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Pharmacokinetics of bisphenol A in humans following a single oral administration

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ABSTRACT

Background: Human exposures to bisphenol A (BPA) are widespread. The current study addresses uncertainties regarding human pharmacokinetics of BPA.
Objective: To reduce uncertainties about the metabolism and excretion of BPA in humans following oral administration.
Methods: We exposed six men and eight women to 100 μg/kg bw of deuterated BPA (d6-BPA) by oral administration and conducted blood and urine analysis over a three day period. The use of d6-BPA allowed administered d6-BPA to be distinguished from background native (unlabeled) BPA. We calculated the rate of oral absorption, serum elimination, half-life, area under the curve (AUC), urinary excretion, and metabolism to glucuronide and sulfate conjugates.
Results: Mean serum total (unconjugated and conjugated) d6-BPA C_{max} of 1711 nM (390 ng/ml) was observed at T_{max} of 1.1 ± 0.50 h. Unconjugated d6-BPA appeared in serum within 5–20 min of dosing with a mean C_{max} of 6.5 nM (1.5 ng/ml) observed at T_{max} of 1.3 ± 0.52 h. Detectable blood levels of unconjugated or total d6-BPA were observed at 48 h in some subjects at concentrations near the LOD (0.001–0.002 ng/ml). The half-times for terminal elimination of total d6-BPA and unconjugated d6-BPA were 6.4 ± 2.0 h and 6.2 ± 2.6 h, respectively. Recovery of total administered d6-BPA in urine was 84–109%. Most subjects (10 of 14) excreted >90% as metabolites within 24 h.
Conclusions: Using more sensitive methods, our study expands the findings of other human oral pharmacokinetic studies. Conjugation reactions are rapid and nearly complete with unconjugated BPA comprising less than 1% of the total d6-BPA in blood at all times. Elimination of conjugates into urine largely occurs within 24 h.
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1. Introduction

Bisphenol A (BPA) is used in the manufacture of polycarbonate plastics, epoxy resins, and as a polymerization inhibitor in the formation of some polyvinyl chloride plastics. Polycarbonates are in consumer products such as plastic dinnerware, microwave ovenware, eyeglass lenses, toys, pacifiers, impact-resistant safety equipment, compact disks and automobile parts. Epoxy resins are used in protective linings of canned food and beverage containers, drinking water storage tanks, wine vat linings, some paints, floorings, and some dental composites (EFSA, 2013; FAO/WHO, 2011; NTP, 2008). Approximately 3% of polycarbonate is used in the manufacture of medical devices (Hensten, 2012). BPA is also a developer in thermal paper products such as cash register receipts and certain medical technical paper (EFSA, 2013; Östberg and Noaksson, 2010). Consequently, the potential for human exposure is widespread. Diet is considered the primary source of exposure to BPA for most people (EFSA, 2006; FAO/WHO, 2011; NTP, 2008), although non-dietary contributions may be significant for certain sub-populations

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such as hospital patients and cashiers (Biedermann et al., 2010; Calafat et al., 2009; Lassen et al., 2011).

BPA has been reported to cause a wide range of adverse health outcomes in experimental animal studies; some similar findings in humans have also been linked to BPA exposure in observational epidemiology studies (WHO, 2011). Exposures during fetal life or early postnatal development are of most concern because of the susceptibility of normal development to potential disruption and because BPA is metabolized and eliminated through conjugation enzyme systems that may not be fully developed in early life (Divakaran et al., 2014; Gerona et al., 2013).

Following ingestion, the majority of BPA is quickly bound to glucuronic acid to produce BPA glucuronide (BPA-G), a metabolic process called glucuronidation that is carried out by enzymes primarily in the liver and gut (NTP, 2008). To a lesser extent, unconjugated parent (commonly referred to as "free") BPA is converted to other metabolites, primarily BPA sulfate, or BPA-S (Fig. 1). Because the conjugated forms of BPA do not bind the estrogen receptor (ER) they are considered biologically inactive; however, a recent study found that conjugated forms of BPA can perturb cellular responses in prolactemia cells, presumably through interactions with membrane ERα which mediates rapid signaling responses (Viñas et al., 2013).

Biomonitoring data document that human exposure to BPA is widespread (Calafat et al., 2008; Teeguarden et al., 2013) but there is debate on the validity of reported measures of unconjugated BPA in whole blood, serum, or plasma. The essence of the controversy is that levels of unconjugated BPA reported in blood from adults collected outside a medical setting of 0.5–2 ng/mL (2.2–8.8 nM) are orders of magnitude higher than would be predicted based on the estimated daily intakes for adults, which are less than 0.5 μg/kg bw/day (EFSA, 2013). Some of the strongest data to support daily intakes in this range (and lower) are based on back calculations from total 24 hour urinary output in a group of 596 German men and women (Koch et al., 2012). Unconjugated BPA was not detectable in serum or urine at any time point in the single previous human oral pharmacokinetic (PK) study where subjects received an oral dose of ~54–90 μg/kg bw (Volkel et al., 2002). However, the limit of detection in that study, 2.28 ng/ml (10 nM), is less sensitive than more recent capabilities of 0.06 to 0.4 ng/ml (0.26 to 1.75 nM) (Mortensen et al., 2014; Vandenberg et al., 2014; Vom Saal et al., 2014). A recent study using a more sensitive method (LOD range of 0.02–0.96 ng/mL) reported a maximum concentration of unconjugated d6-BPA of 0.098 ng/ml (0.43 nM) at 1.6 h following administration of 30 μg/kg bw of BPA in soup to 10 men (Teeguarden et al., 2015). The unconjugated d6-BPA was 0.3% of the total d6-BPA, leading the authors to conclude that exposure from the diet and sublingual absorption are unlikely to account for some reported biomonitoring results for unconjugated BPA in the "ng/ml" range in blood. Furthermore, oral pharmacokinetic studies in mice, rats, and rhesus monkeys using isotopically labeled BPA indicate that intakes of 75 to over 1000 μg/kg bw/day would be required in order to produce the levels of unconjugated BPA reported in the human literature assuming similar kinetic parameters (Doerge et al., 2010a,b, 2011b; Taylor et al., 2011; Vom Saal et al., 2014).

Collectively, these discrepancies led to a concern that detectable levels of unconjugated BPA in blood are artifacts related to sample preparation or storage, background contamination from labware and/or the analytical technique employed, or due to special exposure situations, e.g., hospitals where patients may be exposed to BPA from medical devices or in occupational settings (Calafat et al., 2013; Chapin et al., 2008; Dekant and Volkel, 2008; Longnecker et al., 2013; Mielke et al., 2011; Teeguarden et al., 2013; Twaddle et al., 2010; Ye et al., 2013). Others maintain the validity of the blood biomonitoring results because the reported measurements are consistent across a variety of studies using a range of analytical methods in which authors reported taking great care to avoid background contamination during sample collection and analysis (Vandenberg et al., 2013; Vom Saal and Welshons, 2014). Hypotheses for unconjugated BPA levels reported in the ng/ml range in a subset of human blood biomonitoring samples include unknown sources of exposure to BPA (Vandenberg et al., 2013), storage and release of unconjugated BPA from depot tissues (Stahlhut et al., 2009), and the possibility of dermal, sublingual, or inhalation routes of exposure (Gayrard et al., 2013; Hormann et al., 2014; Vandenberg et al., 2007, 2013).

1.1. Objective

The objective of this oral pharmacokinetic study was to characterize d6-BPA and d6-BPA glucuronide and sulfate in blood and urine over a

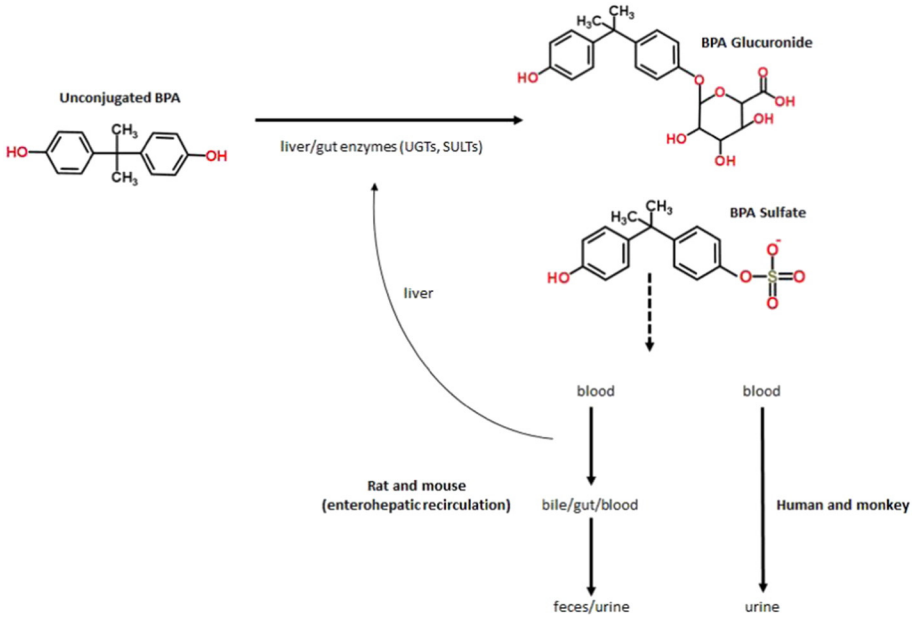

Fig. 1. Overview of BPA metabolism. In humans, elimination is via the urine in the form of BPA or BPA conjugates, mostly BPA-G. The elimination routes in rodents include urine as well as feces. Differences between humans and rodents are attributed to different molecular weight cutoffs for biliary excretion where the molecular weight threshold is higher in humans. Also, in rodents bisphenol A conjugates can be de-conjugated in the gut and be re-circulated back to the liver ("enterohepatic circulation").
Modified from Fig. 1 of Taylor et al. (2011).