Why it's Time to Revisit Your BPA Test Method

Evolving efforts to limit the health and environmental impact of endocrine-disrupting chemicals raise the performance bar for trace analysis

INTRODUCTION

For manufacturers and retailers across an expanding spectrum of market and industry sectors, the level of bisphenol A (BPA) in the products they make or sell is becoming not only an increasingly important measure of their commitment to consumer and environmental health and safety, but also a major compliance issue. An estrogen-like chemical that can interfere with hormonal function, BPA has long been a key component of the polycarbonate polymers and epoxy resins used to create the myriad thermoplastic products and thermosetting plastic materials that pervade modern life. Over the last two decades, the value of BPA as a source of desirable performance characteristics such as optical clarity; durability; and stain, odor, heat, and shatter resistance has gradually been overshadowed by its growing notoriety as an endocrine-disrupting food and environmental contaminant. While BPA remains the focus of a long-standing controversy surrounding the assessment of chemical toxicity, mounting pressure from consumer and environmental advocacy groups continues to drive ever tighter and more extensive government and industry limits on its use in food packaging and other plastic products. For product and environmental testing facilities, the technical and operational implications of this trend center around an increasingly urgent need: the development of test methods that can determine sub-ppb (parts-per-billion) levels of BPA, with a higher degree of certainty, without compromising laboratory efficiency and productivity.

WHY BPA IS A CHEMICAL OF INCREASING SCIENTIFIC CONCERN

Largely impossible to avoid in industrialized nations, exposure to BPA occurs in a variety of ways. The main culprit in human exposure is the food supply. BPA can migrate into food and beverages from plastic packaging and other polycarbonate and epoxy-based food contact articles and materials, including storage containers, disposable tableware, sports drink and water bottles, and the inner coating of cans and water supply pipes. The application of heat to plastic receptacles from microwaving or sun exposure, as well as contact with acidic foods or beverages, increases the rate of BPA migration. Small amounts of BPA can also pass into the human bloodstream from inhaled household dust, skin contact with cosmetics and thermal cash register and ATM receipts, and oral exposure to plastic pacifiers, teething rings, toys, and dental sealants. Ultimately most of these items devolve into trash and litter that together with plastic manufacturing waste release more than more 1 million pounds of BPA annually into the environment, where it can potentially contaminate vital natural resources, including groundwater, public reservoirs, and aquatic habitats.[1]

The results of more than 80 biomonitoring studies from several countries confirm that BPA exposure is virtually ubiquitous in the global population. The Centers for Disease Control and Prevention (CDC) estimate that more than 93 percent of the U.S. population have detectable levels of BPA in their bodies,[2] an occurrence rate consistent with the results of epidemiologic studies in other parts of the world.[3] Although the latest European Food Safety Authority (EFSA) estimates of average daily BPA exposure are quite low, ranging from 0.388 ppb for adults and 0.875 ppb for infants and toddlers to 1.449 ppb from all sources for adolescents,[3] a growing body of research suggests that very small amounts of endocrine disrupters like BPA can cause serious adverse health effects that don't occur at higher doses.[4] The scientific case for this seemingly paradoxical dose-response relationship draws from more than 800 laboratory, environmental, and epidemiologic studies that document a link between low-dose BPA exposure and serious health problems ranging from diabetes, obesity, heart disease, and reproductive and developmental disorders to breast and prostate cancer in lab animals, wildlife, and humans. Animal studies and physiologically based predictive models indicate that the risk of these effects is significantly heightened in newborns and very young children because of their limited capacity to detoxify and eliminate chemical contaminants, as well as their increased BPA exposure levels from frequent feedings.

In contrast, the long-held opinion of government and industry scientists that current BPA exposure levels are too low to pose any health risks derives from research based on the classic toxicological principle that "the dose makes the poison." In other words, the higher the dose, the greater the toxic impact. However, academic researchers who use increasingly advanced test methods to study BPA's subtler epigenetic and physiological effects argue that hormone-like chemicals frequently violate that rule, causing abnormalities at low doses that can't be predicted from the results of high-dose experiments. For instance, animal experiments have shown that fetal exposure to overtly toxic doses of endocrine-disrupting chemicals can result in severe shrinkage of the prostate gland while prenatal exposure to doses as low as 0.2 ppb can lead to significant prostate enlargement in adulthood.[5] Although U.S. government experts continue to dispute the strength of this evidence, they eventually stepped back from their outright dismissal of consumers' safety concerns in a widely published 2008 opinion from the U.S. Department of Health and Human Services' National Toxicology Program (NTP) that acknowledged the possibility that current BPA exposure levels might interfere with the neurological, behavioral, and reproductive development of fetuses, infants, and very young children.

THE CHANGING REGULATORY CLIMATE: WHICH WAY THE WIND IS BLOWING

U.S. government and industry efforts to reduce BPA exposure began on the heels of this 2008 report and remain a work in progress. Within days of the April 16th release of the NTP risk assessment and the April 18th passage of a Canadian law banning polycarbonate baby bottles, a number of major manufacturers announced plans to stop using BPA in their plastic baby products. Retail giants including Walmart and CVS followed suit by phasing out the sale of baby bottles that contained BPA. While the FDA maintained its stance that current BPA exposure levels present no risk to children or adults, state BPA regulations started to emerge in the United States in 2011. To date, 14 states have current or pending legislation prohibiting the use of BPA in an expanding array of child-care items and consumer goods. (See Table 1.) By 2012 the majority of U.S. manufacturers had voluntarily abandoned the use of BPA in baby bottles and toddlers' sippy cups. That same year, the FDA acceded to a request from the plastics industry to formally ban the chemical's use in plastic baby products to help reassure consumers that these items posed no harm to their children. California's Prop 65 began to list BPA as a reproductive toxicant in May 2015, instituting a maximum allowable dose level (MADL) of 3 ug/day for dermal exposure through contact materials such as paper and plastics. In addition, California's Health and Safety Code establishes an upper limit of 0.1 ppb BPA in infant formula, liquid, baby food, food contact material (FCM) bottles or cups for children aged 3 or younger.

Worldwide efforts to minimize the impact of BPA on human health, consumer confidence, and trade revenues continue to evolve toward ever tighter and broader control measures. (See Table 1.) Since banning BPA-containing baby bottles in 2011, the European Union (EU) has faced increasing pressure from individual member states to adopt more far-reaching restrictions on BPA, including a total phase-out of the chemical in food contact materials. In 2017 the European community took steps in that direction when the European Chemicals Agency agreed to proposals from France, Sweden, Denmark, and Austria to recognize BPA as a substance of very high concern (SVHC) and to recommend its addition to a list of compounds subject to the tight constraints imposed by the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulatory framework.

Canada's decision to officially classify BPA as a toxic chemical has likewise opened the way to more extensive regulations, including a proposal to restrict its use in infant formula cans. In the United States, the Environmental Protection Agency (EPA) has developed, but not yet implemented, an action plan that would include monitoring BPA levels in surface water, groundwater, soil, sediment, and landfills. Government and industry efforts to reduce the health and economic effects of BPA continue to emerge in other regions of the world, including Latin America and Asia. In fact, Japanese manufacturers became the forerunners of U.S. industry in voluntarily limiting the use of BPA, by beginning in 1998 to substitute alternative plastics for BPA-containing epoxy resins and polycarbonates in products such as can liners and tableware for school lunches.

Worldwide BPA Regulations[6, 7, 8, 9, 10, 11, 12, 13, 14]

Country	Products	Maximum Limits
Canada	Baby bottles	0
China	Baby bottles, sippy cups	0
EU	Baby bottles	0
	Migration from food contact materials	0.05 mg/kg of body weight daily
	Migration from plastic toys	40 ppb (effective 2018)
	Thermal paper receipts	0.20 percent BPA by weight (effective 2020)
Japan	Migration from food contact materials	2.5 ppm
Malaysia	Baby bottles, sippy cups	0
Mercosur (Argentina, Brazil, Paraguay, Uruguay, Venezuela, and Bolivia)	Baby bottles, sippy cups	0
South Africa	Products for young children	0
Turkey	Baby bottles	0
U.S. (FDA)	Migration limit for toys	100 pb
	Baby bottles, sippy cups, infant formula packaging	0
California	Baby bottles, sippy cups*	0
	Food and beverage packaging and other products that that contain BPA	Must post general warning about BPA at point-of-sale
	Solid materials such as paper and plastic that transmit BPA through dermal contact	3 ppb (products that exceed this ML must carry warning label) 0.1 ppb BPA in infant formula, liquid, baby food, food contact material (FCM) bottles or cups for children aged 3 or younger
Connecticut	Reusable food and beverage containers, infant formula or baby food containers, thermal receipt paper	0
Delaware	Baby bottles, sippy cups	0
Illinois	Children's food and beverage containers	0
Maine	Baby bottles, sippy cups, formula and baby food packaging; reusable food and beverage containers	0
Maryland	Childcare items, infant formula cans*	0
Massachusetts	Thermal receipt paper	0
Minnesota	Formula and children's food containers, sippy cups*	0
Mississippi	Food and liquid containers	0
Nevada	Bottles, sippy cups, formula, and kid's food containers	0

Country	Products	Maximum Limits
New Jersey	Infant products, food and beverage packaging, and containers	0
New York	Children's products (including toys and childcare items),* thermal receipt paper, food and beverage containers, pet products†	0
North Carolina	Children's products	0
Pennsylvania	Food and beverage containers*	0
Rhode Island	Packaging for children's food, reusable food and beverage containers‡	0
Vermont	Formula and baby food jars, reusable food and beverage containers	0
Washington	Children's food and beverage containers (except metal cans), reusable water bottles	0
Wisconsin	Baby bottles and sippy cups	0

**Requires replacement with least toxic alternative.*

†Allows BPA-free products to be labeled as such.

‡Requires labeling of all food packaging that contains BPA and prohibits replacement with toxic alternatives.

HOW ADVANCES IN BPA TESTING CAN HELP LABORATORIES MEET EVOLVING DEMANDS

As the trend toward zero tolerance for BPA spreads across governments and consumer markets, laboratories that monitor the safety of plastic food contact materials, or drinking and environmental water sources, need to continuously improve the quality of their analytic data. "To obtain BPA test results that consistently meet the highest standards of statistical reliability and validity, laboratories need to invest in an instrumental method that's specifically designed for the challenges of determining vanishingly small concentrations of target analytes in complex matrices," said Lingyun Chen, Director of Research and Development at the Massachusetts-based test developer VICAM,™ A Waters Business.

"The current instrument of choice for this type of application combines the power of two highly sensitive and selective analytic techniques, liquid chromatography and mass spectrometry," Chen said. The superior performance of LC-MS lies in its use of multiple criteria, including physio-chemical properties, molecular weight, and structural characteristics, to unambiguously identify target analytes, and precisely measure their concentrations in samples. For laboratories faced with growing demand for increased throughput and shorter turnaround times, LC-MS also provides a major advantage over gas chromatography coupled with mass spectrometry (GC-MS) by eliminating the need for a lengthy and complicated derivatization process. Although somewhat less sensitive and specific than LC-MS, other highly efficient laboratory instrumental techniques such as high and ultrahigh performance liquid chromatography (HPLC and UPLC) instruments equipped with fluorescence detectors are good alternatives that require less specialized training, as well as a smaller capital investment.

Regardless of the instrumental technique used, one of the biggest obstacles to accuracy and precision is the presence of co-eluting matrix components in the test sample that interfere with the intensity of the BPA measurement signal. With LC-MS, for example, matrix components that pass through the chromatography column at the same rate as the target analyte can either suppress or enhance the ion signal from the mass detector, resulting in a high rate of false negatives or false positives. The simplest approach to mitigating this problem is to reduce the concentration of matrix materials by diluting the sample. This method (commonly known as "dilute-and-shoot") saves time and labor by forgoing multi-stage sample preparation. These benefits, however, are often outweighed by the inherent difficulty of determining extremely low but potentially significant BPA levels in matrices such as food, beverages, and drinking and environmental waters. The higher the dilution factor required to compensate for the effects on the detector response of proteins, sugars, volatile organic compounds, or other organic components of the sample in question, the greater the risk that the sample's diminished concentration of BPA will reduce sensitivity and increase the limit of detection to the point where it undermines the precision and reproducibility of test results.

The pitfalls of dilute and shoot exemplify why even the most powerful instruments require an extra measure of optimization to consistently achieve limits of detection low enough to confidently determine the ultra-trace levels of BPA likely to migrate from plastic packaging and containers. To attain this goal, the most reliable instrumental test methods typically begin the analytic process with sample cleanup procedures that minimize matrix interference while increasing the concentration of the target analyte.

Solid Phase Extraction (SPE) is one common approach used for sample cleanup that is both low cost and often simple to use. It is useful to consider the needs of the food testing laboratory, however, for throughput, sustainability, efficiency, and performance for the specific isolation and quantification of Bisphenol A in various sample matrices, from plastic food packaging materials to finished edible products intended for supermarket shelves.

BPA immunoaffinity (IA) columns offer a faster, simpler alternative that capitalizes on the same technology that revolutionized the ultra-trace analysis of other food and environmental contaminants, including bacteria, mycotoxins, and pesticides. The development of highly selective monoclonal antibodies to extract target analytes from complex matrices represented a major step forward for laboratories and businesses striving to adapt to an increasingly stringent regulatory environment.

"Sample cleanup with IA before LC-MS analysis brings together the most sensitive and specific instrumental technique with a proven approach to maximizing recovery of target analytes, while minimizing matrix interferences." said Chen. "This method provides laboratories and their clients with double insurance of accurate, precise determination of minute concentrations of BPA." The proprietary monoclonal antibody technology used in VICAM's BPA cleanup columns, for example, delivers the same performance advantages that have earned the company's line of mycotoxin test kits official validation by government agencies and international standards organizations such as USDA-GIPSA and AOAC International. VICAM's BPA IA columns provide greater gains in sensitivity and specificity than conventional SPE columns, lowering the limits of detection and quantitation established by AOAC, and achieving recovery rates of greater than 86 percent. These benefits are complemented by the test kit's speed and ease of use. The simplicity of this method greatly reduces the risk of procedural errors and enables lab personnel with no special training to isolate BPA from matrix components in as little time as 10 minutes. IA column cleanup also helps lower spending on reagents, and hazardous waste disposal, and reduces the environmental footprint of testing by minimizing the use of organic solvents.

THE ROI OF LOWER LODS

While the direction of regulatory trends may shift as new political regimes, economic conditions, or trade policies come into play, the public mindset toward product and environmental safety issues is a lot harder to change. Ever since Rachel Carson's 1962 bestseller, "Silent Spring," sparked a nationwide campaign to ban the use of the endocrine- disrupting pesticide DDT, people around the globe have grown increasingly wary of the impact of synthetic chemicals on their own well-being, the health and development of their children, and the sustainability of the planet. Whether a facility serves private sector businesses, consumer or environmental safety organizations, or government agencies, the most valuable commodity that testing laboratories provide is the promise that the products people buy pose no threat to human health, or Earth's natural resources, now or for future generations. That promise is only as credible as the test methods a laboratory uses to detect and measure ever shrinking levels of potentially harmful contaminants.

References

1. "Risk Management for Bisphenol A (BPA)," Assessing and Managing Chemicals under TSCA website, https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-bisphenol-bpa (accessed September 10, 2017).
2. "Bisphenol A, (BPA)," Report from National Institute of Environmental Sciences, https://www.niehs.nih.gov/health/topics/agents/sya-bpa/index.cfm (Accessed September 10, 1971).
3. Laura N. Vandenberg, et al, "Urinary, Circulating, and Tissue Biomonitoring Studies Indicate Widespread Exposure to Bisphenol A," *Environmental Health Perspectives*, August 2010, pp. 1055–1070 (Published online March 24, 2010). doi: 10.1289/ehp.0901716.
4. Elizabeth Kolbert, "A Warning from Key Researcher on the Risks of BPA on Our Lives," Yale Environment 360, Yale University of Forestry and Environmental Studies, http://e360.yale.edu/features/a_warning_by_key_researcher_on_risks_of_bpa_in_our_lives (Accessed September 10, 2017).
5. WV Welshons, et al, "Large Effects from Small Exposures. I. Mechanisms for Endocrine Disrupting Chemicals with Estrogenic Activity," *Environmental Health Perspectives*, 2003, 111: 994–1006.
6. Bisphenol A (BPA), Government of Canada, https://www.canada.ca/en/health-canada/services/home-garden-safety/bisphenol-bpa.html (Accessed September 10, 2017).
7. International Baby Food Action Network (IBFAN) website, http://ibfan.org/stop-press-bpa-sept-2012 (Accessed September 10, 2017).
8. "EU Moves to Strengthen BPA Migration in Certain Toys," SGS website, http://www.sgs.com/en/news/2016/07/safeguards-13316-eu-proposes-to-strengthen-bpa-migration-in-certain-toys (Accessed September 10, 2017).
9. "EU Includes BPA Restriction in Thermal Paper under REACH Annex XVII," Chemical Inspection and Regulation Service (CIRS) website, http://www.cirs-reach.com/news-and-articles/EU-Includes-BPA-Restriction-in-Thermal-Paper-under-REACH-Annex-XVII.html (Accessed September 10, 2017).
10. Bisphenol A, Food Safety Watch website, http://www.foodsafetywatch.org/factsheets/bisphenol-a/ (Accessed September 10, 2017).
11. "Mercosur Further Aligning FCM Rules with EU US, Law," Chemical Watch website, https://chemicalwatch.com/23941/mercosur-further-aligning-fcm-rules-with-eu-us-laws (Accessed September 10, 2017).
12. What Are the Food Contact Requirement in South Africa?, PackagingLaw.com website, http://www.packaginglaw.com/ask-an-attorney/what-are-food-contact-requirements-south-africa (Accessed September 10, 2017).
13. Heather Caliendo, "History of BPA, *Packaging Digest*, http://www.packagingdigest.com/food-safety/history-bpa (Accessed September 10, 2017).
14. Bisphenol A, Safer States website, http://www.saferstates.org/toxic-chemicals/bisphenol-a/ (Accessed September 10, 2017).

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