Food and Chemical Toxicology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Invited Review

A systematic review of Bisphenol A "low dose" studies in the context of human exposure: A case for establishing standards for reporting "low-dose" effects of chemicals

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ARTICLE INFO

Article history:
Received 5 April 2013
Accepted 1 July 2013
Available online xxxx

Keywords:
Bisphenol A
Exposure
Risk
Low-dose

ABSTRACT

Human exposure to the chemical Bisphenol A is almost ubiquitous in surveyed industrialized societies. Structural features similar to estrogen confer the ability of Bisphenol A (BPA) to bind estrogen receptors, giving BPA membership in the group of environmental pollutants called endocrine disruptors. References by scientists, the media, political entities, and non-governmental organizations to many toxicity studies as "low dose" has led to the belief that exposure levels in these studies are similar to humans, implying that BPA is toxic to humans at current exposures. Through systematic, objective comparison of our current, and a previous compilation of the "low-dose" literature to multiple estimates of human external and internal exposure levels, we found that the "low-dose" moniker describes exposures covering 8–12 orders of magnitude, the majority (91–99% of exposures) being greater than the upper bound of human exposure in the general infant, child and adult U.S. Population. "low dose" is therefore a descriptor without specific meaning regarding human exposure. Where human exposure data are available, for BPA and other environmental chemicals, reference to toxicity study exposures by direct comparison to human exposure would be more informative, more objective, and less susceptible to misunderstanding.

1. Introduction

Bisphenol A (BPA) is a high production volume monomer used for making a wide variety of polycarbonate plastics and resins used in dental sealants and as liners for food packaging (Tyl et al., 2002), all of which are formed from polymerization of BPA. In some cases, these products contain minute amounts of unreacted monomeric BPA, which can leach from the material and come into contact with or be ingested by humans (Geens et al., 2010; Yonekubo et al., 2008). Human exposure to BPA is frequent and widespread. In industrial nations where biomonitoring has been conducted—e.g. the United States, Germany, and Canada—greater than ninety percent of individuals have measurable amounts of BPA in urine (Bushnik et al., 2010; Calafat et al., 2008; Koch et al., 2012; Lakind et al., 2012). Ingestion of BPA from food is the predominant route of exposure, accounting for 90–99% of exposure in adults and children (Morgan et al., 2011; Wilson et al., 2007; World Health Organization and Food and Agriculture Oranization of the United Nations, 2011).

The BPA molecule has structural features that are similar to 17β-estradiol and other natural estrogenic compounds found in food (e.g. daidzein in soy products) that confer the ability to bind to estrogen receptors when present in high enough concentrations (Hu and Aizawa, 2003). The potential to disrupt normal estrogen-dependent physiology gives BPA membership in the group of environmental pollutants called endocrine disruptors (Degen and Bolt, 2000; Takayanagi et al., 2006). At sufficiently high exposures, BPA can disrupt normal physiology in rodents, non-human primates, and cell culture test systems (Chapin et al., 2008). Public concern over BPA exposure has been amplified by associative studies showing relationships between BPA exposure and increased body mass index (Carwile and Michels, 2011; Wang et al., 2012b), cardiovascular disease (Melzer et al., 2010), behavior (Braun et al., 2011), and other effects in humans, though recent analyses suggest no relationships (Lakind et al., 2012). Although the U.S. EPA (United States Environmental Protection Agency, 1993), the U.S. Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) (European Food Safety Association, 2006), and the Japanese

Abbreviations: BPA, the unmetabolized Bisphenol A molecule; Total BPA, the sum of BPA and its metabolites; NHANES, National Health and Nutrition Examination Survey; EFSA, European Food Safety Authority; LOAEL, Lowest Observable Effect Level; NTP, National Toxicology Program; CHMS, Canadian Health Measures Survey; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.fct.2013.07.007

Institute of Advanced Industrial Science and Technology (Japanese National Institute of Advanced Industrial Science and Technology, 2011) have concluded that human exposure to BPA is below safe exposure levels, some states have banned selected uses of BPA and consumers now see the result of manufacturers moving away from the material in the form "BPA-Free" labeling on products.

At the center of the controversy regarding human exposure to BPA are two competing positions, one holds that a significant body of toxicity data collected at "low-doses" implies current human exposure levels are sufficient to cause toxicity (Vandenberg et al., 2010), and the other holds that human BPA exposures are much lower than exposures consistently causing effects in animal test systems (Dekant and Volkel, 2008; Teeguarden et al., 2011).

"Low-dose" has become a widely used moniker referring to a sub-group of toxicity studies for BPA and other chemicals that have been conducted in an exposure range putatively more informative about potential health effects in humans (Vandenberg et al., 2012) than other higher exposure studies. The label has been a driver of public and political interest.

What is "low-dose?" The answer to this question has significant implications for the current BPA controversy, and by extension, to any environmental pollutant subject to the same extensive lay and scientific scrutiny. The objective of this research was to conduct a systematic, objective, and quantitative comparison of exposures used in "low dose" BPA studies to human external and internal exposures. The assessment clarifies the relevance of the "low-dose" literature to human health assessments, emphasizes the importance of sound human exposure data, and highlights a compelling need for more objective reporting of "low-dose" toxicity data.

2. Methods

2.1. Tabulation of published "low dose" study exposures

To retrieve and objectively review the current "low dose" BPA toxicology literature, a PubMed search was conducted March 5, 2013. Three initial criteria were used for inclusion: (1) exposure of an organism to BPA; (2) primary literature (not reviews); (3) self-reference to one of several terms related to "low-dose" (see below). These criteria were embedded in the Boolean search string: (((BPA OR Bisphenol a)) AND (low dose OR low concentration OR environmentally relevant)) NOT review [Publication Type].

Abstracts from the retrieved literature were further reviewed and manuscripts not meeting the inclusion criteria were eliminated. During the review, terms accepted as self-references were expanded to include the following: low dose/dosage/concentration/exposure; environmentally/ecologically relevant; environmental/low level; far below US EPA LOAEL; below the range of exposure by pregnant women; found in the environment; environmental concentration; low exogenous estrogen environment. The remaining papers were individually reviewed to assure they met the inclusion criteria.

To assure that important contributions to the "low-dose" literature were not missed in our search, we also report the same analysis conducted with the tabulation of "low-dose" studies reported by another group (vom Saal and Welshons, 2006).

2.2. Unit conversions and exposure calculations

Exposures for aquatic and in vitro systems were converted from mass/volume to moles/volume as necessary. Exposures for animal studies were converted to a common μg/kg/day basis from provided study details. Four feeding or drinking water exposure studies provided exposure in ppm (Cagen et al., 1999; Huff, 2001; Kobayashi et al., 2012; NTP, 1982), which was converted to μg BPA per kg body weight per day utilizing the methods described by the European Food Safety Authority (2012). Three studies failed to provide body weight information to calculate mass per body weight doses (Atanassova et al., 2000; Khurana et al., 2000; Navarro et al., 2009). Average published body weights were used to calculate exposures (Chahoud and Paumgartten, 2009).

2.3. Statistics

Box plots showing the trend in exposures by year were generated using Sigma Plot™ 11.

2.4. Sources of human exposure

Human external exposure to BPA has been measured using urine biomonitoring studies and food surveys, while internal exposure has been measured directly through biomonitoring of blood and indirectly by application of human pharmacokinetics and human pharmacokinetic models. In humans, BPA reaching the blood following absorption from any route of exposure (oral, dermal, sublingual, inhalation) is completely eliminated in urine within 24 h, the majority (84–97%) being eliminated in 5–7 h (Völkel et al., 2005, 2002). Twenty-four hour collection of urine is thus recognized as the gold standard for aggregate BPA exposure assessment (Koch et al., 2012; Ye et al., 2011). Spot urine collection, while subject to daily variability in urine concentrations, accurately reflects human exposure for large exposure cohorts (Ye et al., 2011) such as those in the national population scale biomonitoring programs (Lakind et al., 2012; Lakind and Naiman, 2008, 2010) used in our analyses. In contrast, food surveys estimate external BPA from measured concentrations in food items, and distributions of food intake, and because they involve assumptions about the intake of BPA-containing food, and cannot address variability in BPA concentrations in food or absorption of BPA. Therefore, these assessments are subject to a higher degree of uncertainty than those made from urine biomonitoring data in large populations. Direct biomonitoring of blood concentrations of BPA has been conducted, but the eighty percent of these studies were conducted in hospital and clinical settings (Bloom et al., 2011a,b; Cobellis et al., 2009; Gyllenhammar et al., 2012; Kuroda et al., 2003; Liao and Kannan, 2012; Padmanabhan et al., 2008; Schonfelder et al., 2002b; Tan et al., 2003; Wan et al., 2010), where exposure to BPA could be higher due to exposure to medical equipment and medical interventions including surgery and i.v. drug administration (Calafat et al., 2009; Vandentorren et al., 2011). These reported blood concentrations, if accurately representing the clinical exposure scenario, would not reflect average daily exposures in the general U.S. Population. More importantly, analysis of human blood for trace amounts of BPA is confounded by contamination during the sample collection, storage and analysis chain (Doerge et al., 2012; Koch et al., 2012; Markham et al., 2010; Teeguarden et al., 2011) leading to the recent conclusion that accurate analysis for blood BPA is almost unachievable (Ye et al., 2013). In recognition of the limitations of the blood BPA data and food-survey exposure estimates and the strength and consistency of the urine biomonitoring data, we elected to use a series of urine-based exposure estimates from population-level biomonitoring studies in adults and children as measures of exposure for our analysis (Table 1). Exposures in experimental studies were compared to the upper bound of adult human external exposures derived from two representative national scale urine biomonitoring studies from the U.S. (NHANES 2003–2004, $n = 2517$ and NHANES 2005–2006, $n = 2548$) (Lakind and Naiman, 2008, 2010). These adult exposure estimates were similar to or higher than those from other large and small 24 h urine measurements (Koch et al., 2012; Teeguarden et al., 2011) as well as large spot urine biomonitoring studies from

Please cite this article in press as: Teeguarden, J.G., Hanson-Drury, S. A systematic review of Bisphenol A "low dose" studies in the context of human exposure: A case for establishing standards for reporting "low-dose" effects of chemicals. Food Chem. Toxicol. (2013), http://dx.doi.org/10.1016/j.fct.2013.07.007