEL and LOAEL used to derive the RfD.

HUMAN EXPOSURE DATA: BIOMONITORING STUDIES

BPA is one of the highest volume chemicals produced worldwide, with more than 6 billion pounds produced annually and a yearly atmospheric release of at least 100 tons. Thus, some human exposure can occur from environmental sources (i.e., air, drinking water, soil, and dust). The primary source of BPA in adults is commonly believed to be oral intake from canned food.[46,47] Breast milk and polycarbonate feeding bottles are primary sources of BPA among infants, with oral exposure from canned foods becoming more important as children age.[47] Families who replace their use of canned and packaged foods with fresh foods experience substantial decreases in urinary BPA concentrations, averaging 66% over a 3-day period.[48] Cashiers and persons employed in industries using BPA have additional non-dietary exposures.[49,50] For cashiers, it is not clear to what extent dermal transport after contact with BPA-containing receipts plays a role in systemic exposure.[51] Regular consumption of beverages from polycarbonate bottles increases urinary BPA concentrations by two-thirds, regardless of other sources of exposure.[52] Tobacco smoke, including second hand smoke, may be additional sources of BPA exposure, since BPA is used in cigarette filters.

The validity and certainty of any sampling study is dependent on the collecting devices and assay methods. Because of BPA's widespread use and environmental spread, potential contamination of laboratory equipment exists and the use of appropriate controls is essential when analyzing for free BPA concentrations; sample storage conditions also affect the stability of BPA metabolites.[53]

Metabolism and Elimination of BPA

After oral ingestion, the relative rates of metabolism/elimination compared with absorption and distribution determine systemic exposure. In humans, ingested BPA is eliminated via conjugation with glucuronic acid (with minor amounts conjugated with sulfate) and urinary excretion of the conjugates as the major urinary metabolite.[54,55] The enzymes responsible for glucuronidation are present in the small intestine and liver. Significant metabolism of orally ingested drugs or chemicals prior to gaining access to the systemic circulation (presystemic clearance) is termed the "first pass" effect. This process can significantly reduce the bioavailability of orally administered drugs or chemicals, and this appears to be the case with BPA.

After single 5 mg oral doses of radiolabelled BPA, the vast majority is recovered in the urine as the glucuronide conjugate over a 24-hour period with an estimated elimination half-life of the conjugate of less than 6 hours (detection limit of 6 ng/ml for free BPA).[56] The results of this acute dose study have been relied on to make the argument that human exposure to free BPA after oral ingestion is quite limited. With chronic exposure to BPA, an undetermined fraction of the absorbed dose may be sequestered in adipose tissue which may serve as a reservoir.[57]

The elimination of BPA in adult rhesus monkeys is similar to humans with rapid conjugation of free BPA and elimination of the conjugate in the urine; less than 1% of an orally administered BPA dose of 100 ug/kg appears to be bioavailable (maximal plasma concentration (C_{max}) < 1 nM).[49] The C_{max} and bioavailability of BPA is 2 to 3-fold higher in neonatal monkeys, reflecting lower glucuronidation capacity. Rats also eliminate BPA via conjugation but demonstrate a more significant inverse relationship between postnatal age and the elimination of BPA.[58] In adult female rats, oral administration was associated with a bioavailability of about 4% for free BPA. In neonatal rats, internal exposures to free BPA were substantially lower after oral compared with subcutaneous injection, but peak serum concentrations of free BPA were substantially higher than in adults. Rats eliminate BPA conjugates via biliary/fecal routes. Direct comparative analysis of BPA (400 ug/kg) pharmacokinetics suggest that adult rhesus monkeys and CD-1 mice (a species

generally acknowledged as responsive to BPA low dose effects) display similar elimination profiles.[59] Another study suggests that serum BPA pharmacokinetics are substantially similar regardless of route of administration (subcutaneous vs oral) in CD-1 mice.[60] These findings have implications for evaluating human biomonitoring data and the relevance of certain animal models for human disease.

Human Exposure Data-Urine

Biomonitoring studies assess systemic and excreted concentrations to account for exposure from all possible sources; most BPA studies have relied on measuring total BPA after hydrolysis of any conjugated BPA present. Theoretically, free BPA in urine samples could reflect systemic circulation and excretion of unmetabolized BPA, hydrolysis of BPA conjugates in the body by intestinal bacteria or tissue enzymes, degradation of conjugates during storage, or contamination.

With one exception, studies have revealed BPA exposure to be ubiquitous and widespread in industrialized nations. Analysis of more than 80 biomonitoring studies from around the world involving adults, pregnant women and fetuses indicate total BPA concentrations in the range of 0.5-10 ng/ml, with most clustering around 1-3 ng/ml, a concentration known to exert effects in vitro in animal models.[53] BPA and/or its conjugates were detected in more than 85% of subjects evaluated; most of these studies used methods measuring total BPA, although unconjugated BPA was present in samples from all studies (except one) which attempted to measure free BPA.[53]

The Centers for Disease Control and Prevention (CDC) has examined exposure of the general US population to BPA. BPA (measured as total BPA) was detected in 95% of 394 adult participants in the third National Health and Nutrition Examination Survey (NHANES III).[63] A large follow-up study conducted in conjunction with the 2003-2004 NHANES survey found BPA in the urine of 93% of the population with a geometric mean concentration for total BPA of 2.6 ng/ml (range, 0.4 to 149 ng/ml). Average concentrations were higher in children, adolescents, and females, but lower in Hispanics.[64] BPA is present in the urine of more than 90% of US pregnant women and has been correlated with offspring birth weight.[65,66] Pregnant women who worked as cashiers or who consumed canned vegetables had higher concentrations during serial testing.[49] Results of the 2007-2009 Canadian Health Survey were substantially similar to the US experience; 91% of samples were positive and higher normalized values were observed in children ages 6 to 11.[67] BPA concentrations in premature infants undergoing intensive medical treatments who are exposed to BPA-containing medical tubing/devices may be an order of magnitude higher than the general population (>30 ng/mL).[68]

Human Exposure Data-Blood

Large scale biomonitoring studies of free BPA blood concentrations have not been done in the US population. However, several small foreign studies have examined the blood or serum concentrations of BPA in healthy male and nonpregnant female patients using various analytical techniques. The vast majority (14 of 16 studies) have detected free BPA in blood, typically in the range of 1 ng/ml.[53] In the largest study to date examining more than 200 subjects, free BPA was detected in 83% of samples collected from hospitalized patients in France, with 12% exceeding 2 ng/ml.[69]

<u>Studies in Pregnancy</u>

Several, mostly foreign studies have examined total BPA concentrations in serum from pregnant women (0.46-9.04 ng/mL) and from umbilical cord samples (0.62-4.05 ng/mL).[53] One US study

of BPA concentrations in maternal blood at the time of delivery found a mean BPA concentration of 5.9 ng/mL.[70] A similar range of values have been determined in amniotic fluid samples taken at various periods of gestation and from umbilical tissue at birth.[53]

Breast Milk

One small US study (n=20) examining free BPA in human breast milk found a mean concentration of 1.3 ng/ml in 60% of samples.[71] A larger study involving 101 Japanese women 3 days after delivery found substantially higher BPA concentrations in human colostrum (3.4 ng/ml).[72]

EFFECTS OF BPA VS FORMAL RISK ASSESSMENT

Risk assessment is an important public policy tool for making choices to protect public health and the environment. It is an important part of the mission for the US EPA and other federal agencies in evaluating public health concerns and informing regulatory and technological decisions. Because risk assessment provides the scientific underpinning for regulations that have widespread impact, it is subject to significant scientific, political, and public scrutiny. Nowhere is this more apparent than in the case of BPA as improved laboratory techniques and molecular advances have contributed to uncertainty about hazard identification, dose response assessment, exposure assessment, and risk characterization, leading to multiple interpretations.

Formal risk assessments of BPA have been conducted by numerous governmental bodies and commissioned review panels over the last 20 years. As noted above, the EPA established the RfD for BPA at 50 μg/kg/d in 1988. To assess risks, governmental agencies rely on guideline-compliant studies using specified exposures (routes, doses, durations), validated end points linked to adverse outcomes, and sufficient group sizes and numbers. These studies are performed under regulatory testing protocols and in compliance with defined good laboratory practices (GLP) with international harmonization of the testing protocols. Generally, they rely on macroscopic anatomical and developmental features, survival, and mortality endpoints, but include some histology and biochemistry. Revised endpoints for "endocrine disruption" were created in the late 1990s (e.g., acquisition of puberty, estrous cyclicity, andrology, and ovarian primordial follicle counts) but are only now being validated.

The current argument over the safety and risk assessment of BPA revolves, in part, around the GLP standardized test protocols used for hazard evaluation and risk assessment versus the burgeoning evidence from peer-reviewed in vitro and in vivo basic research studies, many of which were conducted in academic settings. Such studies, which employ experimental designs that differ from regulatory protocols, reveal BPA to be a highly active substance at substantially lower doses than have been tested in formal risk assessment paradigms. Exposing tissues to only a narrow range of (high) concentrations can lead to erroneous conclusions about lack of effects. Non-monotonic dose response curves are encountered in endocrinology and for BPA.[73]

Interest in the effects of low doses of BPA was triggered by a 1997 report indicating that male offspring of pregnant mice fed BPA at a dose range of 2-20 μg/kg/day had enlarged prostates. By the end of 2004, 115 in vivo animal studies on low-dose effects of BPA had been published; 82% of these reported significant effects, including 27% that used dose exposures below the RfD.[74] As noted above, in vitro studies had discovered membrane-based and other (non-nuclear) estrogen response pathways in human and animal cells activated at low picomolar through nanomolar concentrations (as low as 0.23 ppt).[74] Rate of growth and sexual maturation, hormone levels in blood, reproductive organ function, fertility, immune function, enzyme activity, brain structure, brain chemistry, and behavior were reported to be affected by exposure to low doses of BPA.

Many of these effects are due to exposure during early development (gestation and/or lactation), but some are likely due to postweaning-through-adult exposure.

A 2007 review on the effects of low doses of BPA (below 50 mg/kg/day) in laboratory animals concluded that such exposures in adults affected the male reproductive tract, and that fetal exposure to BPA resulted in long-lasting effects on the brain, male reproductive system, and certain metabolic processes.[75] Specific low dose effects that have been observed include altered metabolism related to metabolic syndrome; altered adiponectin secretion, which may be a risk factor for heart disease and type 2 diabetes; epigenetic effects; changes in gene expression, precancerous lesions, and different growth patterns of the prostate and mammary glands; and, uterine fibroids, paraovarian cysts, and chromosomal abnormalities in oocytes.[25,27,67-72] Various neuroanatomic, neurochemical, and behavioral abnormalities in animals also have been associated with low doses of BPA. [31,75]

A meeting (Chapel Hill expert panel) sponsored by the National Institute of Environmental Health Sciences, National Institute of Dental and Craniofacial Research, and the EPA further examined the effects of BPA in animals and the potential relevance to trends in human health (i.e., early onset of puberty in females; increases in neurobehavioral conditions in children; increases in childhood obesity and cancers; a regional decrease in sperm count; and hormonally-mediated prostate and breast cancer) at current levels of exposure.[82] This panel concluded that prenatal and/or neonatal exposure to low doses of BPA results in organizational changes and epigenetic effects in the prostate, breast, testis, body size, brain structure and chemistry, and behavior of laboratory animals. Other recent reviews on experimental studies in animals, human exposure to BPA, and their potential relevance for human health are available.[83,84]

The National Toxicology Program (NTP) examined the low dose issue and issued a report in 2001 with the finding that there was credible (but inconsistent) evidence of low-dose effects, but not to the point that low-dose effects could be validated as a general finding or concern.[85] A follow-up study funded by the Association of Plastics Manufacturers and conducted by the Harvard Center for Risk Analysis concluded that the "weight of the evidence for low dose effects was very weak."[86] This study has been criticized for its failure to consider numerous non-industry funded studies in its analysis.[74]

During weight-of-evidence evaluations, panelists are expected to evaluate relevant articles and reports with specific study designs and/or end points, and assign greater/lesser weight based on established criteria. For example, in vitro assessments do not necessarily predict the effects of BPA or a hormone in a fetus or adult animal. Accordingly, endpoints evaluated in such studies do not consider various in vitro effects demonstrating cellular activity or toxicity of BPA, or animal models relying on more complex functional or behavioral end points. Generally, such "weight-of-evidence" assessments have concurred that low oral doses of BPA do not adversely affect human reproductive or developmental health but often have been conducted by industry or industry-funded toxicologists.[87-89]

A recent two-generation reproductive GLP toxicity study of dietary BPA in CD-1 mice was unable to demonstrate any effects of BPA on adult mating, fertility or gestational parameters, ovarian follicles, estrous cycles, offspring sex ratios, sperm parameters, or macroscopic/histopathologic measures of toxicity in testes and prostate glands.[90] BPA doses ranged from 3 μg/kg (0.018 ppm) to 600 mg/kg (3500 ppm) per day. Although conducted according to GLP procedures, the design and interpretation of this study has been criticized as flawed and inadequate for purposes of safety assessment.[91] Another GLP study conducted according to EPA guidelines for the study of developmental neurotoxicity in Sprague-Dawley rats (a species that has lower sensitivity to

developmental estrogen effects) also failed to detect any sensory, motor, or learning deficits, or other neurotoxic or neurobehavioral effects of BPA.[92] BPA dietary doses ranged from 0.15 to 2250 ppm in this study.

Accordingly, virtually all government risk assessments of BPA conducted through 2008 were unwilling to validate the emerging low-dose literature as sufficient for the purposes of hazard evaluation/risk assessment in humans.[87,93-100] This view has changed modestly over the last 2 years. In 2008 Canada became the first government to ban the use of polycarbonate baby bottles that contain bisphenol A.[101,102] However, Canada acknowledged this action was being taken because of uncertainty raised in some studies on the potential effects of low levels of BPA, even though exposure levels for newborns and infants up to18 months of age were judged to be below those that could cause health effects.

The National Toxicology Program's Center for Evaluation of Risks to Human Reproduction (NTP-CERHR) completed a new review of BPA in 2008 expressing some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A, but minimal concern for effects on the mammary gland or earlier age of puberty for females.[103] The NTP study did not include in vivo experiments using non-oral routes of administration. However, a recent study in rats found that, although subcutaneous administration of BPA resulted in a 6-fold higher serum concentrations of free BPA than oral administration, both routes of exposure induced nearly identical susceptibility to prostate intraepithelial neoplasia.[104]

After the FDA released a draft report in 2008 finding that BPA remains safe in food contact materials, a subcommittee of FDA's science board raised questions about whether FDA's review had adequately considered the most recent scientific information available. On January 15, 2010, the FDA issued an interim update on BPA now expressing "some concern" about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children at levels to which humans are exposed.[105]

HUMAN DISEASE OUTCOMES

Some researchers have examined urine or blood BPA concentrations in the context of disease association studies. Concern with human exposure is based on knowledge about the molecular mechanisms and cellular effects of BPA; the fact that in vivo effects have been demonstrated in animal models at concentrations measured in humans; and the fact that human exposure is ubiquitous and widespread, affecting more than 90% of the population. Based on single dose studies, BPA has low bioavailability in humans. Furthermore, single urine or blood concentration values may not reflect the relevant window of exposure for putative developmental, carcinogenic, or chronic disease effects. With these types of epidemiological studies, cause and effect relationships between measured concentrations and chronic disease states cannot be determined or established. Because spot urine or blood BPA concentrations are limited in their prognostic capacity, longitudinal studies also are needed. Following are some reported associations between BPA concentrations and human health.

Cardiovascular Disease/Diabetes

Higher urinary BPA concentration was associated with a diagnosis of cardiovascular disease and diabetes, but not other common diseases in NHANES respondents.[76,106]

Reproductive Outcomes

Urinary BPA concentrations are inversely associated with estradiol concentrations, the number of oocytes retrieved from women undergoing in vitro fertilizations, and sperm counts and sperm vitality; variable associations have been reported between BPA concentrations and serum testosterone.[50,83,107,108] BPA concentrations are higher in obese women and in women with polycystic ovary syndrome. In women, small studies have found relationships between BPA levels in blood and endometrial hyperplasia, endometriosis, recurrent miscarriages, and sterility.[108,109]

Onset of Puberty

Some rodent studies suggest that early life BPA exposure may accelerate pubertal development and increase breast cancer risk. However, NTP-CERHR had minimal concern over BPA accelerating pubertal development.[103] Two epidemiological studies examining the relationship between BPA exposure and pubertal development were largely negative.[110,111]

Fetal and Childhood Growth

Data from in vivo studies have revealed dose-dependent and sex-dependent effects on body weight in rodents exposed perinatally to BPA.[112] Three human studies examined associations between BPA exposure and infant/childhood growth. No consistent relationships with body weight are evident and only a weak correlation exists between urinary BPA and BMI.[65,113,114]

Neurodevelopment

A single prospective birth cohort of 249 mothers and infants from Cincinnati, Ohio examined the association between prenatal BPA exposure and childhood behavior at 2 years of age.[115] The authors measured urinary BPA concentrations twice during pregnancy (16 and 26 weeks gestation) and at birth. Mean gestational BPA concentrations and those from samples taken at 16 weeks were positively associated with externalizing behaviors (aggression and hyperactivity) in children, with effects most evident in females.

Cancer

Early life exposure to BPA may induce or predispose to pre-neoplastic lesions of the mammary gland and prostate gland in adult life, and BPA may be associated with increased cancers of the hematopoietic system and significant increases in interstitial-cell tumors of the testes.[116] BPA concentrations have not been evaluated in breast cancer patients. Although BPA has been suspected to promote carcinogenesis, based on results using cell culture, it also may reduce the efficacy of chemotherapeutic agents in breast cancer cells.[117]

FILLING THE GAPS

In an effort to fill research gaps, the NIEHS has devoted substantial funding to BPA for two-year animal or human studies involving either developmental exposure (in utero or neonatal) or adult chronic exposures to low environmentally relevant doses of BPA, including population-based studies. Some endpoints of interest are related to obesity, diabetes, and metabolic syndrome; reproductive disorders and reproductive system cancers; disorders of the developing immune system; cardiovascular diseases; and phenotypic changes following exposure in one generation that persist for 2 or more subsequent generations. A description of ten such studies can be found at www.niehs.nih.gov/recovery/critical/bpa.cfm.

COMMENT

More than 2 billion pounds of BPA enter the commercial space of the US annually. It is generally believed that most exposure to BPA is dietary, however, dermal (and pulmonary) routes may be important in some individuals. Although single-dose studies indicate that BPA is efficiently conjugated and eliminated by renal excretion, the impact of chronic exposure on BPA disposition is unknown. Free BPA concentrations have been detected in a wide range of both human and animal studies, providing evidence of exposure to free BPA in human adults and fetuses despite rapid first-pass glucuronidation. Thus, in the US we are already facing the prospect of population-wide impacts, and many endpoints (based on experimental evidence) are not trivial.

A large body of research-based evidence now indicates that BPA is an endocrine disrupting chemical that can induce a variety of adverse effects in mammals as well as other vertebrates and invertebrates at current levels of human exposure, but its safety continues to be disputed. The urgent need for clarifying this issue is underscored by the CDC's conclusion that over 90% of people in the US are chronically exposed to BPA, as well as lessons learned from the DES experience. Most government risk assessments have concluded that, at current levels of exposure, BPA is not a significant hazard for humans. However, both Canada and the FDA have recently indicated some concern about potential harmful effects. Accordingly, Canada and some US states, cities, and counties have taken interim risk management actions to protect sensitive populations such as infants and toddlers by banning the sale of baby bottles, food containers, and cups containing BPA (Table 2).

In animal models, the effects of BPA vary depending upon the dose, tissue, and the life stage of exposure, with the fetus and neonate generally believed to be at highest risk. Better understanding of the routes and extent of human exposure are needed. Additionally, confirmation of animal models that are relevant for modeling human exposure and for establishing valid endpoints for risk assessment of low doses are needed. This will assist in addressing uncertainties surrounding the spectrum of BPA's mechanisms of action, the tissue-specific impacts of exposures, and the critical windows of susceptibility during which target tissues are sensitive to BPA exposures. Federally funded studies addressing some of these issues are ongoing.

In the meantime, measures should be taken to reduce BPA dietary exposures and industry should pursue safe alternatives to BPA. For the most part, manufacturers of baby bottles, cups, and food containers have voluntarily removed BPA from their products. Advice for consumers on reducing their dietary exposure to BPA is available from the NIEHS (Table 3). A chart that identifies the meaning of various plastic recycling codes is found in Table 4. BPA-containing polycarbonate plastics have a "7" and the notation PC.

It is important that the FDA actively incorporate current science into the regulation of food and beverage based BPA-containing products and that such incorporation be transparent. In addition, a critical need exists for the EPA to make the risk assessment of environmental chemicals more efficient and responsive to emerging data. The development of new technologies and a strengthened legislative platform for action will assist in this endeavor.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 408-A-10 and the remainder of the report filed.

1. That Policies H-135.942 and D-135.982 be reaffirmed. (Reaffirm HOD Policy)

2. That our AMA support a shift to a more robust, science-based, and transparent federal regulatory framework for oversight of bisphenol A (BPA). (New HOD Policy)

3. That our AMA encourage ongoing industry actions to stop producing BPA-containing baby bottles and infant feeding cups, support bans on the sale of such products, and urge the development and use of safe, nonharmful alternatives to BPA for the linings of infant formula cans and other food can linings. (New HOD Policy)

4. That our AMA recognize BPA as an endocrine-disrupting agent and urge that BPA-containing products with the potential to increase human exposure to BPA be clearly identified. (New HOD Policy)

Fiscal Note: Less than $500

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Table 1. Top Ten Genes Reported as Interacting with Bisphenol A

Gene	Number of Interactions	Number of Organisms
Estrogen Receptor 1 (ESR1)	140	16
Estrogen Receptor 2 (ESR2)	37	5
Progesterone Receptor (PGR)	25	3
Cytochrome P45019A1 (CYP19A1; Aromatase)	22	6
Androgen Receptor (AR)	21	4
Calcium Binding Protein (S100G)	21	2
Luteinizing Hormone Beta Peptide (LHB)	19	2
Mitogen Activated Protein Kinase (MAPK1)	15	4
Nuclear Receptor (NR4A1;nerve growth factor/orphan receptor induced protein)	12	2
Growth Hormone (GH1)	11	2

Table 2. Legislative or Regulatory Bans on BPA

U.S. States & Municipalities	Action
Connecticut	Effective October 1, 2011 BPA is banned from infant formula containers, baby food cans and jars, or reusable food and beverage containers.
Maryland	As of 2014, BPA banned from baby bottles and sippy cups.
Massachusetts	BPA banned in baby bottles and cups in December 2010.
Minnesota	Banned BPA in sippy cups and baby bottles in January 2010. Retailers have until January 1, 2011 to sell existing stock.
New York	BPA banned from young children's products as of December 1, 2010.
Vermont	In May 2010, restricted the manufacture, sale or distribution of canned infant formula, bottled infant formula, plastic baby containers, and reusable food and beverage containers containing BPA.
Washington	March 2010 bill banned BPA from baby bottles, sippy cups, children's dishware and sports bottles beginning in July 2010, with a sports bottle phase-out in July 2011.
Wisconsin	BPA banned from baby bottles and sippy cups for children under the age of 3 effective June 2010.
Counties and Cities	
Albany County, NY	Local law effective January 1, 2010 stating that no one in the county should sell baby bottles or sippy cups containing BPA, or use them with their children.
Schenectady County, NY	Local law effective in late 2009 banning the sale of availability of children's beverage containers containing BPA.
Chicago	First American city to ban BPA in May 2009 from sippy cups and baby bottles; stores required to post signs indicating that products are BPA-free.
Countries	
Canada	In May 2008, imposed a limited ban on BPA in baby bottles.
European Union	Banned the manufacture and sale of baby bottles with BPA, a phase-out that will occur in 2011.

Table 3. Reducing Exposure to BPA

Advice to Reduce Exposure to BPA
• Don't microwave polycarbonate plastic food containers. Polycarbonate is strong and durable, but over time it may break down from overuse at high temperatures. • Polycarbonate containers that contain BPA usually have a #7 on the bottom. • Reduce your use of canned foods. • When possible, opt for glass, porcelain or stainless steel containers, particularly for hot food or liquids. • Use baby bottles that are BPA free.

Table 4. Plastic Recycling Symbols

Plastic	# Symbol	Comment
Polyethylene terephthalate		Found in soft drink, water and beer bottles; mouthwash bottles; peanut butter containers; salad dressing and vegetable oil containers; oven ready food trays. Low risk of leaching product.
High Density Polyethylene		Found in milk jugs, juice bottles; bleach, detergent and household cleaner bottles; shampoo bottles; some trash and shopping bags; motor oil bottles; butter and yogurt tubs; cereal box liners. Low risk of leaching
Polyvinyl Chloride		Found in window cleaner and detergent bottles, shampoo bottles, cooking oil bottles, clear food packaging, wire jacketing, medical equipment, siding, windows, piping. PVC based food packaging should not be heated in contact with food; also, do not burn PVC, because it releases dioxin.
Low Density Polyethylene		Found in squeezable bottles; bread, frozen food, dry cleaning and shopping bags; tote bags; clothing; furniture; carpet.
Polypropylene		Found in some yogurt containers, syrup bottles, ketchup bottles, caps, straws, medicine bottles.
Polystyrene		Found in disposable plates and cups, meat trays, egg cartons, carry-out containers, compact disc cases.
Polycarbonate; Other Plastics		Wide variety of plastic resins that don't fit into the previous categories are lumped into number 7. Polycarbonate is number 7 (PC) and is **BPA-containing**. Found in bottles, cups, food and other containers; leaches on exposure to liquid and heating. Also in bullet-proof' materials, lenses/sunglasses, DVDs, iPod and computer cases, signs and displays, nylon.