1   **Toxicokinetics of bisphenol S in rats for predicting human bisphenol S clearance from**

2   **allometric scaling**

3   Véronique Gayrard[1], Marlène Z. Lacroix[2], Clémence A. Gély[1,2], Flore C. Grandin[1], Roger

4   Léandri[3], Michèle Bouchard[4], Béatrice Roques[2], Pierre-Louis Toutain[2,5], Nicole Picard-Hagen[1]

5

6   [1] ToxAlim (Research Centre in Food Toxicology), Université de Toulouse, INRA, ENVT, INP-

7   Purpan, UPS, Toulouse, France

8   [2]INTHERES, Université de Toulouse, INRA, ENVT, Toulouse, France

9   [3]EA 3694 Human Fertility Research Group, Toulouse University Hospital, 330 Avenue de

10   Grande Bretagne, 31059 Toulouse, France

11   [4] Département de santé environnementale et santé au travail, Centre de recherche en santé

12   publique de l'Université de Montréal (CReSP), Université de Montréal, Montréal, Canada.

13   [5]The Royal Veterinary College, University of London, London, United Kingdom.

14

15   Véronique Gayrard: v.gayrard@envt.fr; Marlène Z. Lacroix: m.lacroix@envt.fr; Clémence A.
16   Gély : clemence.gely@inra.fr; Flore Grandin : flore.grandin@gmail.com; Roger Léandri :
17   leandri.r@chu-toulouse.fr; Michèle Bouchard : michele.bouchard@umontreal.ca; Béatrice
18   Roques : b.roques@envt.fr; Pierre-Louis Toutain: pltoutain@wanadoo.fr; Nicole Picard-
19   Hagen: n.hagen-picard@envt.fr
20

21   **Corresponding author**: V. Gayrard

22   Tel: +33 6 5 61 19 39 18

23   Email: v.gayrard@envt.fr

24   UMR1331 Toxalim, Ecole Nationale Vétérinaire de Toulouse, Laboratoire de Physiologie

25   23 chemin des Capelles, BP 87614, 31076 Toulouse cedex 3, France

Abbreviations:
AUC_{last}: Area under the plasma concentration-time curve from dosing time to the last sampling time, $AUMC_{last}$: Area under the first moment plasma concentration-time curve from dosing time to the last sampling time, BPA: Bisphenol A, BPAG: Bisphenol A glucuronide, BPS: Bisphenol S, BPSG: Bisphenol S glucuronide, BW: Body Weight, Cl: Clearance, Cl_F:Apparent clearance, Cmax : Maximal concentration, IV: Intravenous, LOQ: Limit of Quantification, MRT: Mean Residence Time, Tmax: Time to maximal concentration, TK: Toxicokinetic, V_{SS}: Steady state volume of distribution

26   **Abstract**

27   Previous data obtained in piglets suggested that despite structural analogy with Bisphenol A

28   (BPA), Bisphenol S (BPS) elimination may proceed more slowly, resulting in a much higher

29   systemic exposure to unconjugated BPS than to BPA. Interspecies allometric scaling was

30   applied to predict the toxicokinetic (TK) parameters of BPS, namely plasma clearance in

31   humans from values obtained in animals, and thus contribute to assessment of the human

32   internal exposure to BPS.

33   Allometric scaling was performed using mean BPS plasma clearance values measured in rats

34   after intravenous administration of 5 mg BPS /kg body weight (BW) and those previously

35   obtained in piglets and sheep using identical IV BPS dosing and analytical procedures.

36   The BPS plasma clearance, evaluated at 0.92 L/kg.h in rats, was proportional to species body

37   weight, enabling the prediction of human BPS plasma clearance by extrapolating to a BW of

38   70 kg. The estimated BPS plasma clearance in humans was thus 0.92 L/min (0.79 L/kg.h), i.e.

39   about two times lower than the previously estimated BPA clearance (1.79 L/min).

40   By increasing systemic exposure to the active moiety of an environmental estrogenic chemical,

41   this less efficient clearance of BPS in humans, as compared with BPA, might worsen the

42   harmful consequences of replacing BPA by BPS.

43

44   **Keywords:** Toxicokinetics; bisphenol S; allometric scaling, clearance

Introduction

Owing to great concern regarding the adverse effects of bisphenol A (BPA) on human health, restrictive measures have been applied that have led to its gradual replacement by structural analogues. Bisphenol S (BPS) is one of the main alternatives to BPA as a color developer in thermal papers and in the manufacture of plastics and epoxy resins (Wu et al. 2018).

The widespread and increasing use of BPS in consumer products is reflected by the high prevalence of BPS in urine from a cohort of US populations (Lehmler et al. 2018) and Asian countries (Liao et al. 2012). Despite insufficient data to assess the origin of such wide internal exposure, relevant pathways of human exposure to BPS could be the ingestion of BPS-contaminated food or dust and direct contact of BPS-contaminated hands with the mouth resulting from hand-to-mouth activity. A review of the literature suggests that substituting BPA with BPS may not lower the risk of endocrine disruption since BPS has been shown to display estrogen-like effects at concentrations similar to BPA (Pelch et al. 2019). Both BPS and BPA are largely conjugated to glucuronides (Le Fol et al. 2015; Skledar et al. 2016; Zhou et al. 2014), which are considered inactive due to their lack of estrogenicity (Matthews et al. 2001; Skledar et al. 2016). So, by increasing the internal exposure to the active form of BPA, a lower *in vivo* BPS plasma glucuronidation rate, as shown in piglets (Gayrard et al. 2019), may still aggravate the harmful consequences of BPA substitution by BPS. Indeed in piglets, the 3.5 times lower plasma clearance (Cl) of BPS as compared with BPA, combined with its 100 times lower first-pass glucuronidation following oral dosing, accounted for the 250 times higher systemic exposure to active unconjugated BPS (Gayrard et al. 2019). The relevance of this result for humans is supported by the higher serum concentrations of BPS, compared with BPA, that have been predicted for peroral exposure from a physiologically based toxicokinetic (TK) model (Karrer et al. 2018). However, the impossibility of directly measuring basic TK parameters in humans, such as plasma clearance, volume of distribution and mean residence time, limits our

3

70   understanding of the TK mechanisms underlying the different fates of bisphenol analogues,

71   thus requiring assumptions when predicting BPS plasma kinetic profiles for external

72   environmentally-relevant exposures. Clearance represents the most important TK parameter

73   because it is the only parameter controlling the internal exposure following intravenous (IV)

74   administration, as measured by the Area Under the plasma concentration vs time Curve (AUC).

75   For an oral route of exposure, AUC is entirely controlled by both Cl and bioavailability (noted

76   F). The steady-state volume of distribution (noted Vss) not only reflects the extent of

77   distribution of a substance in the body but, in conjunction with Cl, also controls its persistence

78   as measured by the Mean Residence Time (MRT). MRT is defined as the average time that a

79   single molecule of the substance of interest remains in the body. Direct calculations of Cl, Vss

80   and MRT require an IV injection that is impossible to carry out in man and an alternative

81   approach consists of estimating these TK parameters by applying an indirect approach such as

82   allometry. So-called simple allometric scaling consists of relating body size to a parameter of

83   interest using a power equation (Chappell and Mordenti 1991). This has proved to be a useful

84   tool for predicting human clearance of BPA from animal data (Collet et al. 2015). In the present

85   study, this approach was used to estimate the Cl, Vss and MRT of BPS in humans from plasma

86   BPS kinetic profiles obtained in rats following IV BPS dosing and TK data previously obtained

87   using identical IV BPS dosing and analytical procedures in piglets (Gayrard et al. 2019) and in

88   pregnant and non-pregnant ewes (Grandin et al. 2017, 2018).

89

90   Materials and methods

91   *Animal handling procedures and sample collection*

92   The experiment was declared to the regional Ethical Committee "Toxcomethique" (C2EA

93   n°86) and to the French Ministry of Research. It was authorized by the French Ministry of

94   Research under the number #5215_2016042815224143). The experiment was carried out with

95   15 female Wistar rats (Envigo, Gannat, France) weighing 266±26 g. They were fed *ad libitum*

96   a commercial rat chow (2016 Teklad global 16% protein rodent diets, Envigo) and were housed

97   individually in metabolism cages during the sampling periods.

98   The rats, briefly anesthetized using volatile anesthesia (2 % isoflurane, AErrane®, Baxter SA,

99   Maurepas, France, in 0.7 L/min of O_2), were administered BPS into the lateral tail vein at a

100 dose of 5 mg/kg. Serial blood samples (0.25 ml) were collected in propylene tubes before and

101 at each of the designated time points post-administration: 10 min (n=8), 20 min (n=6), 30 min

102 (n=8), 40 min (n=6), 60 min (n=8), 1.5h (n=6), 2h (n=8), 4h (n=5), 8h (n=8), 12h (n=6), 24h

103 (n=8) and 36h (n=4), through a catheter surgically inserted in the left femoral vein under volatile

104 anesthesia at least two days before BPS administration. After each blood sampling,

105 physiological saline was administered at a volume equivalent to the withdrawn blood volume.

106 The catheter was then filled with 200 µL of heparinized saline (50 IU/mL). Total urine was

107 collected in propylene tubes at 3, 6, 9, 12, and 24 h after BPS administration in 9 rats. The

108 volume of each urine sample and the sampling time were recorded. Blood and urine samples

109 were immediately chilled on ice and centrifuged for 10 min at 3000 g at 4°C and the supernatant

110 was stored in propylene tubes at -20°C until assayed.

111 *Test material and treatments*

112 All materials for the preparation of solutions, including the materials used for sampling,

113 processing and analysis, were made of glass or polypropylene. BPS (purity >99%) was

114 purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France). BPS dosing solutions were

115 extemporaneously prepared by dissolving BPS in ethanol-saline (1:4, vol:vol) at 5 mg/ml.

116 *BPS assay*

117 Analytes were quantified by Acquity ultra performance liquid chromatography coupled to a

118 Xevo triple quadrupole mass spectrometer (Waters, Milford, MA, USA). BPS and BPSG in

119   plasma and urine samples were measured simultaneously, without resorting to a hydrolysis step,

120   using the method described previously (Grandin et al. 2017).

121   *Toxicokinetic analyses*

122   The plasma mass concentrations were converted into molar concentrations before analysis. The

123   cumulated molar quantities of excreted BPS (BPSG) in urine were calculated by multiplying

124   the molar concentrations of BPS (BPSG) by the volume of urine at each sampling time.

125   Plasma concentration-time profiles of BPS were analyzed using Phoenix (version 8.0 Pharsight

126   Corporation) according to a non-compartmental approach (NCA) involving a sparse data

127   option. Sparse data methodology consists of calculating TK parameters based on the mean

128   profile of all the subjects in the dataset and is appropriate when no rich data series can be

129   obtained, as in the present experiment. The AUC and the Area under the first moment curve

130   from the time of dosing to the last measurable concentration, AUC_{last} and $AUMC_{last}$ were

131   calculated using the linear trapezoidal rule. The mean plasma concentration-time profile of

132   BPSG was used to derive the maximum concentration (Cmax), the time to maximum

133   concentration (Tmax), and the AUC_{last} and $AUMC_{last}$ values. The Cl of BPS and apparent

134   clearance of BPSG (Cl_F) were estimated after IV administration of BPS by dividing the dose

135   by the AUC_{last} calculated for each analyte as previously described. V_{ss} and MRT were computed

136   using the usual pharmacokinetic equations and the moment statistical approach (Gibaldi and

137   Perrier 1983).

138   *Allometric approach*

139   Allometric scaling was based on the mean clearance and body weight data obtained in rats and

140   those previously obtained using identical 5mg/kg IV BPS dosing and analytical procedures in

141   female piglets (Gayrard et al. 2019), and in pregnant and non-pregnant female sheep (Grandin

142   et al. 2017, 2018). The data used for allometric scaling are given in Table 1.

143   The mean clearance values (Cl) obtained in each animal species were plotted against the mean

144   animal BW using the following standard power equations:

145    $C_l = a \times BW^b$ Eq1

146   where a and b are the allometric coefficient and the exponent of the allometric equation,

147   respectively.

148   The Cl and BW were transformed logarithmically and fitted to Equation 2 by linear regression

149   analysis using Systat[R] (Version 11, Systat Software, Inc., San Jose California USA).

150    $logC_l = loga + b \times logBW$ Eq2

151   where $log\ a$ is the y-intercept, and b is the slope.

152   Based on the animal data, the predicted value of Cl in humans was obtained by solving the

153   allometric equation for a standard BW of 70 kg. Vss and MRT were scaled using the same

154   approach as for Cl. Since the classical allometric relationship for Vss produced a very low and

155   unexpected computed exponent (0.526) and predicted an unrealistically low Vss (0.267L/kg,

156   see discussion), this approach was no longer considered to estimate Vss in man. The alternative

157   approach proposed by Bachmann et al. (1996), based exclusively on rat Vss, was implemented

158   to predict Vss in man using a power model with slope and intercept values of 0.91 and 0.705

159   respectively. MRT was deduced from Cl and Vss estimates according to Equation 3.

160    $MRT = V_{SS}/Cl$ Eq3

161

162   **Results**

163   BPS was not detected in any of the control samples obtained before the administrations,

164   suggesting that little-to-no sample contamination had occurred during sample collection,

165   processing and assay. The time course of plasma concentrations of BPS and BPSG in rats after

166   IV administration is shown in Figure 1. Table 2 gives the values estimated by NCA for TK

167   parameters of BPS and BPSG after IV BPS administration. The plasma concentration-time

168   profile of BPS was characterized by a phase of rapid decay of concentrations during the first

169   four hours followed by a slow elimination phase. Plasma BPSG concentrations increased

170   rapidly after IV administration of BPS, and the maximum BPSG concentration (C_{max}) was

171   attained within the first 10 minutes. After a rapid decline, an increase of BPSG plasma

172   concentrations was observed about 4 h after BPS injection, after which the concentrations then

173   decreased slowly from 12 h post dosing. The BPS Cl and BPSG Cl_F values were 0.92 L/kg.h

174   and 0.18 L/kg.h, respectively. The respective values of BPS Vss and MRT were 3.64 L/kg and

175   3.96 h. By 24h, the mean fraction of the BPS dose (± SD) recovered in urine was 37.5 ± 12.3%

176   (n=9) mostly as BPSG (93.5 ± 7.1%), unconjugated BPS in urine representing 1.9 ± 2.1 % of

177   the BPS dose.

178   The allometric relationship between BW and Cl is shown in Figure 2. Data were fitted using

179   equation 1 and the resulting allometric equation 4 was used to predict Cl according to BW.

180     $Cl = 0.0151 \times BW^{0.968}$ Eq4

181   with Cl in L/min, and BW in kg

182   The 95 % confidence interval for the slope of the allometric relationship between BW and Cl

183   (b value) was 0.8437 to 1.100 meaning that the slope was not significantly different from 1 with

184   P > 0.05. On applying Equation 4, the estimated BPS Cl for a 70-kg human was 0.92 L/min

185   (0.79 L/kg.h). Using the empirical model proposed by Bachmann et al. (1996), the estimated

186   BPS Vss was 2.26 L/kg in man, based on the rat Vss value of 3.6L/kg, and the deduced value

187   of MRT was 2.86 h.

188

189   **Discussion**

190   Our estimates of BPS Cl, Vss and MRT in humans, based on scaling from animal data, provide

191   some additional TK data for BPS. While the TK properties of BPA have been the subject of a

192   large number of studies, to our knowledge this is the first study to describe the TK parameters

193   of BPS and BPSG after BPS IV dosing in rats, a species commonly used in toxicological

194   studies.

195   The BPS clearance in rats (0.92 L/kg.h) was shown to be equivalent to that previously estimated

196   in larger species such as sheep (Grandin et al. 2017, 2018) and piglets (Gayrard et al. 2019)

197   while the persistency of BPS as reflected by the MRT was 5 to 13 times higher (4 h) due to its

198   5 to 21 times higher V_{SS} (3.6 L/kg). The rebound in BPSG plasma concentrations, that peaked

199   12 h post BPS IV dosing, may reflect the BPS enterohepatic recirculation previously suggested

200   by the rather high fecal excretion of BPS and its metabolites following IV administration in rats

201   (32.5% of the dose, Waidyanatha et al. 2018). In the present experiment, the mean fraction of

202   BPS dose recovered in urine over the 0-24 h post-dosing period was 37.5%, mostly in the form

203   of BPSG, indicating that the renal clearance of unconjugated BPS was minimal. This result is

204   consistent with those of other authors who reported that 42% of the radioactivity was eliminated

205   in urine following injection of radiolabeled BPS in rats (Waidyanatha et al. 2018). This suggests

206   that the clearance of BPS is driven by its biotransformation to more hydrophilic secondary

207   metabolites (mainly BPSG) with subsequent elimination either in urine or bile. Enterohepatic

208   recycling of BPA has been shown to occur in rats (Kurebayashi et al. 2003). An enterohepatic

209   recirculation pathway has also been incorporated in the PBTK model of BPS for peroral

210   exposure (Karrer et al. 2018) to improve the fitting of model predictions for BPS data

211   biomonitoring (Oh et al. 2018) and to account for the longer persistence of BPS compared with

212   BPA. The relevance of this modality of BPS elimination in humans is however questionable

213   since BPSG has been shown to be cleared mostly by renal clearance in humans (Oh et al. 2018).

214   The main result of our study is that BPS Cl can be estimated in man, with a good degree of

215   confidence, by applying a simple allometric approach and selecting three species with BWs

216   spanning a large range (from 0.2 to 77Kg BW). We were thus able to estimate Cl by

217   interpolation and thereby reduce the uncertainties associated with extrapolation. In addition, the

218   coefficient of determination (R^2) associated with the linear regression was very high (0.99)

219   meaning that 99 % of the variability in BPS Cl between species was captured by the interspecies

220   variation of BW. For the three species investigated, the allometric model predicted that the

221   plasma Cl of BPS was directly related to BW and that the allometric exponent was not

222   significantly different from 1. It has been argued that if the exponent of a simple allometric

223   equation lies between 0.71 and 1, the product of Maximum Life-span potential (MLP) and

224   clearance will predict Cl better than simple allometry (Mahmood and Balian 1996). We

225   explored this so-called exponent rule to estimate the Cl in humans but did not find that such a

226   correction was justified. The plasma Cl in man was thus estimated at a typical value of

227   0.92 L/min for a BW of 70 kg (0.79 L/kg.h). Assuming that the plasma and blood BPS

228   concentrations are equal, as observed in sheep (unpublished observations), it can be concluded

229   that the blood BPS Cl in humans is equal to 18% of the cardiac output (about 5 L/min) and 60%

230   of the hepatic blood flow rate (1.24 L/kg.h, i.e. 1.45L/min for a 70-kg BW, Davies and Morris

231   1993). The mechanism of BPS Cl in man is unknown but assuming that all BPS is solely cleared

232   by the liver (better case scenario for an oral exposure to an endocrine disruptor), the estimated

233   hepatic extraction ratio (ERh) would therefore be 60%. The resulting fraction of BPS

234   administered by oral route that escapes a hepatic first-pass effect can be as high as 40% (i.e. 1-

235   ERh). This percentage will be even higher if a significant fraction of BPS is actually

236   metabolized by some extra-hepatic mechanism such as renal clearance. This result is consistent

237   with the bioavailability of BPS (57.4 %) that we directly measured in pigs (Gayrard et al. 2019).

238   From our allometric estimate of BPS Cl in humans, it can therefore be tentatively concluded

239   that if the liver is the only clearing organ of BPS in man (i.e. only an hepatic first-pass effect

240   and no intestinal first-pass effect as we recently predicted in pigs, Gayrard et al. 2019), the oral

241   bioavailability of BPS in man could be 50% or more. The relevance of a high BPS oral

242   bioavailability in humans is strengthened by the similar values obtained for human BPS plasma

243   clearance estimated by allometry (0.79 L/kg.h) and the apparent clearance values computed

244   from observed time courses in volunteers reported by Oh et al. (2018), using the area under the

245   curve of unconjugated BPS (61 L/h *i.e.* 0.88L/kg.h). The predicted BPS oral bioavailability in

246   man is much higher than the systemic oral BPA bioavailability that has been evaluated at less

247   than 1% in adult monkeys (Doerge et al. 2010). It should be understood that when the hepatic

248   clearance approaches a value close to the hepatic blood flow (1.5 L/min in man), the resulting

249   increased hepatic first-pass effect leads to a much higher than proportional decrease of the oral

250   bioavailability. This is likely the main explanation for the much higher BPS oral bioavailability

251   compared with BPA, as shown in piglets (57.4% vs 0.50%, Gayrard et al. 2019). Indeed, the

252   clearance of BPA in man (1.5 L/kg.h, Collet et al. 2015), mainly hepatic (Trdan Lušin et al.

253   2012) is close to the human hepatic blood flow (1.24 L/kg.h, Davies and Morris 1993) thereby

254   allowing a near total first-pass effect. On the other hand, BPS clearance (0.79L/kg.h), although

255   only two times lower than that of BPA, is not enough to ensure a near total hepatic first-pass

256   effect, and results in a much higher than proportional increase of BPS bioavailability compared

257   with BPA. In humans, the lower estimated BPS clearance compared with that of BPA (0.79 *vs*

258   1.5 L/kg.h, Collet et al. 2015) is consistent with the lower intrinsic hepatic clearance (0.4 vs 4.2

259   L/kg/h) predicted from the BPS and BPA glucuronidation kinetic parameters in human liver

260   microsomes (Karrer et al. 2018).

261   The classical allometric relationship for Vss led to an unexpectedly low computed exponent of

262   0.526 whereas for most drugs this exponent is around 1 (Mahmood 2010), and therefore

263   predicted an unrealistically low Vss in man. This is why we implemented the approach

264   proposed by Bachmann et al. (1996) who showed that the human volume of distribution for 100

265   xenobiotics could be well predicted solely from the rat Vss. Using this empirical model, the

266   BPS Vss estimated from the rat V_{SS} value (3.6 L/kg) was 2.26 L/kg in man. This prediction is

267   close to the reported human Vss/F that can be approximated at 5.15 L/kg by computing Vss/F

268   from the human oral TK data published by Oh et al. (2018) and using equation 5.

269   $V_{SS} = Cl \times MRT$ Eq 5

270   where Cl represents the apparent clearance of BPS (0.88 L/kg.h) and MRT is equal to 5.85 h

271   An additional step for understanding the BPS disposition consists of considering the minimal

272   model for Vss, as given by equation 6:

273   $V_{SS} = V_P + \frac{fu}{fuT} \times V_T$ Eq 6

274   where V_P is the plasma volume, V_T is the tissue volume, and fu and fuT are the fraction of

275   unbound drug in plasma and tissue respectively. The unbound fraction of BPS in plasma has

276   been shown to be slightly different in rats (0.15) and pregnant women (0.10, Gayrard,

277   unpublished observation). Solving equation 6 with fu values for humans and rats and

278   physiological values for human and rat tissues and plasma volumes (De Buck et al. 2007)

279   predicts that fuT (a measure of BPS tissue affinity) would be very similar in rats (0.038) and

280   man (0.053); this means that the difference in Vss between men and rats may simply reflect

281   differences in the extent of BPS binding to plasma proteins. The lower V_{SS} of BPS in humans

282   compared with rats resulted in a lower MRT (2.86 h).

283   Conclusion

284   Based on our allometric approach, we conclude that BPS is less efficiently metabolized than

285   BPA in humans, as reflected by its at least two-times lower plasma clearance. Since BPA

286   substitution by BPS should lead to equivalent external exposures in terms of doses and routes,

287   this lower BPS plasma clearance might lead to much higher oral serum concentrations of

288   unconjugated BPS, as compared with BPA, due to the direct effect of a lower plasma clearance

289   of BPS and indirectly by a much lower hepatic first-pass effect. Considering that BPA and BPS

290   have comparable estrogen-like effects, our results suggest that oral BPS exposure might be

291   associated with higher risks for human health than BPA.

References

Bachmann K, Pardoe D, White D. 1996. Scaling basic toxicokinetic parameters from rat to man. Environ Health Perspect 104:400–407; doi:10.1289/ehp.96104400.

Chappell WR, Mordenti J. 1991. Extrapolation of Toxicological and Pharmacological Data from Animals to Humans. In: *Advances in Drug Research* (B. Testa, ed). Vol. 20 of *Advances in Drug Research*. Academic Press. 1–116.

Collet SH, Picard-Hagen N, Lacroix MZ, Puel S, Viguié C, Bousquet-Melou A, et al. 2015. Allometric scaling for predicting human clearance of bisphenol A. Toxicol Appl Pharmacol 284:323–329; doi:10.1016/j.taap.2015.02.024.

Davies B, Morris T. 1993. Physiological parameters in laboratory animals and humans. Pharm Res 10:1093–1095; doi:10.1023/a:1018943613122.

De Buck SS, Sinha VK, Fenu LA, Nijsen MJ, Mackie CE, Gilissen RAHJ. 2007. Prediction of human pharmacokinetics using physiologically based modeling: a retrospective analysis of 26 clinically tested drugs. Drug Metab Dispos 35:1766–1780; doi:10.1124/dmd.107.015644.

Doerge DR, Twaddle NC, Woodling KA, Fisher JW. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicol Appl Pharmacol 248:1–11; doi:10.1016/j.taap.2010.07.009.

Gayrard V, Lacroix MZ, Grandin FC, Collet SH, Mila H, Viguié C, et al. 2019. Oral Systemic Bioavailability of Bisphenol A and Bisphenol S in Pigs. Environ Health Perspect 127:77005; doi:10.1289/EHP4599.

Gibaldi and Perrier. 1983. Pharmacokinetics, 2nd Ed. By Milo Gibaldi and Donald Perrier. Marcel Dekker, 270 Madison Avenue, New York, NY 11016. 1982. 494 pp. 16 × 23 cm. Price: $34.50 (20% higher outside the U.S. and Canada). Journal of Pharmaceutical Sciences 72:1370–1371; doi:10.1002/jps.2600721139.

Grandin F, Picard-Hagen N, Gayrard V, Puel S, Viguié C, Toutain P-L, et al. 2017. Development of an on-line solid phase extraction ultra-high-performance liquid chromatography technique coupled to tandem mass spectrometry for quantification of bisphenol S and bisphenol S glucuronide: Applicability to toxicokinetic investigations. J Chromatogr A 1526:39–46; doi:10.1016/j.chroma.2017.10.020.

Grandin FC, Lacroix MZ, Gayrard V, Gauderat G, Mila H, Toutain P-L, et al. 2018. Bisphenol S instead of Bisphenol A: Toxicokinetic investigations in the ovine materno-feto-placental unit. Environ Int 120:584–592; doi:10.1016/j.envint.2018.08.019.

Karrer C, Roiss T, von Goetz N, Gramec Skledar D, Peterlin Mašič L, Hungerbühler K. 2018. Physiologically Based Pharmacokinetic (PBPK) Modeling of the Bisphenols BPA, BPS, BPF, and BPAF with New Experimental Metabolic Parameters: Comparing the Pharmacokinetic Behavior of BPA with Its Substitutes. Environ Health Perspect 126:077002; doi:10.1289/EHP2739.

335   Kurebayashi H, Betsui H, Ohno Y. 2003. Disposition of a low dose of 14C-bisphenol A in
336   male rats and its main biliary excretion as BPA glucuronide. Toxicol Sci 73:17–25;
337   doi:10.1093/toxsci/kfg040.

338   Le Fol V, Aït-Aïssa S, Cabaton N, Dolo L, Grimaldi M, Balaguer P, et al. 2015. Cell-specific
339   biotransformation of benzophenone-2 and bisphenol-s in zebrafish and human in vitro
340   models used for toxicity and estrogenicity screening. Environ Sci Technol 49:3860–
341   3868; doi:10.1021/es505302c.

342   Lehmler H-J, Liu B, Gadogbe M, Bao W. 2018. Exposure to Bisphenol A, Bisphenol F, and
343   Bisphenol S in U.S. Adults and Children: The National Health and Nutrition
344   Examination Survey 2013-2014. ACS Omega 3:6523–6532;
345   doi:10.1021/acsomega.8b00824.

346   Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon H-B, et al. 2012. Bisphenol S in urine
347   from the United States and seven Asian countries: occurrence and human exposures.
348   Environ Sci Technol 46:6860–6866; doi:10.1021/es301334j.

349   Mahmood I. 2010. Theoretical versus empirical allometry: Facts behind theories and
350   application to pharmacokinetics. J Pharm Sci 99:2927–2933; doi:10.1002/jps.22073.

351   Mahmood I, Balian JD. 1996. Interspecies scaling: predicting clearance of drugs in humans.
352   Three different approaches. Xenobiotica 26:887–895;
353   doi:10.3109/00498259609052491.

354   Matthews JB, Twomey K, Zacharewski TR. 2001. In vitro and in vivo interactions of
355   bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors
356   alpha and beta. Chem Res Toxicol 14: 149–157.

357   Oh J, Choi JW, Ahn Y-A, Kim S. 2018. Pharmacokinetics of bisphenol S in humans after
358   single oral administration. Environ Int 112:127–133;
359   doi:10.1016/j.envint.2017.11.020.

360   Pelch K, Wignall JA, Goldstone AE, Ross PK, Blain RB, Shapiro AJ, et al. 2019. A scoping
361   review of the health and toxicological activity of bisphenol A (BPA) structural
362   analogues and functional alternatives. Toxicology 424:152235;
363   doi:10.1016/j.tox.2019.06.006.

364   Rochester JR, Bolden AL. 2015. Bisphenol S and F: A Systematic Review and Comparison of
365   the Hormonal Activity of Bisphenol A Substitutes. Environ Health Perspect 123:643–
366   650; doi:10.1289/ehp.1408989.

367   Skledar DG, Schmidt J, Fic A, Klopčič I, Trontelj J, Dolenc MS, et al. 2016. Influence of
368   metabolism on endocrine activities of bisphenol S. Chemosphere 157:152–159;
369   doi:10.1016/j.chemosphere.2016.05.027.

370   Trdan Lušin T, Roškar R, Mrhar A. 2012. Evaluation of bisphenol A glucuronidation
371   according to UGT1A1*28 polymorphism by a new LC-MS/MS assay. Toxicology
372   292:33–41; doi:10.1016/j.tox.2011.11.015.

373   Waidyanatha S, Black SR, Snyder RW, Yueh YL, Sutherland V, Patel PR, et al. 2018.
374   Disposition and metabolism of the bisphenol analogue, bisphenol S, in Harlan Sprague

375   Dawley rats and B6C3F1/N mice and in vitro in hepatocytes from rats, mice, and
376   humans. Toxicol Appl Pharmacol 351:32–45; doi:10.1016/j.taap.2018.05.008.

377 Wu L-H, Zhang X-M, Wang F, Gao C-J, Chen D, Palumbo JR, et al. 2018. Occurrence of
378   bisphenol S in the environment and implications for human exposure: A short review.
379   Sci Total Environ 615:87–98; doi:10.1016/j.scitotenv.2017.09.194.

380 Zhou X, Kramer JP, Calafat AM, Ye X. 2014. Automated on-line column-switching high
381   performance liquid chromatography isotope dilution tandem mass spectrometry
382   method for the quantification of bisphenol A, bisphenol F, bisphenol S, and 11 other
383   phenols in urine. J Chromatogr B Analyt Technol Biomed Life Sci 944:152–156;
384   doi:10.1016/j.jchromb.2013.11.009.

385

386   Table 1: Mean species body weight and toxicokinetic parameters used for allometric scaling

387

Species	n	Body weight (kg)	Clearance (L/kg.h)	V_{SS} (L/kg)	MRT (h)	Reference
Female rats	15	0.27 ± 26.2	0.92	3.64	3.96	Present study
Female piglets	16	11.2 ± 1.42	0.95 ± 0.24	0.75 ± 0.38	0.75 ± 0.53	(Gayrard et al. 2019)
Female sheep (not pregnant)	4	59.6 ± 13.5	0.57 ± 0.13	0.17 ± 0.04	0.30 ± 0.04	(Grandin et al. 2017)
Sheep (pregnant)	6	77.4 ±12.3	0.99	0.38	0.38	(Grandin et al. 2018)

388   V_{SS}: Steady state volume of distribution
389   MRT: Mean Residence Time

390

391   Table 2: Toxicokinetic parameters of BPS and BPSG estimated by NCA analysis after BPS

392   intravenous dosing.

393

Toxicokinetic parameters	BPS	BPSG
Cmax (μM)	27.3	17.0
Tmax (h)	NA	0.17
AUC_{last} (μM.h)	21.8	106.1
Cl (L/kg.h)	0.92	NA
Cl_F (L/kg.h)	NA	0.18
V_{SS} (L/kg)	3.64	NA
MRT (h)	3.96	14.2

394   The toxicokinetic parameters of BPS and BPSG were estimated after IV administration of BPS
395   at 20 μmoles/kg (5mg/kg).
396   AUClast: Area under the plasma concentration-time curve from dosing time to the time of the
397   last measurable plasma concentration
398   BPS: Bisphenol S
399   BPSG: Bisphenol S glucuronide
400   Cl: Clearance
401   Cl_F: Apparent clearance
402   V_{SS}: Steady state volume of distribution
403   MRT: Mean Residence Time
404   NA: not applicable

Figure captions

Figure 1: Semi-logarithmic plots of the plasma concentrations (μM) of BPS and BPSG versus time (h) in rats (n=15) following IV administration of BPS at 5 mg/kg.

Figure 2: Allometric scaling plot for BPS plasma clearance (Cl). Data were obtained in rats (open circle), piglets (closed circle), non-pregnant sheep (open triangle), and pregnant sheep (closed triangle). The continuous line represents linear regression analysis of all the data points. The allometric equation is provided and the open square indicates where a 70-kg BW adult human falls with the corresponding equation.