Interpreting bisphenol a absorption in the canine oral cavity: gayrard et Al. Respond.

Véronique V. Gayrard-Troy, Marlène Z. Lacroix, Séverine Collet, Catherine Viguié, Alain Bousquet-mélou, Pierre-Louis Toutain, Nicole Picard-Hagen

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Exposure Conditions and Pharmacokinetic Principles: Interpreting Bisphenol A Absorption in the Canine Oral Cavity

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Gayrard et al. (2013) reported significant (~ 80%) absorption of bisphenol A (BPA) from solutions applied to the oral cavity of dogs, leading to higher serum BPA (aglycone) concentrations than occurred when BPA was absorbed through the gastrointestinal tract. This finding is consistent with first principles and experience with orally absorbed drugs. The implications for human exposure and health will be clear when experimental evidence is available regarding the extent and frequency of sublingual absorption in orally exposed humans.

Arguments made by Gayrard et al. that "nanograms-per-milliliter" serum concentrations of BPA resulting from sublingual absorption are plausible in humans ignore key pharmacokinetic and exposure data and conflate issues of serum BPA concentrations with serum BPA/BPAG (BPA glucuronide) ratios.

For a given dose, bolus dosing yields peak concentrations of a parent compound that are higher than those with nonbolus dosing. Peak concentrations in mixed systemic serum following sublingual exposure cannot exceed those following intraveneous (iv) dosing. Therefore, in humans, peak systemic serum concentrations following sublingual exposure cannot be higher than those resulting from bolus iv administration of a given BPA dose. Scaling by dose from pharmacokinetic studies of nonhuman primates (Patterson et al. 2013), the human serum concentration of aglycone BPA immediately after an iv bolus administration of a dose equivalent to a 95th percentile of aggregate daily U.S. human exposure (0.22 µg/kg body weight; Lakind and Naiman 2010) would be < 0.1 ng/mL, which is below current quantification limits (LOQ) using state-of-the-art technology. Therefore, peak systemic serum concentrations of aglycone BPA following sublingual exposure/absorption of this dose would also be < LOQ. This result is consistent with the data of Gayrard et al. (2013) in which dog serum BPA concentrations would be ~ 0.07 ng/mL (i.e., < LOQ) when sampled from a site reflecting systemic exposure (e.g., leg vein). Therefore, in 95% of the U.S. population, serum aglycone BPA concentrations of nanograms per milliliter are not possible, even with complete sublingual absorption.

Several studies in the literature have reported BPA/BPAG ratios in human serum samples higher than those (< 1%) consistently observed in human and animal oral pharmacokinetic studies (Vandenberg et al. 2007). Gayrard et al. (2013) introduced a new hypothesis (i.e., sublingual exposure/absorption) to justify this discrepancy. Previously proffered hypotheses for high BPA and BPA/BPAG ratios in human serum samples included exposures 10,000 times higher (Vandenberg et al. 2007) than those measured in humans (Lakind and Naiman 2010), extensive dermal exposure/absorption (Vandenberg et al. 2013), and sample contamination (Teeguarden et al. 2011). Only the latter hypothesis is supported by ample evidence that contamination of blood samples is not only common, but difficult to avoid (Ye et al. 2013).

Finally, extrapolation of BPA levels from BPAG levels using the measured ratio of < 1% following ingestion of BPA is appropriate under conditions where BPA reaches the systemic blood via gastrointestinal tract absorption [e.g., food (see Teeguarden et al. 2011)]. Similarly, values of approximately 10–20% would be valid for serum levels 0–4 hr after iv dosing or complete sublingual absorption, when sampled from a site representing systemic exposure.

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Justin G. Teeguarden,[1] Jeffrey W. Fisher,[2] Daniel R. Doerge[2]

[1]Pacific Northwest National Laboratory, Richland, Washington, USA; [2]National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, Arkansas, USA
E-mail: jt@pnl.gov

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The comments by Teeguarden et al. offer us the opportunity to explain some possible pharmacokinetic (PK) and PK/pharmacodynamic (PK/PD) consequences of sublingual bisphenol A (BPA) absorption. Nowhere in our paper (Gayrard et al. 2013) did we report that "nanograms-per-milliliter serum concentrations of BPA resulting from sublingual absorption are plausible in humans."

Using elementary PK computation, Teeguarden et al. concluded that peak concentrations in mixed systemic serum should be < 0.1 ng/mL even after a bolus intraveneous (iv) administration based on the 95th percentile of the aggregate daily U.S. human exposure (0.22 µg/kg body weight). Using the same scaling approach but considering a subpopulation of children 6–11 years of age with a 95th percentile of 0.481 µg/kg/day (Lakind and Naiman 2011), and taking into account our own data from dogs, the maximum initial plasma BPA concentration would be about 0.6 ng/mL. More important, what should be highlighted from our study is that, within 1 hr after administration of the low BPA dose (0.05 mg/kg), the BPA concentrations in blood collected from the jugular vein (i.e., downstream from the BPA absorption site) were higher than those measured after the corresponding iv administration (see Figure 1B of Gayrard et al. 2013). Teeguarden et al. should not be confused by the question of validity of a sampling site for making a sound pharmacokinetic computation and the biological relevance of a local concentration that is a biological fact that needs to be considered. Scaling our local jugular concentrations by human BPA exposure (0.22 µg/kg) leads to the computation of a jugular BPA concentration > 1 ng/mL. What is true for sublingual absorption and the jugular vein could be true for any sampling site located downstream of any other

absorption site, such as the human cubital vein after percutaneous absorption of BPA from thermal receipt paper, leading to serum BPA concentrations > 1 ng/mL (vom Saal FS, personal communication). This means that high BPA concentrations that are neither contamination (vom Saal 2013) nor a violation of PK principles can be observed in humans.

More generally, it is our opinion that it is unwise to consider that "mixed systemic serum following sublingual exposure" and blood samples obtained "from a site reflecting systemic exposure" are the only valuable ways to describe the PK of BPA and to discuss the PK/PD relationship. The buccal absorption of BPA can be viewed as a direct infusion of BPA into the internal jugular vein (in humans) likely to lead downstream to a totally different pattern of BPA biophase exposure compared with intestinal absorption. Buccal absorption should generate a series of BPA peaks (associated with meals) and troughs (during the interdigestive period) in the blood rather than a low steady exposure following intestinal absorption. In addition, the amplitude of these intermittent jumps in BPA concentration could be higher in arterial blood that those measured peripherally. Chiou (1989) reported that after iv administration, measured peripheral venous concentrations could be initially lower or much lower than the corresponding arterial concentrations, which are the driving concentrations to consider for drug action. Chiou also showed that the shorter the terminal half-life, the greater the arteriovenous concentration difference during the distribution/redistribution phase. BPA's half-life is short, and it makes sense to postulate that the peripheral venous blood BPA concentration measured following buccal absorption could systematically underestimate the arterial BPA concentration.

Finally, our article points to new alternative hypotheses for interpretation of the current epidemiological urinary data and also for better understanding blood BPA concentrations. First, the bioavailability of BPA is now theoretically up to 100% rather than about 1%, as expected following oral gavage. Second, given the typical feeding behavior of humans, the lack of uniformity of blood BPA concentrations after buccal absorption should not be ignored in terms of the PK/PD relationship. We are now exploring the hypothesis that sublingual absorption can lead to a possible first-pass disrupting effect on pituitary secretions.

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Véronique Gayrard, Marlène Z. Lacroix, Séverine H. Collet, Catherine Viguié, Alain Bousquet-Melou, Pierre-Louis Toutain, Nicole Picard-Hagen

INRA (Institut National de la Recherche Agronomique), UMR1331 (Unité Mixe de Recherche 1331), Toxalim (Research Center in Food Toxicology), Université de Toulouse, Toulouse, France
E-mail: pltoutain@wanadoo.fr

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