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Comparative toxicokinetics of bisphenol S in rats and mice following gavage administration

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Abstract

Bisphenol S (BPS) is a component of polyether sulfone used in a variety of industrial applications and consumer products. We investigated the plasma toxicokinetic (TK) behavior of free (unconjugated parent) and total (parent and conjugated) BPS in rats and mice following a single gavage administration (34, 110, or 340 mg/kg). In male rats, BPS was rapidly absorbed with free BPS maximum concentration (C_{max}) reached at 2.27 h. Elimination of free BPS in male rats was dose-dependent with estimated half-lives of 5.77–11.9 h. C_{max} and area under the concentration versus time curve (AUC) increased with dose although the increase in AUC was more than dose proportional. In male rats, total BPS C_{max} was reached 2.77 h with both C_{max} (10-fold) and AUC (15-fold) higher than free BPS demonstrating rapid and extensive conjugation of BPS. In male mice, the increase in C_{max} and AUC of free BPS was dose-proportional; C_{max} was higher and AUC was lower than in male rats. BPS was cleared more rapidly in male mice (half-life 2.86–4.21 h) compared to male rats (half-life 5.77–11.9 h). Similar to rats, total BPS C_{max} (6-fold) and AUC (12-fold) were higher than corresponding free BPS. Oral bioavailability of free BPS was low to moderate (rats, 21%; mice, 19%). There were some species differences in TK parameters of free and total BPS and limited sex difference in rats and mice. In addition, there were dose-related effects of plasma TK parameters in rats.

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Declaration of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Keywords

bisphenol S; absorption; distribution; elimination; toxicokinetics; oral bioavailability

Introduction

Bisphenol S (BPS) (Figure 1) is a component of polyether sulfone, a thermoplastic. Polyether sulfone is used in a variety of consumer products and applications, including but not limited to, developer in thermal paper, wash fastening agent in cleaning products, and in microwaveable dishes (Clarke, 2012; Liao *et al.*, 2012c; Rochester and Bolden, 2015). In addition, BPS is a chemical intermediate in preparation of fire retardants, electroplating chemicals and colorant, and as a modifier for leather, fiber, and epoxy curing agents (Clarke, 2012; Liao *et al.*, 2012c; EPA, 2014). Annual U.S. production of BPS in 2012 was between 1 to 10 million pounds (EPA, 2010).

BPS has been detected in personal care products, food stuffs, and indoor house dust (Liao and Kannan, 2012; Liao and Kannan, 2013). In addition, there is growing evidence of exposure to BPS in the general population based on urinary biomarkers (Liao *et al.*, 2012a; Liao *et al.*, 2012b; Zhou *et al.*, 2014; Thayer *et al.*, 2016; Lehmler *et al.*, 2018; Philips *et al.*, 2018; Wan *et al.*, 2018a; Wan *et al.*, 2018b; Ghayda *et al.*, 2019; Husoy *et al.*, 2019; Frederiksen *et al.*, 2020). Despite the human exposure potential, the data for hazard characterization of BPS are limited at the present time. In rats and mice, the oral LD₅₀ of BPS was 1600 and >5000 mg/kg, respectively (ECHA, 2012). Summaries submitted to Registration, Evaluation, Authorisation and Restriction of Chemical (REACH) indicate that exposure to BPS can result in mortality and induce hepatic, renal, thymus, reproductive, and hematologic changes (ECHA, 2012). Other data available suggest uterine growth following subcutaneous exposure in rodents, reduced testosterone levels and the potential to reduce spermatogenesis following repeated oral exposure and altered estrus cycle in rats, and reproductive disruption in Zebrafish (Yamasaki *et al.*, 2004; Naderi *et al.*, 2014; Ullah *et al.*, 2016; Rochester *et al.*, 2017; Ahsan *et al.*, 2018). A variety of in vitro endpoints has been investigated including estrogen activity, adipogenesis and gene expression (Kang *et al.*, 2002; Grignard *et al.*, 2012; Vinas and Watson, 2013b; Vinas and Watson, 2013a; Gramec Skledar and Peterlin Masic, 2016). BPS was not genotoxic in *Salmonella typhimurium* or *Escherichia coli* in the presence or absence of S9, but was positive in mouse lymphoma L5178Y cells. BPS did not increase mutation frequency in CHO cells in the presence or absence of S9, but did increase chromosomal aberration formation in the absence of metabolic activation.

Lack of adequate data to assess potential adverse human health effects from exposure to BPS led the National Toxicology Program (NTP) to study BPS following oral exposure of rodents (NTP, 2020a). Absorption, distribution, metabolism and excretion (ADME) and toxicokinetic (TK) data are important in designing toxicology studies and interpreting study data. We have previously shown that following gavage administration of 50, 150, and 500 mg/kg [¹⁴C]BPS in male Hsd:Sprague Dawley® SD® (HSD) rats, BPS was well-absorbed and excreted predominantly via urine. In bile duct cannulated male rats, 53% of a gavage

dose was secreted in bile suggesting extensive enterohepatic recirculation of [^{14}C]BPS (Waidyanatha *et al.*, 2018). The urinary excretion decreased (72 to 48%) and the fecal excretion increased (16 to 30%) with increasing dose suggesting a dose-related difference in disposition in male rats. The disposition was similar in female rats and male and female B6C3F1/N mice following gavage administration. The total radioactivity remaining in tissues at 72 h in both species and sexes was 2.4%. BPS urinary metabolites included the glucuronide and sulfate conjugates and the parent (Waidyanatha *et al.*, 2018).

However, at the present time, TK data available for BPS are limited. In pregnant sheep, following subcutaneous injection of BPS at 0.5 mg/kg, half-life of elimination of BPS in the fetal compartment was higher than in the maternal compartment (Gingrich *et al.*, 2019). In another study in Lacaune ewes, following oral administration of 5 mg/kg, plasma elimination half-life and clearance of BPS was reported as 1.80 h and 0.57 L/kg·h, respectively (Grandin *et al.*, 2017). In male and female piglets (28–42 d), following a 40 µg/kg oral dose of BPS, ~ 99% of the administered dose was absorbed with the maximum concentration, C_{max} , reached at 0.5 h. In this study the estimated systemic bioavailability was 57.4% (Gayrard *et al.*, 2019). Using rat and pig data obtained from intravenous (IV) administration and allometric scaling, the plasma clearance of BPS in humans was estimated to be 0.921 L/min (Gayrard *et al.*, 2020). Oh *et al.* investigated the disposition of deuterated BPS following a single oral administration of 8.75 µg/kg in seven healthy young adults (Oh *et al.*, 2018). Total BPS was observed in serum within 1 h after administration and excreted in urine with terminal half-life of ~ 7 h. The fraction of total BPS in urine in 48h was 67–104% for men and 59–77% for women. In another study, six human volunteers administered 0.1 mg/kg deuterated BPS orally, C_{max} was reached at 0.7 h and 1.1 h for BPS and its glucuronide, respectively, with plasma elimination half-lives of 7.9 h and 9.3 h, respectively, with an estimated systemic bioavailability of 62% (Khmiri *et al.*, 2020). In the same study, following dermal application of 1 mg/kg deuterated BPS on 40 cm² of the forearm and washed 6 h after application, peak plasma levels were reached more slowly (5–8 h); however, levels were found to be below the limit of quantitation (LOQ) of the assay (BPS, 0.05 ng/mL and BPS-glucuronide, 5 ng/mL) for later time points.

TK data for rodents could not be located in the literature. Hence, the current studies were designed to investigate the TK behavior of BPS in rodents to generate data to support of NTP toxicology studies. Data for free BPS (unconjugated parent) and total BPS (free and conjugated forms) in rodents were generated following oral and IV administration. The rat and mouse strains used were the same as those used in ADME and toxicology studies (NTP, 2020b).

Materials and Methods

Chemicals and reagents:

BPS (lot IF20140175) was procured from Ivy Fine Chemicals (Cherry Hills, NJ). The chemical identity was confirmed by infrared spectroscopy, proton and carbon-13 nuclear magnetic resonance spectroscopy, mass spectrometry, and elemental analysis. The purity was determined to be > 99% based on high-performance liquid chromatography (HPLC) with ultraviolet detection (UV) at 210 nm. Male Sprague Dawley rat plasma used for matrix

calibration curve preparation was obtained from Bioreclamation IVT Inc. (Westbury, NY). [$^2\text{H}_9$]BPS (internal standard) was from Toronto Research Chemicals (Toronto, Canada). β -glucuronidase from *Helix pomatia* (at least 300,000 units/g and 10,000 units/g for β -glucuronidase and sulfatase activity, respectively) was obtained from Sigma-Aldrich (St. Louis, MO). All other chemicals and reagents were procured from commercial sources.

Animals and maintenance:

Studies were conducted at Mispro Biotech Services (RTP, NC) and were approved by their Institutional Animal Care and Use Committee. Animals were housed in facilities that are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Animal procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals" (NRC, 2011). Male and female HSD rats were obtained from Envigo (Indianapolis, IN). Male and female B6C3F1/N mice were obtained from Taconic Farms (Germantown, NY). The animals were quarantined for at least one week before they were randomized into dosing groups and used in a study. Mice and rats had ad libitum access to certified, irradiated NTP 2000 feed (Ziegler Bros, Inc., Gardners, PA) and certified, irradiated Advanced Protocol Verified Casein Diet 1 IF (5K96, PMI Nutrition International, St. Louis, MO), respectively. Feed was used within 180 days of milling. All animals had access to city (Durham, NC) tap water. Environmental conditions included: room temperature $72 \pm 3^\circ\text{F}$ ($22 \pm 2^\circ\text{C}$), relative humidity 23 to 75% and a 12-h light/dark cycle. Male (286–347 g) and female (193–238 g) HSD rats were 9–10 weeks old and male (23.0–33.8 g) and female (18.4–24.4 g) mice were 10–11 weeks old at the time of dosing.

Study design and dose administration:

The study design is given in Table 1. The doses used were 34, 110 or 340 mg/kg. Doses were selected after taking into consideration the oral gavage LD50 of BPS in rats (1600–5000 mg/kg), the doses used in BPS ADME studies (50–500 mg/kg), the doses used in BPAF TK study for a direct comparison of the two compounds (34–340 mg/kg) as well as to be within the feed doses (mice, 600–5000 ppm; rats, 5000–20000 ppm) selected for the NTP toxicology studies (Waidyanatha *et al.*, 2018; Waidyanatha *et al.*, 2019; NTP, 2020a). To aid in the interpretation of oral data and to estimate oral bioavailability, limited studies were conducted following IV administration of 34 mg/kg.

Gavage dose formulations of BPS (3.4, 11, or 34 mg/mL for mice and 6.8, 22, or 68 mg/mL for rats) were prepared in 0.5% methyl cellulose and analyzed using a validated high-performance liquid chromatography (HPLC) method with ultra violet (UV) detection (linear range, 0.4 to 100 mg/mL; $r = 0.99$; relative standard deviation 5%; relative error $\pm 10\%$). IV dose formulations (17 mg/mL for mice and 8.5 mg/mL for rats) were prepared in Kolliphor EL:95% ethanol:deionized water (20:10:70) and analyzed using a validated HPLC-UV method (linear range, 0.4 to 30 mg/mL $r = 0.99$; relative standard deviation 5%; RE $\pm 10\%$). All formulations used in studies were within 10% of the target concentration. Prior to study initiation, stability ($\pm 10\%$ of day 0) of formulations was confirmed at ambient temperature.

Each animal was weighed prior to dosing and its weight was used to determine the dosing volume. Oral doses were administered in a volume of 5 mL/kg for rat and 10 mL/kg for mouse via intragastric gavage. The IV dose was administered into a lateral tail vein in a volume of 2 mL/kg for rats and 4 mL/kg for mice. Following dose administration, blood samples were collected from 3 animals per timepoint at target times as given in Table 1. Time points were selected based on a preliminary TK study (data not shown). A maximum of three blood samples were obtained from each rat, with up to two samplings by tail venipuncture (ca. 250 μ L). Mice were sampled only once. Terminal rat and (all) mouse sampling was by cardiac puncture following CO₂ euthanasia. The actual times for blood collection were recorded at each time point. Immediately following collection, blood was dispensed into tubes containing K₃EDTA, mixed by inversion and placed on ice. Plasma was prepared by centrifugation within 1 h of blood collection. Immediately following blood collection, each animal was humanely terminated via exsanguination and brains were collected and weighed. All samples were stored at -70°C .

Quantitation of free and total BPS:

Samples were analyzed for free and total BPS using a validated analytical method (Silinski *et al.*, 2020). Briefly, two stock solutions of BPS were prepared in methanol at 100 $\mu\text{g/mL}$ and further diluted in the same solvent to generate spiking solutions (25 to 5000 ng/mL), using alternate stocks. A stock solution of [²H₉]BPS to be used as the internal standard was prepared in methanol at 2250 ng/mL. The deconjugating enzyme solution containing β -glucuronidase and sulfatase for total BPS determination was prepared in 1M ammonium acetate buffer (pH 5) to yield a final solution of at least 2 units/ μL β -glucuronidase and 0.4 units/ μL sulfatase. Seven-point matrix calibration curves (5 to 1000 ng/mL), QC samples (10 and 500 ng/mL), matrix blanks, and study samples were prepared as below.

To a 50 μL aliquot of plasma, 10 μL of methanol or appropriate BPS spiking solution (matrix calibration standards and QC samples only), and 10 μL of internal standard was added. To all samples, 25 μL of 1 M ammonium acetate buffer (for free analysis) or the β -glucuronidase/ sulfatase solution (for total analysis) was added. Samples were briefly mixed and either stored at $\sim 5^{\circ}\text{C}$ for 2 h (for free analysis) or incubated at $\sim 37^{\circ}\text{C}$ for 2 h (total analysis). Matrix blanks and study samples were prepared similarly except no BPS was added. To each sample, 300 μL of acetonitrile was added, mixed briefly, and centrifuged at 4°C for 10 min at $\sim 20,000\text{ g}$. The supernatant was analyzed by Ultra-performance liquid chromatography coupled with a tandem mass spectrometer (UPLC-MS/MS).

The UPLC-MS/MS system consisted of Waters Acquity UPLC (Waters Corp., Milford MA) liquid chromatograph coupled to an Applied Biosystems API-4000 Q-Trap (Waltham, MA) mass spectrometer. Chromatography was performed using a BEH C18 column ($2.1 \times 50\text{ mm}$, $1.7\text{ }\mu\text{m}$) (Waters Corp., Milford MA). Mobile phases A (water) and B (acetonitrile) were run with a linear gradient from 5% B (1 min) to 95% B in 5 min followed by a 2 min hold with a flow rate of 0.3 mL/min. The column temperature was maintained at 30°C . The electrospray ion source was operated in negative mode with a source temperature of 650°C and an ion spray voltage of -3000 V . Transitions monitored were $248.9\text{ ([M-H]}^{-}) \rightarrow 107.9$

for BPS, and 257.0 → 112.0 for [²H₉]BPS. The retention times were ~ 3.3 min for BPS and [²H₉]BPS.

A linear regression with 1/X² weighing was used to relate LC-MS/MS peak area response ratio of analyte to internal standard and concentration of BPS in plasma. The concentration of free and total BPS was calculated using response ratio, the regression equation, initial sample volume, and dilution factor when applicable. Study samples that exceeded the matrix calibration range were diluted into the validated concentration range using respective control matrix. Each study sample set was bracketed by method blanks, matrix calibration standards, and QC samples. Data from study samples were considered valid if: the matrix calibration curve was linear (r = 0.99); at least 75% of matrix standards were within 15% of nominal values (except at the LOQ where it was within 20%); at least 67% of the QC samples were within 15% of nominal values. All QCs were within 15% of nominal value. The LOQ for both free and total analyses was 5 ng/mL. The limit of detection (LOD), estimated as the standard error (SE) of the LOQ was 1.15 ng/mL for free BPS and 0.862 ng/mL for total BPS. All concentrations above LOD were reported.

Toxicokinetic analysis.

Doses received by animals were within 10% of target dose and hence target doses were used in analysis. Where actual blood collection times differed by >10% from the nominal time, the actual collection time was used in the model. For mice, all blood samples were collected within 10% of the nominal collection time. For rat, 13 samples were >10% from nominal time and hence the actual collection time was used in TK analysis. All free and total BPS concentrations above the LOD of the assay were used in TK analysis.

Phoenix WinNonlin (Version 6.4, Certara, Princeton, NJ) was used for TK analysis. A variety of compartmental models were tested for BPS concentration versus time data sets. For each compartmental model, data sets were analyzed with and without weighting. The model and the weighting factor that resulted in the best goodness of fit (evaluated using the Akaike Information Criterion and Schwarz Bayesian Criterion) was selected as the final model. Based on this, the following models were selected for TK analysis using individual animal data per each timepoint: rat gavage, one-compartment model with first-order input and output and 1/y weighting (Model 3, equation 1); mouse gavage, two compartment model with bolus input, first-order output and 1/y weighting (Model 7, equation 2) except for male mouse 340 mg/kg total BPS where one compartment model with first-order input, first-order output and 1/y weighting was used to fit the mean data (Model 3, equation 1); rat and mouse IV, two-compartment model with bolus input, first order output and 1/y² weighting (Model 7, equation 2). A glossary of TK parameters estimated are given in Supplementary Table S1.

$$C_{(t)} = A(e^{-k_{01}t} + e^{-k_{01}t}) \quad (1)$$

$$C_{(t)} = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

Results

All study data are available in the Chemical Effects of Biological Systems (CEBS) database at <https://manticore.niehs.nih.gov/cebssearch/paper/14930/private/104AC49XYZ>

Toxicokinetic analysis in rats following a single gavage and IV administration:

Free and total BPS concentrations were above the LOD at all post dosing time points for all gavage groups, except for free BPS at the 48-h time point in the lowest dose (34 mg/kg) where values were below LOD. Following IV administration, both free and total BPS concentrations were above the LOD at all time points except free BPS concentration in male rat plasma for the 32-h time point where it was below the LOD.

Plasma concentration of free or total BPS versus time data following gavage administration showed a short absorption phase followed by an apparent first order elimination. Some groups showed increases in concentration also at later time points (e.g., female 110 mg/kg group) which is indicative of enterohepatic recirculation. Plasma concentration versus time data and corresponding model fits for free and total BPS are shown in Figures 2 and 3, respectively, and TK parameters estimated are given in Table 2. In male rats, at the lowest dose of 34 mg/kg, BPS was absorbed rapidly with the time (T_{max}) to reach C_{max} of 0.350 h. However, T_{max} increased with dose with 1.17 and 1.97 h for 110 and 340 mg/kg, respectively. C_{max} for free BPS increased proportionally to the dose in male rats. The clearance of free BPS decreased approximately 2-fold when the dose was increased from 34 to 340 mg/kg; concomitantly, plasma elimination half-life (K_{10} half-life) increased approximately 2-fold with 5.77 and 11.9 h for 34 and 340 mg/kg, respectively. Consistent with this, the area under the concentration versus time curve (AUC), increased more than proportional to the dose with a 23-fold increase (2710–62400 h*ng/mL) with a 10-fold increase in the administered dose (34 to 340 mg/kg); the dose-normalized AUC (AUC/D) was 2-fold higher for 340 mg/kg compared to 34 mg/kg (Table 2). There was sex difference in some plasma TK parameters of rats. In female rats following administration of a single 110 mg/kg dose, BPS was absorbed slower than in male rats; the time to reach C_{max} was higher (female 5.88 h and male 1.17 h) and elimination half-life was lower (female 4.11 h; male 8.06 h) than males. However, systemic exposure parameters, C_{max} and AUC, for BPS were similar between male and female rats (Table 2).

In male rats, T_{max} of total BPS was short and increased with the dose (0.991 to 2.77 h) (Table 2, Figure 3). The systemic exposure parameters C_{max} and AUC increased with the dose. Unlike AUC where the increase was dose proportional, C_{max} increased less-than proportionally to the dose when the dose was increased from 34 to 340 mg/kg. Total BPS C_{max} and AUC were 10-fold and 15-fold higher, respectively, than free BPS. Taken collectively, these data demonstrate rapid and extensive conjugation of BPS following gavage administration in male rats. In male rats, the elimination half-lives for total BPS increased with the dose with 8.54, 11.2, and 17.2 h for 34, 110, and 340 mg/kg, respectively. Total BPS was cleared slower than free BPS with no dose-related effect. There were no apparent sex differences in plasma toxicokinetic parameters for total BPS (Table 2).

In male and female rats, following a single IV administration of 34 mg/kg, plasma concentration versus time profiles were biphasic with an initial distribution phase followed by an elimination phase. Plasma concentration versus time data and corresponding model fits for free and total BPS are shown in Figure 4 and TK parameters estimated are given in Table 3. Both $C_{\max}$ and AUC were similar between sexes for free and total BPS. Free and total BPS were eliminated rapidly with half-lives (K10 half-life) of 0.198–0.238 h and 0.517–0.784 h, respectively. For free BPS, AUC for a unit dose ($\text{AUC/D, (h*ng/mL)/(mg/kg)}$) was higher following IV administration (876) compared to gavage administration of a similar dose in male rats (79.7); however, for total BPS, the values were similar for IV (3790) and gavage (2520) administration (Tables 2 and 3).

Toxicokinetic analysis of BPS in mice following a single gavage and IV administration:

Free BPS concentrations in plasma following a single gavage administration in mice were above the LOD at all time points except the final 24-h time point where the concentrations were below the LOD for all groups except the high dose which had a measured concentration in one sample. Total BPS concentrations were above the LOD at all post dosing time points for all mouse gavage groups, except for one sample at the 24-h time point in the low dose (34 mg/kg) group for which the concentration was below the LOD. Following IV administration of 34 mg/kg BPS to male and female mice, both free and total BPS concentrations were above the LOD at all time points except for the 24-h time point.

In mice, plasma concentration versus time data following gavage administration did not contain a discernable absorption phase indicating rapid absorption. Hence, as mentioned under methods, the individual animal data versus timepoints were fitted using a bolus input model (Model 7) for all groups except for 340 mg/kg total BPS. For this male mouse group, no model fit the individual animal data and hence mean data per timepoint was used for modeling and the best fit was found to be a one compartmental model with first order input and output, 1/y weighting (Model 3). Plasma concentration versus time data and corresponding model fits for free and total BPS are shown in Figures 5 and 6, respectively and estimated TK parameters are given in Table 4. Plasma concentration versus time plots were biphasic with an initial distribution phase followed by an elimination phase. Some groups showed concentration increases at later time points (e.g., male and female 110 mg/kg groups) which is indicative of enterohepatic recirculation.

In male mice, $C_{\max}$ of free BPS increased less than proportionally to the dose with concentration increasing only 5-fold with the 10-fold increase in the dose (Table 4). The volume of distribution was high and exceeded the reported body water volume in mice (725mL/kg) (Davies and Morris, 1993) indicating distribution of free BPS into the peripheral compartment. The elimination of free BPS from plasma was rapid with half-lives (beta half-lives) of 2.86–4.21 h with no distinct dose-related effect. AUC (2550–26100 (h*ng/mL)) increased linearly with the dose (Table 4). Following administration of a similar dose (110 mg/kg), there was no difference in plasma TK parameters between male and female mice.

Systemic exposure parameters, $C_{\max}$ and AUC, of total BPS increased linearly with the dose for 34 and 110 mg/kg in male mice (Table 4, Figure 6). Plasma elimination half-lives (beta

half-lives) were similar between 34 and 110 mg/kg groups (2.92–3.04 h) and was similar to free BPS (2.86–4.21 h). Similarly, there was no dose-related difference in other TK parameters. Based on the 110 mg/kg dose in male and female mice, there was no sex difference in TK parameters (Table 4). For the 340 mg/kg male mouse group, although, AUC increased 10-fold from the 34 mg/kg group, $C_{\max}$ didn't increase with the dose with similar values observed for both 34 and 340 mg/kg groups. Although the reason for this is not it is not clear, it may partly be due to the different model used for the 340 mg/kg group.

In male and female mice, following a single IV administration of a 34 mg/kg dose, plasma concentration versus time profiles showed a biphasic profile with an initial distribution phase followed by an elimination phase. Plasma concentration versus time data and corresponding model fits for free and total BPS are shown in Figure 7 and TK parameters estimated are given in Table 3. In male and female mice, free and total $C_{\max}$ and AUC were similar between the sexes. Free and total BPS were eliminated rapidly with slightly longer half-lives (beta half-lives) for total BPS (2.83–2.95 h), compared to free BPS half-lives (beta half-life 1.93–3.00 h). For free BPS, AUC for a unit dose (AUC/D , (h.ng/mL)/(mg/kg)) was higher following IV administration (332–409) compared to gavage administration of a similar dose (75.0); however, for total BPS, the values were similar for IV (1970–2180) and gavage (1010) administration (Tables 2 and 4). There was no apparent sex difference in TK parameters of free or total BPS in mice following a single IV administration.

Oral Bioavailability of BPS in rats and mice following gavage administration.

Oral bioavailability of parent BPS was calculated using AUC following gavage and IV administration, adjusted for the dose administered (Table 5). In male rats following gavage administration, the bioavailability was low to moderate; values increased with dose administered with 9.1, 15.2, and 20.9% estimated for 34, 110, and 340 mg/kg, respectively. In female rats, following a 110 mg/kg dose bioavailability was similar to male rats given a similar dose. As with rats, in mice, bioavailability was low to moderate. However, unlike in rats, in mice, there was no dose-related effect with estimated values ranging between 11.2–18.7%; there was no sex difference in bioavailability in mice (Table 5).

Discussion

Due to paucity of data to characterize the hazard from BPS exposure, the NTP has undertaken toxicity testing of BPS in rodent models (NTP, 2020b). ADME and TK data are essential to design toxicology studies and provide broader context to study data. We have previously reported the ADME data for BPS following a single gavage administration of [^{14}C]BPS in rodents (Waidyanatha *et al.*, 2018). To the best of our knowledge, there is a gap in the current literature on comprehensive investigation of TK behavior of BPS in rodent models following oral exposure. In the current investigation, we report the plasma TK data of free and total BPS following a single gavage and IV administration of BPS in male and female rats and mice. Free and total BPS concentrations were measured using a validated analytical method (Silinski *et al.*, 2020).

Our data showed that the TK behavior of BPS following gavage administration is somewhat similar to other structural analogues such as BPA and BPAF (Willhite *et al.*, 2008;

Waidyanatha *et al.*, 2019). BPS was absorbed rapidly following gavage administration in rats and mice and rapidly and extensively conjugated. Systemic exposure of free BPS increased with the dose in male rats and the increase was dose-proportional for C_{max} . However, AUC increased more than proportionally to the dose with dose-normalized AUC (AUC/D , D ($h \cdot ng/mL$)/(mg/kg)) values of 79.7, 134, and 184 for 34, 110, and 340 mg/kg, respectively, suggesting saturation of metabolism and clearance pathways likely beginning at or below 110 mg/kg in rats. In parallel, plasma elimination half-life (K_{10} half-life) increased approximately 2-fold from 5.77 to 11.9 h when the dose was increased from 34 to 340 mg/kg. Similar to male rats, in male mice the absorption of BPS following gavage administration was rapid. In mice, the absorption phase for free BPS could not be defined due to rapid absorption indicating that T_{max} occurred before the first post dose sample collection time of 15 min. As with male rats, the systemic exposure parameters of free BPS increased with the dose. The increase in free BPS C_{max} in male mice was less than dose-proportional with only a 5-fold increase in concentration with a 10-fold increase in the dose. There was no distinct dose-related effect in AUC in mice. Consistent with this, there was no dose-related difference in clearance of free BPS in male mice; the plasma elimination half-lives were 0.181–0.461 h. When compared between the two species, male mice (half-life 2.86–4.21 h) eliminated free BPS faster than male rats (half-life 5.77–11.9 h). When the systemic exposure parameters of free BPS were compared between male rats and mice, C_{max} in male mice was 12- to 24-fold higher than in male rats although the AUC between the 2 species were similar (mouse/rat ~ 0.34 - to 0.94). In both rats and mice, there was no sex-difference in TK parameters for free BPS based on a single gavage administration of 110 mg/kg. Similar to rodents, in piglets and humans following an oral dose, C_{max} of free BPS was reached rapidly (piglets, 0.5 h; human, 0.7 h) (Gayrard *et al.*, 2019; Khmiri *et al.*, 2020). Estimated plasma elimination half-life of free BPS in human volunteers (7.9 h) (Khmiri *et al.*, 2020) were similar to rats (4.11–11.9 h) but slightly longer than mice (2.86–4.21 h) in our investigation.

BPS underwent rapid intestinal and hepatic first-pass metabolism following gavage administration as evident by quick appearance of total BPS following administration. In male rats, total T_{max} (0.991–2.77 h) was only slightly lagged behind that of free BPS (0.350–1.97 h). In male mice, as observed with free BPS, the absorption phase could not be defined for total BPS indicating that T_{max} for total BPS also occurred before the first post-dose sample collection time of 15 min. Systemic exposure parameters C_{max} and AUC for total BPS increased with the dose in male rats. Although less-than dose proportional increase in AUC was expected for total BPS based on higher than dose-proportional increase in free BPS, the increase in AUC of total BPS was dose-proportional suggesting metabolism pathways leading to sulfation and glucuronidation of BPS were likely not saturated. In mice, systemic exposure parameters for 34 and 110 mg/kg dose groups increased proportionally to the dose similar to free BPS. Total BPS concentration versus time data for 340 mg/kg male mouse group didn't give a good model fit when individual animal data and a two-compartment model was used as for other groups. Hence average concentration data per timepoint was modeled using a one-compartment model. The estimate for C_{max} for the 340 mg/kg was similar to that of 34 mg/kg demonstrating potential underprediction of total BPS C_{max} for this group.

In both male rats and male mice, total BPS concentrations were much higher than the corresponding free concentrations, demonstrating extensive first-pass metabolism following gavage administration of BPS. In male rats, total BPS, based on $C_{\max}$, was 10- to 21-fold higher and AUC was 15- to 32-fold higher than corresponding free BPS. In male mice, based on $C_{\max}$ total BPS was 6- to 7-fold higher (excluding 340 mg/kg group) and based on AUC was 12- to 15-fold higher than free BPS. When the systemic exposure parameters of total BPS were compared between male rats and mice, $C_{\max}$ in male mice was 7-fold higher than in male rats although the AUC between the 2 species were similar (mouse/rat ~ 0.19- to 0.42). In both rats and mice, there was no sex-difference in TK parameters of total BPS based on a single gavage administration of 110 mg/kg. Extensive first pass conjugation is further confirmed based on much higher free BPS AUC (h*ng/mL) following IV administration of a 34 mg/kg dose in male rats (gavage, 2710; IV, 28900) and mice (gavage, 2550; IV, 13900).

Consistent with the extensive conjugation of BPS following gavage administration, the estimated oral bioavailability was low to moderate. In male rats, there was an apparent increase in bioavailability with the dose with 9, 15.2, and 20.9% for 34, 110, and 340 mg/kg, respectively, although the effect was not apparent in male mice with estimated values of 18.3, 11.2, and 18.7 % for 34, 110, and 340 mg/kg, respectively. There was no sex-related difference in oral bioavailability of BPS in rats and mice. A higher oral bioavailability of BPS was reported in piglets (57.4%) following gavage administration of 40 µg/kg dose (Gayrard *et al.*, 2019) and in human volunteers (62%) following an oral dose of 0.1 mg/kg (Khmiri *et al.*, 2020) suggesting a significant species difference in oral bioavailability of free BPS.

We have compared the data from the current investigation for BPS with those reported in the literature for two structural analogues, BPA and BPAF (Table 6) (Doerge *et al.*, 2010; Taylor *et al.*, 2011; Waidyanatha *et al.*, 2019). All 3 compounds were absorbed rapidly following gavage administration in both species. In rodents, plasma (or serum) elimination half-lives were similar for BPS (~ 3 to 4 h) and BPA (~ 3 to 5 h) but was higher for BPAF (~ 9 to 13 h). In rats, dose-normalized systemic exposure parameters, $C_{\max}$ and AUC, for the parent (free, aglycone) followed the rank order BPS >> BPAF > BPA demonstrating highest exposure following BPS administration and lowest following BPA exposure. In mice also, dose-normalized $C_{\max}$ and AUC were highest for BPS and followed the rank order BPS >> BPA > BPAF. These data demonstrate that of the 3 analogues, BPS gives the highest systemic exposure per unit dose administered following oral exposure in rodents.

In rodents, $T_{\max}$ of total (or conjugated forms) of BPA, BPS, and BPAF slightly lagged behind the aglycone following oral exposure demonstrating rapid first pass conjugation in the intestine and liver. In adult female Sprague-Dawley rats following a single gavage administration of 100 µg/kg BPA, total BPA $C_{\max}$ and AUC, respectively, were ~ 187- and ~ 261-fold higher than the corresponding free values (Doerge *et al.*, 2010). Following a single 100 mg/kg oral dose of BPA in adult female CD-1 mice, total $C_{\max}$ and AUC, respectively, were ~ 120- and ~ 124-fold higher than the corresponding free values. (Taylor *et al.*, 2011). In our previous work with BPAF, total $C_{\max}$ and AUC, respectively, in rats were 43- and 120-fold higher following a 110 mg/kg dose, and in mice were 38- and 23-fold higher

following a 34 mg/kg dose, than the corresponding free values (Waidyanatha *et al.*, 2019). In the current investigation with BPS, total C_{max} and AUC, respectively, were 16- and 15-fold higher in female rats and 7- and 11-fold higher in female mice following a single dose of 110 mg/kg. These data demonstrate that the conjugation capacity of BPS was the lowest and BPA was the highest in rodents. This is consistent with the highest systemic exposure for free BPS compared to BPAF and BPA as described previously. Consistent with this, the oral bioavailability reported for BPA was 3% (Willhite *et al.*, 2008; Doerge *et al.*, 2010) and for BPAF was 1–6% (Waidyanatha *et al.*, 2019). The values estimated for BPS (9–21%) in the current study were higher than for BPA or BPAF. Overall, these comparisons demonstrate kinetic differences between bisphenol analogues and provide data to demonstrate that systemic exposure of parent is highest following exposure to BPS compared to BPAF or BPA and hence may have potential toxicological impact.

Conclusion

Our data demonstrate that BPS was rapidly absorbed in male and female rats and mice following a single gavage administration. Plasma elimination of free BPS in mice was slightly faster (half-life 2.86–4.21 h) than in rats (half-life 5.77–11.9 h). BPS was extensively conjugated in both rats and mice. Total BPS concentrations were 10-fold and 15-fold higher in rats and 6-fold and 12-fold higher in mice compared to free BPS, based on C_{max} and AUC, respectively. Estimated oral bioavailability was low to moderate (rats, 9–21%; mice, 11–19%). For free BPS, although the sex-related difference in TK parameters were limited in both species, there was a species and a dose-related difference in rats.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Bisphenol S (BPS) is a structural analogue of bisphenol A.

We investigated the toxicokinetics of BPS in rodents via gavage exposure.

BPS was rapidly absorbed in rodents following gavage exposure.

Plasma elimination was rapid in mice compared to rats.

BPS was highly conjugated with low to moderate bioavailability.

Figure 1:
Structure of bisphenol S (BPS)

Figure 2.

Plasma concentration versus time profiles of free bisphenol S following a single gavage administration of 34, 110, or 340 mg/kg bisphenol S in male and female rats. One-compartmental model with first order input, first order output and $1/y$ were used to fit the data. Lines represent model fits. M, male; F, female.

Figure 3.

Plasma concentration versus time profiles of total bisphenol S following a single gavage administration of 34, 110, or 340 mg/kg bisphenol S in male or female rats. One-compartmental model with first order input, first order output and $1/y$ were used to fit the data. Lines represent model fits. M, male; F, female.

A)

B)

Figure 4.

Plasma concentration versus time profiles of A) free bisphenol S and B) total bisphenol S following a single intravenous administration of 34 mg/kg bisphenol S in male and female rats. Two compartment model with bolus input, first-order output and $1/y^2$ weighting was used to fit the data. Lines represent model fits.

M, male; F, female.

Figure 5.

Plasma concentration versus time profiles of free bisphenol S following a single gavage administration of 34, 110, or 340 mg/kg bisphenol S in male or female mice. Two compartment model with bolus input, first-order output and 1/y weighting was used for all groups. Lines represent model fits.

M, male; F, female.

Figure 6.

Plasma concentration versus time profiles of total bisphenol S following a single gavage administration of 34, 110, or 340 mg/kg bisphenol S in male or female mice. Two compartment model with bolus input, first-order output and 1/y weighting was used for all groups using individual animal data except one compartment model with first-order input, first-order output and 1/y weighting using mean data per time point was used for 340 mg/kg total bisphenol S. Lines represent model fits. M, male; F, female.

A)

B)

Figure 7.

Plasma concentration versus time profiles of A) free bisphenol S and B) total bisphenol S following a single intravenous administration of 34 mg/kg bisphenol S in male and female mice. Two compartment model with bolus input, first-order output and $1/y^2$ weighting was used to fit the data. Lines represent model fits.

M, male; F, female.

Table 1.

Single gavage and intravenous administration TK study design of bisphenol S

Species (Sex)	Route	Dose (mg/kg)	Blood collection time points (h) ^a
Rat (Male)	Gavage	34, 110, 340	0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 32, 48, 72 (340 mg/kg only)
Rat (Female)	Gavage	110	0 (pre-dose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 32, 48
Mouse (Male)	Gavage	34, 110, 340	0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24
Mouse (Female)	Gavage	110	0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24
Rat (Male, Female)	Intravenous	34	0 (pre-dose), 0.0833, 0.33, 1, 2, 4, 8, 12, 24, 32
Mouse (Male, Female)	Intravenous	34	0 (pre-dose), 0.0833, 0.33, 1, 2, 4, 8, 12, 24

^aN=3 animals per time point. A maximum of three blood samples was obtained from each rat, with interim collections by tail venipuncture. Each mouse was sampled once.

Table 2.

Plasma toxicokinetic parameters of free and total bisphenol S following a single gavage administration in male or female rats^{a,b}

Parameter	Dose (mg/kg)			
<i>Free BPS</i>	34 (Male)	110 (Male)	340 (Male)	110 (Female)
C _{max} (ng/mL)	313 (52.4)	1140 (145)	3240 (215)	804 (159)
C _{max} /D (ng/mL)/(mg/kg)	9.20	10.4	9.53	7.31
T _{max} (h)	0.350 (1.02)	1.17 (0.544)	1.97 (0.311)	5.88 (1.71)
K01 Half-Life (h)	0.0509 (0.186)	0.219 (141)	0.385 (0.0871)	4.04 (155)
K10 Half-Life (h)	5.77 (1.40)	8.06 (1.73)	11.9 (1.35)	4.11 (157)
Cl/F (mL/h/kg)	12500 (2390)	7480 (1260)	5450 (474)	8500 (2030)
V/F (mL/kg)	104000 (15200)	87000 (13600)	93600 (7720)	50800 (194000)
AUC (h*ng/mL)	2710 (517)	14700 (2480)	62400 (5420)	12900 (3050)
AUC/D (h*ng/mL)/(mg/kg)	79.7	134	184	117
<i>Total BPS</i>				
C _{max} (ng/mL)	6420 (432)	18500 (1550)	32800 (1840)	13000 (1400)
C _{max} /D (ng/mL)/(mg/kg)	189	168	96.5	118
T _{max} (h)	0.991 (0.224)	1.75 (0.365)	2.77 (0.339)	0.620 (0.494)
K01 Half-Life (h)	0.172 (0.0531)	0.336 (0.0996)	0.537 (0.0947)	0.0829 (0.0825)
K10 Half-Life (h)	8.54 (0.989)	11.2 (1.64)	17.2 (1.81)	14.3 (2.88)
Cl/F (mL/h/kg)	397 (35.5)	331 (36.8)	373 (29.5)	398 (66.1)
V/F (mL/kg)	4890 (394)	5350 (555)	9260 (642)	8200 (981)
AUC (h*ng/mL)	85700 (7670)	333000 (37000)	911000 (71900)	277000 (45900)
AUC/D (h*ng/mL)/(mg/kg)	2520	3030	2680	2520

^aBased on one compartment model with first-order input, first-order output and 1/y weighting (WinNonlin Model 3).

^bValues given are mean (standard error) for N = 3.

Table 3.

Plasma toxicokinetic parameters of free and total bisphenol S following a single intravenous administration of 34 mg/kg in rats and mice ^{a,b}

Parameter	Male Rat	Female Rat	Male Mouse	Female Mouse
<i>Free BPS</i>				
C _{max} (ng/mL)	73000 (27700)	94900 (26000)	55900 (14300)	59600 (19700)
K ₁₂ (1/h)	0.225 (0.0643)	0.273 (0.0753)	0.161 (0.0354)	0.213 (0.0607)
K ₂₁ (1/h)	0.163 (0.0171)	0.100 (0.0156)	0.241 (0.0385)	0.374 (0.0531)
Alpha Half-life (h)	0.258 (0.0488)	0.184 (0.0238)	0.165 (0.0178)	0.126 (0.0189)
Beta Half-life (h)	4.67 (0.426)	7.46 (1.10)	3.00 (0.464)	1.93 (0.262)
K ₁₀ Half-Life (h)	0.238 (0.0564)	0.198 (0.0238)	0.172 (0.0192)	0.131 (0.0202)
Cl (mL/h/kg)	1140 (261)	1250 (240)	2450 (424)	3010 (649)
Cl ₂ (mL/h/kg)	105 (51.6)	97.9 (41.4)	98.2 (36.9)	121 (55.8)
V ₁ (mL/kg)	466 (177)	358 (98.3)	608 (155)	570 (189)
V ₂ (mL/kg)	643 (295)	976 (398)	407 (147)	325 (141)
AUC (h*ng/mL)	28900 (6790)	27200 (5200)	13900 (2390)	11300 (2430)
AUC/D (h*ng/mL)/(mg/kg)	876	800	409	332
<i>Total BPS</i>				
C _{max} (ng/mL)	114000 (23200)	155000 (41000)	144000 (25900)	183000 (37500)
K ₁₂ (1/h)	0.995 (0.230)	1.39 (0.453)	0.360 (0.0712)	0.177 (0.0430)
K ₂₁ (1/h)	0.248 (0.0379)	0.114 (0.0335)	0.279 (0.0239)	0.264 (0.0262)
Alpha Half-life (h)	0.344 (0.0601)	0.248 (0.060)	0.272 (0.0293)	0.260 (0.0272)
Beta Half-life (h)	6.38 (0.46)	12.7 (2.91)	2.95 (0.196)	2.83 (0.249)
K ₁₀ Half-Life (h)	0.784 (0.131)	0.517 (114)	0.324 (0.0352)	0.280 (0.0295)
Cl (mL/h/kg)	263 (19.1)	293 (33.5)	506 (53.3)	459 (62.5)
Cl ₂ (mL/h/kg)	296 (63.1)	305 (99.9)	85.3 (21.5)	32.9 (10.6)
V ₁ (mL/kg)	298 (60.4)	219 (57.9)	237 (42.6)	186 (38.1)
V ₂ (mL/kg)	1190 (154)	2690 (739)	305 (65.6)	124 (35.5)
AUC (h*ng/mL)	129000 (9360)	116000 (13200)	67100 (7060)	74100 (10100)
AUC/D (h*ng/mL)/(mg/kg)	3790	3410	1970	2180

^aBased on two compartment model with bolus input, first-order output and 1/y² weighting.

^bValues given are mean (standard error) for N = 3.

Table 4.

Plasma toxicokinetic parameters of free and total bisphenol S following a single gavage administration of BPS in mice^{a,b}

Parameter	Dose (mg/kg)			
<i>Free BPS</i>	34 (Male)	110 (Male)	340 (Male)	110 (Female)
C _{max} (ng/mL)	7540 (2770)	19400 (3590)	39200 (22700)	21300 (13500)
T _{max} (h)	NE	NE	NE	NE
K ₁₂ (1/h)	1.50 (0.587)	1.31 (0.274)	1.20 (1.19)	1.12 (0.869)
K ₂₁ (1/h)	0.377 (0.185)	0.25 (0.11)	0.312 (0.283)	0.273 (0.379)
Alpha Half-life (h)	0.151 (0.0415)	0.133 (0.0158)	0.244 (0.151)	0.134 (0.0552)
Beta Half-life (h)	2.86 (1.41)	3.77 (1.78)	4.21 (3.17)	3.29 (4.78)
K ₁₀ Half-Life (h)	0.235 (0.0677)	0.181 (0.0266)	0.461 (0.246)	0.173 (0.0804)
Cl/F (mL/h/kg)	13300 (2100)	21700 (1950)	13000 (4670)	20600 (6130)
Cl _{2/F} (mL/h/kg)	6760 (2140)	7420 (1740)	10400 (7600)	5780 (4600)
V _{1/F} (mL/kg)	4510 (1660)	5660 (1050)	8670 (5030)	5150 (3270)
V _{2/F} (mL/kg)	18000 (10300)	29700 (17400)	33200 (26400)	21200 (38400)
AUC (h*ng/mL)	2550 (402)	5070 (455)	26100 (9350)	5340 (1590)
AUC/D (h*ng/mL)/(mg/kg)	75.0	46.1	76.8	48.5
<i>Total BPS</i>				
C _{max} (ng/mL)	47000 (10500)	140000 (23300)	43700 (24900)	142000 (48000)
T _{max} (h)	NE	NE	3.08 (3.13)	NE
K ₁₂ (1/h)	1.10 (0.465)	1.44 (0.292)	-	1.13 (0.569)
K ₂₁ (1/h)	0.469 (0.197)	0.39 (0.101)	-	0.325 (0.209)
Alpha Half-life (h)	0.258 (0.0733)	0.180 (0.0263)	-	0.185 (0.054)
Beta Half-life (h)	2.92 (0.958)	3.04 (0.763)	-	3.18 (1.99)
K ₁₀ Half-Life (h)	0.509 (0.106)	0.309 (0.0446)	3.05 (5.23)	0.277 (0.0778)
Cl/F (mL/h/kg)	986 (109)	1770 (131)	878 (619)	1940 (325)
Cl _{2/F} (mL/h/kg)	794 (226)	1130 (162)	-	874 (347)
V _{1/F} (mL/kg)	724 (162)	788 (132)	3870 (7150)	775 (262)
V _{2/F} (mL/kg)	1690 (547)	2900 (783)	-	2690 (1860)
AUC (h*ng/mL)	34500 (3790)	62100 (4600)	387000 (273000)	56700 (9500)
AUC/D (h*ng/mL)/(mg/kg)	1010	565	1140	515

^aBased on two compartment model with bolus input, first-order output and 1/y weighting except for 340 mg/kg total BPAF where one compartment model with first-order input, first-order output and 1/y weighting was used.

^bValues given are mean (standard error) for N = 3.

Table 5.

Oral bioavailability of free bisphenol S following a single gavage administration in Harlan Sprague Dawley rats and B6C3F1/N mice

Dose (mg/kg)	Bioavailability (%) ^a			
	Male Rats	Female Rats	Male Mice	Female Mice
34	9.1	NA	18.3	NA
110	15.2	14.7	11.2	14.6
340	20.9	NA	18.7	NA

^a Bioavailability (%F) was calculated as AUC/Dose (oral) ÷ AUC/Dose (IV) x 100.

Table 6.

Comparison of toxicokinetic parameters of bisphenol S (BPS), bisphenol AF (BPAF) and bisphenol A (BPA) following gavage administration in female rats and mice

	BPS ^a		BPAF ^b		BPA	
	SD rats	B6C3F1/N Mice	SD Rats	B6C3F1/N Mice	SD Rats ^c	CD-1 Mice ^d
Dose (mg/kg)	110	110	110	34	0.1	100
Dose (mmol/kg)	0.440	0.440	0.440	0.101	0.00044	0.439
Half-life (h)	4.11	3.29	12.8	9.02	3.0	4.90
C _{max} (nmol/mL)	3.22	85.2	0.729	0.313	0.00039	4.16
Dose-normalized C _{max} (nmol/mL)/(mmol/kg)	7.32	194	1.66	3.099	0.886	9.47
AUC (nmol* ^h /mL)	51.6	21.4	4.38	1.47	0.0026	13.1
Dose-normalized AUC (nmol* ^h /mL)/(mmol/kg)	117	48.6	9.94	14.6	5.91	29.8

^aData from the current study for female 110 mg/kg group. For rats and mice, respectively, C_{max} (ng/mL) values were 804 and 21300 and AUC (ng*^h/mL) values were 12900 and 5340. Molecular weight of 250 g/mol was used for conversion.

^bData from Waidyanatha et al., 2019 for female rat 110 mg/kg and female mice 34 mg/kg group. For rats and mice, respectively, C_{max} (ng/mL) values were 245 and 105 and AUC (ng*^h/mL) values were 1470 and 495. Molecular weight of 336 g/mol was used for conversion.

^cData from Dorege et al., (2010). C_{max} and AUC values reported for female rats were 0.39 nM and 2.6 nmol.h/L, respectively.

^dData from Taylor et al., (2015) for female mice. C_{max} values reported were 949 ng/mL and AUC values reported were 2991 ng*^h/mL. Molecular weight of 228 g/mol was used for conversion.