Reproductive Toxicology 59 (2016) 167–182

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

A review of the carcinogenic potential of bisphenol A

Darcie D. Seachrist[a,1], Kristen W. Bonk[a,1], Shuk-Mei Ho[b], Gail S. Prins[c], Ana M. Soto[d], Ruth A. Keri[a,*]

[a] Department of Pharmacology, Case Western Reserve University, Cleveland, OH 44106-4965, USA
[b] Department of Environmental Health, University of Cincinnati, Cincinnati, OH 45267-0056, USA
[c] Departments of Urology, Physiology and Biophysics, University of Illinois, Chicago, IL 60612-7310, USA
[d] Department of Integrative Physiology and Pathobiology, Tufts University, Boston, MA 02111, USA

ARTICLE INFO

Article history:
Received 21 April 2015
Received in revised form 9 September 2015
Accepted 18 September 2015
Available online 19 October 2015

Keywords:
Bisphenol A
Cancer
Mammary
Prostate
Uterus
Ovary
Estrogen receptor
Testes

ABSTRACT

The estrogenic properties of bisphenol A (BPA), a ubiquitous synthetic monomer that can leach into the food and water supply, have prompted considerable research into exposure-associated health risks in humans. Endocrine-disrupting properties of BPA suggest it may impact developmental plasticity during early life, predisposing individuals to disease at doses below the oral reference dose (RfD) established by the Environmental Protection Agency in 1982. Herein, we review the current *in vivo* literature evaluating the carcinogenic properties of BPA. We conclude that there is substantial evidence from rodent studies indicating that early-life BPA exposures below the RfD lead to increased susceptibility to mammary and prostate cancer. Based on the definitions of "carcinogen" put forth by the International Agency for Research on Cancer and the National Toxicology Program, we propose that BPA may be reasonably anticipated to be a human carcinogen in the breast and prostate due to its tumor promoting properties.

Contents

Abbreviations: BPA, bisphenol A; ER, estrogen receptor-α; PND, postnatal day; GD, gestational day; ED, embryonic day; DES, diethylstilbestrol.

* Corresponding author at: Department of Pharmacology, Case Western Reserve University, School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106-4965, USA. Fax: +1 216 368 1300.
E-mail address: keri@case.edu (R.A. Keri).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.reprotox.2015.09.006
0890-6238/

1. Introduction

Incidence and prevalence of cancers of endocrine target organs, including prostate, breast, and testis, as well as other diseases such as infertility and obesity began steadily increasing in the 1970's and reached an elevated plateau in 2002 [1,2]. The incidence of breast cancer increased by 26% during this time period, while prostrate and testicular cancers increased by 94 and 56%, respectively. Increased exposure to environmental synthetic estrogens, such as BPA, has been postulated to contribute, in part, to this increasing incidence [3,4]. BPA is a synthetic monomer used in the production of polycarbonate plastics, epoxy resin linings of canned foods and beverage containers, dental sealants, and thermal receipt paper. In 2003, more than 6 billion pounds of BPA were produced worldwide [5], and production is expected to exceed 5.4 million tons this year (for detailed international market analysis, see Bisphenol A (BPA): 2015 World Market Outlook and Forecast up to 2019 from mcgroup.co.uk). The United States Environmental Protection Agency (EPA) estimates that over 1 million pounds of BPA leaches into the environment each year and over 90% of tested humans have detectable BPA in their systems with the highest levels found in infants and children [6–11].

BPA is an estrogenic compound [12]. It has a similar structure as the highly potent estrogen receptor (ER) agonist, diethylstilbestrol (DES), and binds classical nuclear ER alpha and beta, as well as membrane-associated GPR30, (Fig. 1) albeit with lower affinity [13]. Thus, BPA is expected to have effects on ER function in addition to other nuclear hormone receptors and most of the studies on BPA action have focused on hormone sensitive tissues. The ubiquitous presence of BPA in the environment, concomitant with the increased prevalence of endocrine-related cancers, has led to numerous studies evaluating the role of BPA in carcinogenesis. In 1982, the National Toxicology Program (NTP) conducted a toxicology analysis and concluded that while pharmacological doses of BPA induced some cancers in both male and female adult rodents, it was not a robust carcinogen at doses relevant to human exposure [14,15]. Hence, the EPA and the U.S. Food and Drug Administration established a safe reference dose (RfD) for humans at 50 μg/kg/day, based on a 1000-fold reduction of the dose used in the NTP study (www.epa.gov/iris/subst/0356.htm). While dose scaling is valid for agents that follow linear dose-response relationships, many endocrine-disruptors, like their endogenous hormonal counterparts, demonstrate a non-monotonic dose-response curve. In this case, lower doses are as relevant as higher doses [16–18]. In addition, cancer susceptibility may be established during fetal and postnatal organ development and exposure during these times was not assessed by the NTP study. During various developmental windows, tissues are finely attuned to endocrine input for establishing tissue architecture. Altering this milieu can predispose individuals to diseases manifested later in life (reviewed in [19]). BPA has been measured in maternal serum and ovarian follicular fluid, as well as in amniotic fluid and fetal plasma, indicating passage across the placenta during pregnancy [20,21]. Furthermore, studies in primate and rodent fetuses and newborns suggest that the liver has a limited ability to metabolize BPA, creating the potential for BPA to be detrimental during critical developmental stages [22,23]. Given these limitations, the impact of BPA on sex-steroid responsive organs required additional study beyond the NTP analysis.

RTI International conducted a study sponsored by the Polycarbonate/BPA Global Group, an organization that promotes the interests and welfare of the major manufacturers of polycarbonate plastic and BPA, to evaluate the effects of early life BPA exposures on multiple reproductive parameters utilizing the rat strain, Crl:CD(SD), derived from Sprague-Dawley by Charles River Laboratories. [24]. The three-generation study revealed no increase in cancer of any organ system examined with chronic BPA exposure from gestation through adulthood at both low (0.001–5 mg/kg/day) and high doses (50–500 mg/kg/day) [24]. While these data suggest that fetal BPA exposure does not increase cancer incidence, limitations of the study included use of an animal model that is resistant to endocrine disruption and a narrow selection of organs analyzed. Additionally, animals were examined in young adulthood (3–4 months of age) prior to when cancer endpoints are typically observed without a carcinogenic challenge [17,25]. In an attempt to address some of these concerns, RTI conducted a subsequent two-generation study utilizing CD-1 mice, estrogen treatment as a positive control, and low-doses of BPA (0.003–600 mg/kg/day) from gestation through adulthood [26]. While histopathological analysis revealed no cancer in any tissue examined, animals were only aged ~15–20 weeks, a time point too early for most cancers to become evident. Further, the mice displayed a relative insensitivity to estrogen compared to other studies as well as other strains, diminishing the ability to make strong conclusions regarding the effects of low doses of BPA [26,27]. Indeed, many studies on the reproductive effects of BPA exposure continue to report dichotomous results due to disparity in the use of animal models, dose, timing, and route of exposure [28–30].

The debate over the health risk of BPA exposure spurred the National Institutes of Health (NIEHS, NIDCR) and the EPA to assemble a panel of experts in endocrine-disruption to review the literature and compile a consensus report evaluating the association between BPA exposure and human health risk. As a result of this meeting, we extensively reviewed the weight of evidence for the carcinogenicity of BPA in 2007. Based on the scientific evidence at that time, we were confident that BPA displayed estrogenic properties and acted as an endocrine-disruptor [28]. We also concluded that BPA was likely to be associated with increased malignancies of the testes and hematopoietic system and increased susceptibility to neoplastic lesions in mammary and prostate glands following early-life exposures. However, insufficient data on tumor formation in response to BPA *in vivo*, coupled with vastly varying experimental designs, precluded conclusions specifically on the carcinogenic impact of BPA. The review panel then established guidelines to address these discrepancies with the purpose of firmly addressing BPA-induced health risks using environmentally relevant doses, often referred to as 'low doses' or doses below the LOAEL (50 mg/kg/day). These guidelines have since been followed by numerous groups evaluating the carcinogenic impact of BPA, resulting in an expansion of our understanding of the effects of this endocrine disruptor.

Herein, we present an updated analysis of the weight of evidence for the carcinogenicity of BPA. Studies using BPA doses at or below the RfD (50 μg/kg/day) are given greater weight and are considered here as 'low dose' because they more closely model the most conservative estimates of environmentally relevant BPA exposures and the RfD is the dose considered "safe" by the EPA and the U.S. Food and Drug Administration. While we refer to all other BPA doses as