

Bisphenol A: The Breast Cancer Hope Review & Discussion of Health and Regulatory Implications

UMAR WAZIR and KEFAH MOKBEL

The London Breast Institute, Princess Grace Hospital, London, UK;

Correspondence to: *Professor Kefah Mokbel, London Breast Institute, the Princess Grace Hospital, 45*

Nottingham Place, London W1U 5NY, UK. E-mail: kefahmokbel@hotmail.com

Abstract

Background: Bisphenol A (BPA) is a ubiquitous substance found in a wide array of consumer products and healthcare consumables, which is present at low doses in drinking water. Currently, in the UK, it is classed as a low-risk substance with little potential for harm. It has been known to have effects on oestrogen receptors. The implications this has for public safety is currently subject to debate.

Methodology: In this study, we shall review the recent literature regarding the effects and safety of BPA, and discuss the potential implications, in particular from the perspective of human breast oncogenesis. **Results and Conclusion:** Recent evidence suggests that low-doses of endocrine disruptors, such as BPA, could have profound effects in breast development and cancer risk. Recent studies in murine models suggest that BPA could contribute to breast oncogenesis via several pathways. The position of regulators should shift accordingly to safeguard the public interest.

Key Words: Breast cancer; oncogenesis; Bisphenol A; toxins; endocrine disruption.

Introduction

Bisphenol A (BPA) is a near-ubiquitous substance in today's world. It is widely used for the manufacture of epoxy resins, which are found in the protective lining of plastic food containers, healthcare equipment, steel drums and pipes. BPA is a food contact material, and is thus practically ubiquitous in household kitchenware and in canned food items. BPA-based epoxy resins are also widely used for their adhesive properties [1].

BPA is also important in the production of polycarbonate plastics, and is thus found in eye-ware, optical devices and medical equipment. BPA is also an additive in the manufacture of polyvinyl chloride plastics, which have wide applications in healthcare consumables, piping, wire insulation and construction materials [1,2].

The annual world production of BPA for 2009 was at least 2.2 million tonnes, with the USA producing a fifth of the total [1]. BPA was discovered in 1891, and has been in mass production since at least the interwar era [3]. Consequently, BPA has permeated our ecosystem, making human exposure to BPA near-universal. Calafat *et al.* have found that 93% of Americans above the age of six had detectable levels of BPA in their urine [4]. Arnold *et al.* found the maximum quantified BPA concentration in European drinking water to be 0.014 µg/l. They were also at pains to note that the exposure levels observed were well below the stated toxic thresholds for BPA [5]. This coincides with the current position of the Food and Safety Agency (FSA) of the UK [6].

Endocrine Disrupting Chemicals

The endocrine effects of BPA have been known since the 1930s. In comparison to other substances studied at the time, the oestrogen affinity of BPA was relatively weak. Unlike, for instance, diethylstilbestrol (DES), BPA never found a commercial role as a synthetic oestrogen [3]. However, since the 1980s, there has been concerns regarding the endocrine effects of BPA, especially since the ban of DES in 1979, after it was implicated in the causation of uterine tumours in young

women who were exposed *in utero* to DES [7]. The issues surrounding DES had identified molecules with endocrine effects to be of specific interest regarding oncogenesis. BPA has been evaluated as one such endocrine disruptor chemicals (EDC) [8]. In a commentary on reviews on the effect of BPA at the toxic thresholds recognised at the time, vom Saal *et al.* observed that a plurality of studies they reviewed shown effects due to BPA at significantly below the stated safety threshold. Furthermore, they noted that there was a discernible effect of funding source on the results of the studies. More than 90% of government-funded studies shown BPA to have effects at low dose, while industry-funded studies shown no effects [9].

Low-dose toxicity

Since then, there have been multiple studies regarding the effects of BPA. In a review of murine studies, Wang *et al.* found a preponderance of evidence for BPA as a potential causative agent for breast, uterine, ovarian, liver, testes, and prostate cancers at toxic doses. However, they also collated a significant body of studies showing potential breast oncogenesis at low doses (<25 µg/kg/day) [10]. This is consistent with the findings of Vandenburg *et al.* of a dose-dependent response of mammary budding to xeno-oestrogens in murine models. Specifically, they found that low to moderate doses of oestrogens induced duct and bud growth in murine breast tissue, while this was inhibited in higher doses [11].

In recent *in vitro* studies by Williams *et al.*, breast cancer cell lines were exposed to low levels of EDCs, including BPA. These levels were intended to simulate the exposure due to environmental contamination. The cell lines incubated with the low doses of BPA exhibited increased mRNA expression of aromatase, increased synthesis of 17β-estradiol, and increased proliferation of ER positive cells [12].

Furthermore, Sprague *et al.* found a positive association between serum BPA levels and mammographic breast density in post-menopausal women. They found mammographic breast

density to increase from 12% to 17% when serum BPA levels increased from undetectable to .055 ng/ml [13]. This has significant implications for cancer risk, as mammographic breast density is an independent predictor of breast cancer risk [14]. A 5 percent increase of density, as reported in relation to BPA exposure, is believed to increase the risk of breast cancer by 5-10% [15].

Similar findings were reported by Binder et al., who found a positive association between urinary levels of EDCs and mammographic breast density in adolescent females, with a difference in mammographic breast density of 7% seen between patients with the highest and lowest urinary levels of EDCs. The authors speculate that these effects may impact breast cancer risk later on in life [16].

These findings are in keeping with the observation that exposure to environmental stimuli at key points in human development could increase the risk of various pathologies later in life, including cancer [17]. Pertinent to human breast cancer, exposure to radiation or EDCs during puberty, in pregnancy or *in utero* are believed to be at an increased risk of developing breast cancer later on in life. This risk has been better characterised in the case of DES, in which *in utero* exposure had led to a higher risk of several neoplastic diseases, including breast cancer [18,17].

In the absence of adequately powered epidemiological studies, evidence derived from *in vitro* and *in vivo* studies and human studies using surrogate markers for breast cancer such as breast density become critical. These findings make the low but ubiquitous ambient exposure to EDCs such as BPA all the more a cause for concern. Additionally, recent studies have posited that BPA may induce oncogenic pathways other than those related to hormone receptors, including those pertaining to stem cell differentiation [19], DNA repair [20], and immunomodulation [21].

Furthermore, it has been found that despite a limited half-life, BPA accumulates in adipose tissue in its active unconjugated form [13,22]. This could serve as a continuous source of exposure in humans, which cannot be effectively modelled for in murine models. It would not be unreasonable to expect exposure to and effects of BPA to be worse than that predicted by murine studies [4].

This accumulation of evidence has led to mounting concerns within the market and at the regulatory level. BPA-free products are currently being offered [2], and certain regulators have revised their previous rulings regarding BPA. A full ban was considered in France [23]. Most recently, the US National Toxicology Programme has concluded its study on the effects of BPA, and shall be publishing their final report in the fall of 2019 [24].

Safer alternatives to BPA have been developed. For example, syringaresinol has been characterised as a renewable and safer alternative to BPA in the manufacture of epoxy resins. Such alternatives make the phasing out of BPA from consumer goods feasible [25].

Conclusion

In view of the developments in our understanding of the effects of low-dose xeno-oestrogens, it is imperative that measures should be taken to curb further cancer risk to our populations. BPA, and indeed other EDCs, should be phased out as soon as feasible. The full extent of their effects is difficult to predict, and what we have determined is highly suggestive of an increased risk of human oncogenesis, including breast cancer. It would be imperative to phase out BPA from use in the manufacture of consumer and healthcare goods in favour of safer alternatives [25].

Compliance with Ethical Standards

Funding

This study was funded by grants from the Breast Cancer Hope Foundation (London, UK; Grant #2018-12).

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

This article does not contain any studies with human participants performed by any of the authors.

Disclosure of Potential Conflicts of Interest

UW declares that he has no conflict of interest.

KM declares that he has no conflict of interest.

References

1. Konieczna A, Rutkowska A, Rachon D (2015) Health risk of exposure to Bisphenol A (BPA). *Rocz Panstw Zakl Hig* 66 (1):5-11
2. Vogel SA (2009) The politics of plastics: the making and unmaking of bisphenol a "safety". *Am J Public Health* 99 Suppl 3:S559-566. doi:10.2105/AJPH.2008.159228
3. Dodds E, Lawson W (1936) Synthetic oestrogenic agents without the phenanthrene nucleus. *Nature* 137 (3476):996
4. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL (2008) Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect* 116 (1):39-44. doi:10.1289/ehp.10753
5. Arnold SM, Clark KE, Staples CA, Klecka GM, Dimond SS, Caspers N, Hentges SG (2013) Relevance of drinking water as a source of human exposure to bisphenol A. *J Expo Sci Environ Epidemiol* 23 (2):137-144. doi:10.1038/jes.2012.66
6. BPA in plastic. . (2018) Food Safety Agency (UK). <https://www.food.gov.uk/safety-hygiene/bpa-in-plastic>. Accessed 1st of May, 2019 2019
7. Hutt P (1982) Regulatory history of DES. *Am Stat* 36 (3):267
8. Rochefort H (2017) Endocrine disruptors (EDs) and hormone-dependent cancers: Correlation or causal relationship? *C R Biol* 340 (9-10):439-445. doi:10.1016/j.crv.2017.07.007
9. vom Saal FS, Hughes C (2005) An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ Health Perspect* 113 (8):926-933. doi:10.1289/ehp.7713
10. Wang Z, Liu H, Liu S (2017) Low-Dose Bisphenol A Exposure: A Seemingly Instigating Carcinogenic Effect on Breast Cancer. *Adv Sci (Weinh)* 4 (2):1600248. doi:10.1002/advs.201600248

11. Vandenberg LN, Wadia PR, Schaeberle CM, Rubin BS, Sonnenschein C, Soto AM (2006) The mammary gland response to estradiol: monotonic at the cellular level, non-monotonic at the tissue-level of organization? *J Steroid Biochem Mol Biol* 101 (4-5):263-274. doi:10.1016/j.jsbmb.2006.06.028
12. Williams GP, Darbre PD (2019) Low-dose environmental endocrine disruptors, increase aromatase activity, estradiol biosynthesis and cell proliferation in human breast cells. *Mol Cell Endocrinol* 486:55-64. doi:10.1016/j.mce.2019.02.016
13. Sprague BL, Trentham-Dietz A, Hedman CJ, Wang J, Hemming JD, Hampton JM, Buist DS, Aiello Bowles EJ, Sisney GS, Burnside ES (2013) Circulating serum xenoestrogens and mammographic breast density. *Breast cancer research : BCR* 15 (3):R45. doi:10.1186/bcr3432
14. Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S (2010) Breast tissue composition and susceptibility to breast cancer. *J Natl Cancer Inst* 102 (16):1224-1237. doi:10.1093/jnci/djq239
15. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ (1995) Quantitative Classification of Mammographic Densities and Breast Cancer Risk: Results From the Canadian National Breast Screening Study. *JNCI Journal of the National Cancer Institute* 87 (9):670-675. doi:10.1093/jnci/87.9.670
16. Binder AM, Corvalan C, Pereira A, Calafat AM, Ye X, Shepherd J, Michels KB (2018) Prepubertal and Pubertal Endocrine-Disrupting Chemical Exposure and Breast Density among Chilean Adolescents. *Cancer Epidemiol Biomarkers Prev* 27 (12):1491-1499. doi:10.1158/1055-9965.EPI-17-0813
17. Biro FM, Deardorff J (2013) Identifying opportunities for cancer prevention during preadolescence and adolescence: puberty as a window of susceptibility. *J Adolesc Health* 52 (5 Suppl):S15-20. doi:10.1016/j.jadohealth.2012.09.019
18. Teitelbaum SL, Belpoggi F, Reinlib L (2015) Advancing research on endocrine disrupting chemicals in breast cancer: Expert panel recommendations. *Reprod Toxicol* 54:141-147. doi:10.1016/j.reprotox.2014.12.015
19. Lillo MA, Nichols C, Seagroves TN, Miranda-Carboni GA, Krum SA (2017) Bisphenol A Induces Sox2 in ER(+) Breast Cancer Stem-Like Cells. *Horm Cancer* 8 (2):90-99. doi:10.1007/s12672-017-0286-5

20. Langie SA, Koppen G, Desaulniers D, Al-Mulla F, Al-Temaimi R, Amedei A, Azqueta A, Bisson WH, Brown DG, Brunborg G, Charles AK, Chen T, Colacci A, Darroudi F, Forte S, Gonzalez L, Hamid RA, Knudsen LE, Leyns L, Lopez de Cerain Salsamendi A, Memeo L, Mondello C, Mothersill C, Olsen AK, Pavanello S, Raju J, Rojas E, Roy R, Ryan EP, Ostrosky-Wegman P, Salem HK, Scovassi AI, Singh N, Vaccari M, Van Schooten FJ, Valverde M, Woodrick J, Zhang L, van Larebeke N, Kirsch-Volders M, Collins AR (2015) Causes of genome instability: the effect of low dose chemical exposures in modern society. *Carcinogenesis* 36 Suppl 1:S61-88. doi:10.1093/carcin/bgv031
21. Casey SC, Vaccari M, Al-Mulla F, Al-Temaimi R, Amedei A, Barcellos-Hoff MH, Brown DG, Chapellier M, Christopher J, Curran CS, Forte S, Hamid RA, Heneberg P, Koch DC, Krishnakumar PK, Laconi E, Maguer-Satta V, Marongiu F, Memeo L, Mondello C, Raju J, Roman J, Roy R, Ryan EP, Ryeom S, Salem HK, Scovassi AI, Singh N, Soucek L, Vermeulen L, Whitfield JR, Woodrick J, Colacci A, Bisson WH, Felsher DW (2015) The effect of environmental chemicals on the tumor microenvironment. *Carcinogenesis* 36 Suppl 1:S160-183. doi:10.1093/carcin/bgv035
22. Fernandez MF, Arrebola JP, Taoufiki J, Navalon A, Ballesteros O, Pulgar R, Vilchez JL, Olea N (2007) Bisphenol-A and chlorinated derivatives in adipose tissue of women. *Reprod Toxicol* 24 (2):259-264. doi:10.1016/j.reprotox.2007.06.007
23. Rochefort H, Jouannet P (2011) Rapport complet de l'Académie de médecine sur perturbateurs endocriniens, www.academie-medecine.fr. Endocrine disruptors and hormone-dependent cancers. *Bull Acad Natl Med* 195 (8):1965–1979
24. NTP CLARITY-BPA. National Toxicology Program (NTP). <https://manticore.niehs.nih.gov/cebssearch/program/CLARITY-BPA>.
25. Janvier M, Hollande L, Jaufurally AS, Pernes M, Menard R, Grimaldi M, Beaugrand J, Balaguer P, Ducrot PH, Allais F (2017) Syringaresinol: A Renewable and Safer Alternative to Bisphenol A for Epoxy-Amine Resins. *ChemSusChem* 10 (4):738-746. doi:10.1002/cssc.201601595