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The occurrence and risk assessment of bisphenol A and its analogues – bisphenol B, F, S, Z and AF in the urine of lactating sows

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Abstract: Bisphenols (BP) are pollutants that are globally and widely distributed and adversely affect the health of humans. However, knowledge of their presence in animals, especially farm animals such as pigs, remains limited. In this study, the incidence of bisphenol A (BPA) and its five analogues – bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), bisphenol Z (BPZ) and bisphenol AF (BPAF) – was monitored in lactating sows on an actual pig farm. The urine samples of 27 sows were collected twice on the 3rd day after parturition, and stored at −20 °C until analysis using MDGC/MS. None of the lactating sows produced bisphenol-free urine. In contrast, the urine of all sows contained at least two bisphenols (eight females), most often five (10 females) or all six bisphenols (five females). The average concentrations of bisphenols in urine were in the order of BPB > BPA and BPS > BPZ > BPAF > BPF. The most frequently detected bisphenol was BPB (96.0% of samples) followed by BPA (89.0%), BPAF (78.0%), BPS (63.0%), BPF (52.0%) and BPZ (37.0%). Additionally, the proportion of BPB in the total bisphenol concentration in urine samples was the highest (28.74 to 93.85%) while that of BPF was the lowest (2.33 to 16.70%). Estimated daily intakes of bisphenols as well as hazard quotients were much lower than risk thresholds established for the human population, indicating safe doses for the health status of lactating sows. However, these findings are limited as the mechanism of BPA analogue' activity is still unclear, and the long-term effects of small doses of bisphenols and the potential harmful impact of BP mixtures are unknown. Knowledge of the occurrence of bisphenols in pig farming may contribute to the elimination of BPA and its analogues from this sector, which is crucial for the safety of animal products as well as the welfare of pigs.

Keywords: endocrine disruptor; pig; urine; estimated daily intake

Humans as well as animals are exposed to many pollutants such as pesticides, heavy metals, dioxins or biphenyls, which have the potential to adversely affect their health status or production efficiency (Rose et al. 2005; Antunovic et al. 2021; Ketta et al. 2021). One of the most widespread synthetic pollutant is bisphenol A [BPA; 2,2-bis(4-hydroxyphenol)propane], considered a chemical capable of disrupting the endocrine system. BPA is a primary bisphenol, mainly used in the plastic industry as epoxy resins, food and drink cans, baby bottles, thermal receipt paper, personal care

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products, and dental sealants (Huang et al. 2017). Its production is still increasing globally despite restrictions in some parts of the world (EU, USA, China, Canada, Australia, etc.). After detecting the harmful effects of BPA on living organisms, it began to be replaced by several other substances, so-called "BPA structural analogues" or "substitutes", e.g., bisphenol B, F, S, Z, AF and many others.

Bisphenol B [BPB; 2,2-bis(4-hydroxyphenyl)butane] has been found in environmental samples such as indoor dust, and sewage sludge (Cesen et al. 2019) or in various foods such as beverages and canned seafood (Cunha et al. 2011, 2012).

Bisphenol F [BPF; bis(4-hydroxyphenyl)methane] has been used in flooring and lining materials, food packaging, plastic (epoxy resins) and the pharmaceutical industry (Fiege et al. 2000). The occurrence of this bisphenol was also recorded in various foodstuffs such as fish and seafoods, meat and meat products, vegetables, and soft drinks (Liao and Kannan 2014). BPF displays hormonal activity, similar to oestrogen-like BPA (Rochester and Bolden 2015), affecting adipogenesis and lipid metabolism (Boucher et al. 2016).

Bisphenol S (BPS; 4,4'-sulfonylbisphenol) is widely used in thermal receipt papers (Rochester and Bolden 2015), canned and packaged foods (Lehmler et al. 2018). This compound is considered a substance with oestrogenic, androgenic and antiestrogenic activity similar to BPA (Rochester and Bolden 2015). It can adversely affect the growth and maturation of ovarian follicles, oocyte quality in females and testosterone levels in males, resulting in reproductive and embryo development disorders (Zalmanova et al. 2016). Several studies have also demonstrated its ability to influence lipid metabolism and adipogenesis (Boucher et al. 2016), induce oxidative stress, and affect genes and the immune system of organisms (Qiu et al. 2019).

Bisphenol Z [BPZ; 1,1-bis(4-hydroxyphenyl)cyclohexan] is a precursor to specialty polycarbonate plastics and epoxy resins.

Bisphenol AF [BPAF; 4,4-(hexafluoroisopropylene)diphenol] is mainly used as a crosslinker in the synthesis of specialty fluoroelastomers.

Pig farming is widespread throughout the world and pork consumption has remained high for a long time. One of the main assumptions for the success of pig breeding is the maintenance of good health and high reproductive and productive performance. It is also well known that pigs are anatomically, physiologically and metabolically similar to humans. For this reason, they are considered a suitable animal model for the study of various disorders caused by chemical substances including bisphenols. To the best of our knowledge, almost no data are available in the literature to evaluate the incidence and concentrations of BPA and its analogues as well as risk exposure to these compounds in pigs. Therefore, the aim of the study was to monitor the occurrence of six selected bisphenols in lactating sows under conditions of a real pig farm. We also tried to calculate potential risk from their exposure. This was a pilot study project focused on the incidence of bisphenols in various pig body tissues and organs and the impact on their health status and performance.

MATERIAL AND METHODS

Reagents and chemicals

Chemical standards of BPAF (CAS 1478-61-1), BPZ (843-55-0), BPS (CAS 80-09-1), BPB (CAS 77-40-7), BPF (CAS 620-92-8), BPA (CAS 80-05-7) and internal standard (IS) BPA-d16 (CAS 96210-87-6) were purchased from Sigma-Aldrich Inc. (St. Louis, MO, USA). To obtain the information about the total concentration (free + conjugated form) of bisphenol compounds, β-glucuronidase/arylsulfatase from Helix pomatia type H1 (Sigma-Aldrich, Merck, St. Louis, MO, USA) was used. A 1 M (pH = 5.0) ammonium acetate/acetic acid enzymatic solution was prepared daily to obtain a solution of 30 000 IU/ml. N,O-bis(trimethylsilyl) trifluoroacetamide with trimethylchlorosilane (CAS 25561-30-2) (BSTFA/1% TMCS) and ethyl acetate (CAS 141-78-6) were purchased from Merck KGaA, (Darmstadt, Germany). Ultra-pure water was generated from Aqual 35 (Aqual, Brno, Czech Republic).

Sample collection

The experiment was carried out on a pig farm located in the northwestern part of the Czech Republic. Samples of urine from 27 lactating sows (LW-Large White, on their first to seventh litters) were taken on the third day after parturition by skilled person. The first samples were collected in the morning,

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between 7:00 and 8:00 am, and the second samples in the afternoon between 15:00 and 16:00, each of ca. 150 ml. The samples collected from each sow were mixed to obtain an average sample of day, delivered to the laboratory and stored without any preservatives in a refrigerator at –20 °C until analyses. The urine samples were taken into glass ware covered by clean polytetrafluoroethylene/silicone (PTFE/SIL) caps to avoid any chemical contamination. Disposable products (glass ware and PTFE/SIL seals) were tested for the presence of monitored compounds before sample collection.

Sample preparation

The sample preparation was based on the procedure described by Wang et al. (2019) and derivatization of extracted products by Vela-Soria et al. (2014) with minor modifications. Briefly, 0.5 ml of sow urine samples were transferred into 4 ml glass vials with a PTFE/SIL caps. For free and conjugated analyte determination, β-glucuronidase/arylsulfatase enzymatic solution (30 kIU/ml) was added. The mixtures were vortexed for 10 s and incubated at 37 °C for 12 h (overnight). The next day, the samples were spiked with internal standard (IS) (BPA-d16, 0.1 μg/ml in ethyl acetate), again vortexed for 30 s and centrifuged at 6 000 rpm (3 420 g). The resulting supernatants were transferred into new 4 ml glass vials and extracted with 1.5 ml pure ethyl acetate in an ultrasonic bath for 5 minutes. Subsequently, the mixtures were centrifuged (3 420 g for 10 min), and the upper layers were transferred into new 4 ml vials. This last step was performed two times with a new addition of 1.5 ml ethyl acetate. Both extracts were taken together and evaporated gently under nitrogen at laboratory temperature (at 22 °C). The reconstitution of the solutions was carried out by 100 μl of a mixture of ethyl acetate and BSTFA/1% TMCS at a ratio of 80 : 20 (v/v). The solutions were vortexed for 5 s and heated at 60 °C for 20 minutes. Two microlitres of those final solutions were immediately injected into the inlet of the gas chromatographic system.

Control of contamination

Before and during the analysis, the whole sample preparation process was checked. Before using laboratory ware and consumables, some special measures were carried out. In addition, glassware, e.g., Pasteur and Hamilton pipettes, was preferred instead of plastic. Laboratory material used for sample preparation was also BPA-, BPB-, BPF-, BPS-, BPZ- and BPAF-free or contained levels below the detection limit.

MDGC/MS analysis

The analysis of bisphenol compounds was performed by multidimensional gas chromatography-mass spectrometry (MDGC-MS). The chromatographic device consisted of two ovens GC-2010 Shimadzu (Kyoto, Japan) and two columns with different stationary phases. In the first oven (GC1), the SLB-5ms (30 m, i.d. 0.32 mm, 1.0 μm d.f., Supelco, Bellefonte, PA, USA) column was used. In the second oven (GC2), the SPB-50 column (30 m, i.d. 0.32 mm, 0.25 μm d.f., Sigma-Aldrich, Merck, Germany) was connected. For the analysis, 2 μl was injected in the constant heated injection port at 250 °C. As a carrier gas, helium (5.0) was used with a flow pressure of 180 kPa (approximately 2.33 ml/min). The injector operated in a splitless mode with splitless period of 2 minutes. After GC1 was connected to the "Deans switching system" Shimadzu 221-71468-91 (Switching Assy, Shimadzu, Kyoto, Japan), part of the eluent was switched from GC1 to GC2 with 100% switching recovery. The switching pressure was set at 110 kPa, and the switching time window was 7.5–26.50 minutes. The analysis was realized by the following temperature and pressure program: initial temperature was 160 °C, and it was held for 1 minute. After that, the temperature was increased to 280 °C at a rate of 40 °C per min and this value was held at 280 °C for 22.5 min to the end of the analysis. In GC2, the same temperature program was applied, but the final temperature was 10 °C lower due to the ingestion polar column. The pressure program was started at 180 kPa for 21 minutes. After that, the pressure ramped to 200 kPa at a rate of 30 kPa per minute. At 200 kPa, the pressure was held for 4.83 min until the end of the analysis. The whole MDGC-MS analysis time was 26.5 minutes.

The GCMS-QP2010 Ultra (MS) (Shimadzu, Kyoto, Japan) mass detector was utilized for analyte detection after GC2. The transfer line was held

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at 230 °C. The ion source temperature was 230 °C. The detector used the selected ion monitoring mode using the monitored target and reference ions for all the observed compounds. The calibration curves used for the selected bisphenols are illustrated in Figure 1. MDGC Solution v1.01.00 and GC Solution v240.00 (Shimadzu, Kyoto, Japan) software were used for control of the MDGC-MS system.

BP daily intake

The urinary concentrations of six bisphenols measured in lactating sows were used to estimate their daily intakes using the following equation:

$$\text{EDI} = \frac{\text{Urinary BP concentration (ng/ml)} \times \text{urinary excretion rate (l/day)} \times 1\,000}{\text{body weight (kg)}} \quad (1)$$

where:

EDI – the estimated daily intake (ng/kg body weight/day).

Five litres of urine was calculated as the average daily excretion of lactating sows. All sows were weighed before moving to farrowing pens. The hazard quotient (HQ) was calculated as the ratio of EDI and t-TDI (temporary tolerable daily intake). The threshold level of 4 000 ng/kg bw/day was established by EFSA as BPA-safe daily intake. HQ values less than 1 were considered tolerable daily dose.

RESULTS

Bisphenols in urine

Urinary concentrations and detection frequency for six selected bisphenols are shown in Table 1. The total concentration of bisphenols in a single urine sample varied from 1.40 to 38.98 ng/ml. The highest average concentration was found for BPB, the concentration of which was almost 4-fold that of BPA, and the BPS concentration was up to 10-fold that of BPF. The highest individual concentration of bisphenol was also observed for BPB (30.45 ng/ml). With the exception of one sow, bisphenol B was found in all urine samples, representing a detection frequency of 96%. The average concentrations of BPA and BPS were the same (2.31 ng/ml); however, the detection frequency was higher for BPA (24 samples) than for BPS (17 samples). The lowest average concentration was found for BPF (0.93 ng/ml), but the lowest frequency was detected for BPZ – only in 10 samples (37%).

At least two different bisphenols were found in the urine of all monitored sows (Figure 2). The most common were combinations of five (10 sows), two (eight sows) and all six (five sows) bisphenols. The highest proportion of single bisphenol from the total concentration was observed for BPB, ranging from 28.74% to 93.85%. The proportions of other bisphenols were lower, namely, 8.93–75.77% for BPS, 4.50–42.14% for BPAF, 4.74–27.94 for BPA, 11.70–22.32% for BPZ and 2.33–16.70% for BPF.

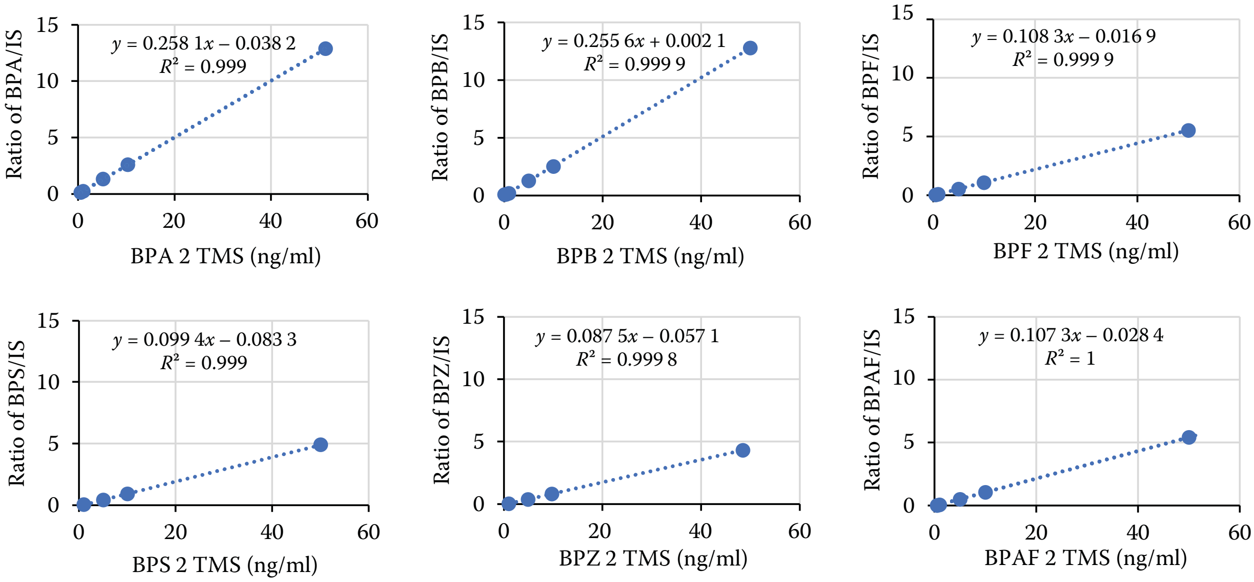

Figure 1. Calibration curves of selected bisphenols

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Table 1. The basic statistical parameters of bisphenols in urine samples of lactating sows (*n* = 27)

Bisphenol (ng/ml)	LOQ	LOD	AM	Median	25%	75%	Min.–max.	DF (%)
BPA	0.211	0.692	2.31	2.15	1.05	2.99	< LOQ–5.21	89
BPB	0.428	1.44	9.04	7.88	4.70	10.1	< LOQ–30.5	96
BPF	0.213	0.687	0.933	0.802	0.718	1.05	< LOQ–1.97	52
BPS	0.234	0.746	2.31	1.84	1.75	2.98	< LOQ–4.30	63
BPZ	0.167	0.564	1.68	1.46	1.42	1.61	< LOQ–3.54	37
BPAF	0.147	0.488	1.10	1.05	0.775	1.39	< LOQ–2.41	78

AM = arithmetic mean; DF = detection frequency; LOD = limit of detection; LOQ = limit of quantification

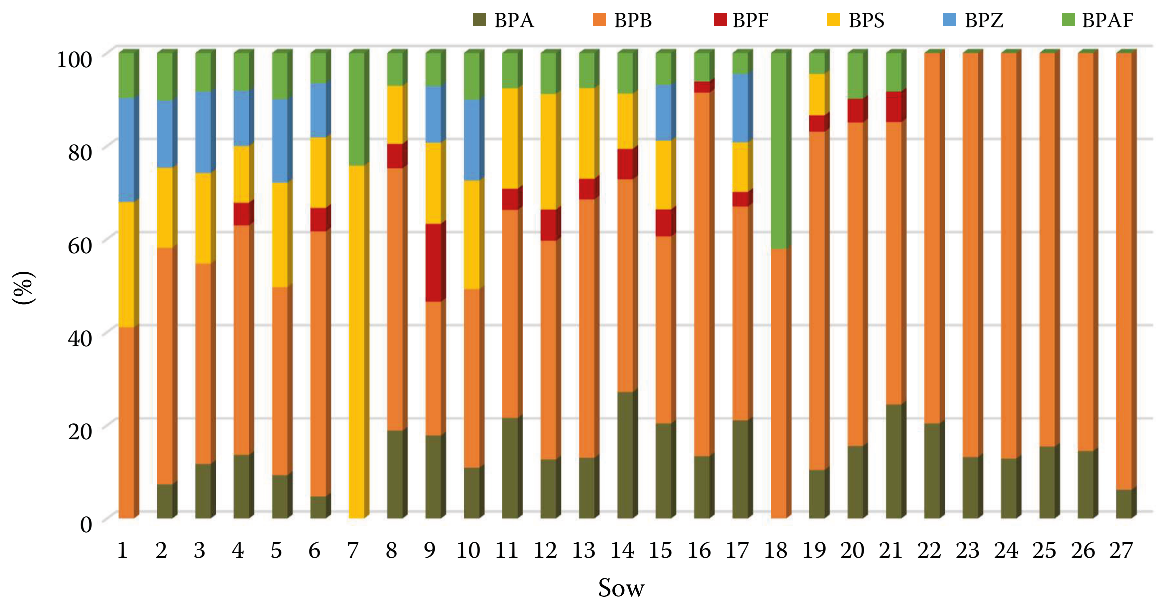

Figure 2. Proportions of bisphenols in urine of all sows (*n* = 27)

Daily bisphenol intake

The calculated daily intakes of target bisphenols and hazard quotients are reported in Table 2. The results showed that the estimated daily intake of all six bisphenols was much lower than the t-TDI value recommended by EFSA (4 μg/kg bw/day). A similar tendency was found for HQ values that were below 1. Both – EDI and HQ values were the highest for BPB, followed by BPA > BPS > BPAF > BPZ > BPF.

Table 2. Estimated daily intake (EDI) and hazard quotient (HQ) of selected bisphenols

Chemical	BPA	BPB	BPF	BPS	BPZ	BPAF
EDI (ng/kg body weight/day)	39.0	165	9.23	27.8	11.7	16.3
HQ	0.010	0.041	0.002	0.007	0.003	0.004

DISCUSSION

Urinary bisphenol concentrations and detection frequencies

To the best of our knowledge, only two studies have monitored the occurrence of BPA or its substitutes in pigs (Zhang et al. 2014; Wang et al. 2023). As pigs are very similar to humans in physiology and metabolism, we also compared our results to studies conducted on humans with one exception that reported bisphenol concentrations in typical pets – dogs and cats (Karthikraj et al. 2020). The variability in BPA concentrations in various studies may reflect the differences in environmental pollution in given parts of the world or the frequency of exposure to products containing BPA. Several studies were found to have higher BPA contamination than that in our study, e.g., in sows and boars

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from Chinese farms – 12.8 and 5.5 ng/ml (Wang et al. 2023), 346 to 414 ng/ml in sows from another part of China (Zhang et al. 2014) or in cats from New York State, USA – 22.3 ng/ml (Karthikraj et al. 2020). On the other hand, some studies revealed lower BPA concentrations compared to the present study – in pregnant women in Sweden (1.51 ng/ml – Derakhshan et al. 2019), or in dogs from New York State (1.3 ng/ml – Karthikraj et al. 2020).

In the present study, the detection rate of BPA was 89%. Similar or higher detection rates were observed in many other studies, ranging from 88% to 100% (Lehmler et al. 2018; Wang et al. 2023). In contrast, lower detection rates have been reported by other authors, e.g. Karthikraj et al. (2020) – 52 and 26%.

Bisphenol B was the major compound found in sow urine in this study with a detection rate of 96%. Higher detection rate (100%) at lower concentrations (6.4 and 3.5 ng/ml) was reported in the urine of boars and sows from China (Wang et al. 2023). It is quite surprising that BPB was highly prevalent (over BPA) in the urine of lactating sows. Its concentrations were also much higher than those of BPA. We suppose that sows in the farrowing pens on the farm are exposed to bisphenols in feed, drinking water, and inhaled air. Moreover, current automated feed systems use feed hoppers and conveyors that are made of plastic materials. In addition to primary contamination with bisphenols in the production of feed mixtures, there is certainly secondary contamination, which is caused by the rolling of the inner plastic parts of the hoppers and conveyors during the transport of the feed to the barn. In addition, sows stand on perforated plastic floors and receive feed from partially plastic automatic feeders, which increase contact with possible bisphenol contamination. It seems that all or part of these plastic elements contain higher levels of BPB than BPA, the production of which is restricted in the EU, USA or Canada in favour of its analogues such as BPB, BPF, BPS, etc.

Bisphenol S in our study was detected in 63% of urine samples with an average concentration of 2.31 ng/ml, ranging from < LOQ to 4.30 ng/ml. Wang et al. (2023) detected much higher concentrations and detection rates (8.2 and/or 25.4 ng/ml, 100%) in boars and sows. In humans in Saudi Arabia, the concentration of BPS was higher (13.3 ng/ml) than that in our study (Asimakopoulos et al. 2016). Another study from China reported BPS concentrations in children aged 3–5 years (28 ng/l). The concentrations of BPS in dogs and cats were higher than those in our study (3.2, 8.9 vs. 2.31 ng/ml – Karthikraj et al. 2020). Regarding detection frequency, higher values have been found in populations of adults in Brasil (Rocha et al. 2019) – 100%, women in South China (Zhang et al. 2020) – 100%, children and adults in the USA (Lehmler et al. 2018) – 89.4%, children in South China (Chen et al. 2018) – 89%. In dogs and cats from New York State, USA, values of 96% and 78%, respectively, were reported (Karthikraj et al. 2020).

Concentrations of two other bisphenols, BPAF and BPZ, in our study were similar (1.10 and 1.68 ng/ml, respectively). Lower concentrations of BPAF and BPZ were observed in the urine of children from South China (0.01 and 0.03 µg/l – Chen et al. 2018). In individuals in Saudi Arabia, the concentration of BPAF was higher (1.52 ng/ml) but that of BPZ was lower (0.16 ng/ml) than that in our study (Asimakopoulos et al. 2016). Although the average concentration of BPAF was the second lowest in our study, this bisphenol was detected in 78% of urine samples. The concentration of this compound was higher in this study than in children in South China (66% – Chen et al. 2018). Additionally, very low or no detection of BPAF was found in various human populations, e.g., in Brazil (Rocha et al. 2019), or Saudi Arabia (Asimakopoulos et al. 2016). Concurrently, other studies reported the incidence of BPAF in all urinary samples (100%) of pregnant women living near an e-waste dismantling area in South China (Zhang et al. 2020) or in pig populations from Chinese farms (Wang et al. 2023).

The lowest detection frequency in our study was obtained for BPZ (37%). The same frequency was observed in a Saudi Arabian population (Asimakopoulos et al. 2016). Very low or no detection frequencies were found in several studies performed on populations of adults and children in Brazil (Rocha et al. 2019) as well as in boars and sows from China (Wang et al. 2023). Children in South China were detected at a frequency of 18% (Chen et al. 2018).

BPF in the present study was found at the lowest concentration (0.93 ng/ml) among all target bisphenols. This is in line with findings of other studies with concentrations below 1.0 ng/ml (Chen et al. 2018; Karthikraj et al. 2020). The detection frequency (52%) was higher than that in the studies of Karthikraj et al. (2020) – 30%, Rocha et al.

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(2019) – 40% but lower than that of Lehmler et al. (2018) – 66.5% and Derakhshan et al. (2019) – 88%. In contrast, higher concentrations and detection rates (2.9 and 3.2 ng/ml, 100%) were found in boars and sows from China (Wang et al. 2023).

Daily bisphenol intake

BPA and its analogues are metabolized to glucuronides (Gramec Skledar et al. 2015) and almost completely excreted in urine within 24 h after exposure (Taylor et al. 2011). Therefore, the daily intake of BPA and its analogues may be calculated using a 24 h urine sample (Lakind and Naiman 2008). In 2015, European Food Safety Authority (EFSA) determined BPA safe oral daily intake to be less than 4 µg/kg body weight (EFSA 2015). However, based on all the new scientific research assessed, EFSA's experts established a TDI of 0.2 ng per kilogram of body weight per day, replacing the above mentioned level (EFSA 2023). As shown, the EDI values for BPA, BPB, BPF, BPS, BPZ and BPAF in our study are deeply below these recommended levels. Similar results were presented by other studies – e.g. for BPA in pregnant Australian women in the range 0.01–0.14 µg/kg bw/day (Callan et al. 2013). EDI below t-TDI was also estimated in other studies performed on Chinese children – for BPA 0.051 µg/kg bw/day (Gao et al. 2016) as well as for BPA, BPF, BPS, BPZ and BPAF (22.2, 5.17, 1.52, 0.72 and 0.38 ng/kg bw/day – Chen et al. 2018). An extensive study on EDI worldwide reported global average for BPA, BPB, BPS, BPZ and BPAF of 2.53, 0.29, 0.60, 0.24 and 0.06 µg/person/day, respectively (Wang et al. 2020). Although all these values reported are far lower than the TDI, a study by Huang et al. (2017) noted that the actual daily intakes of some people (adults, children, infants, pregnant women) in various countries (USA, Canada, Australia, Taiwan, China, Korea, Germany, France, etc.) exceeded the t-TDI, so has the potential to cause health disorders.

The hazard quotients in our study were also much lower than the limit, suggesting safe daily doses for all six bisphenols. Similar values for BPS were reported in dogs (0.002) and cats (0.003), (Karthikraj et al. 2020).

Although the values of the calculated daily intake of bisphenols and hazard quotient are well below the risk thresholds, we are aware of some limitations of our study. First, tolerable daily intake was established for humans, not for animals. However, no study has yet been conducted on pigs. All current investigations have focused on the *in vitro* effect of bisphenols on various cells and systems in pig bodies. Thus, we could compare our results only with studies on humans or with one study on dogs and cats. Second, the metabolism of bisphenols in pig bodies may be different in detail compared with humans, although we expect a similar function since pigs are physiologically very similar to humans. It seems that the average concentrations and daily intake of bisphenols in the present study are safe compared to those established for humans. However, we do not know the effect of long-term exposure (3–4 years) of even very small doses on sows' health, their performance or progeny. Several studies have proven that BPA may adversely affect the health of humans at doses that are much lower than the TDI (Hessel et al. 2016). Third, several studies on humans and rodents have revealed that urinary excretion is the main pathway of bisphenol elimination from their bodies (Taylor et al. 2011). Almost the whole daily dose of BPA is excreted in urine over 24 h, therefore, the calculation of daily BPA intake using 24 h urine samples seems to be reliable (Lakind and Naiman 2008). However, the pharmacokinetics and toxic thresholds of BPA substitutes remain unclear (Schmidt et al. 2013). Therefore, the appraisal of human/animal exposure to these chemicals based on measuring their urinary concentrations may not be reliable and cause underestimation in daily exposure. For example, the elimination of BPS is two times slower than that of BPA, and urine volume excreted is not almost completed but only 80%. Finally, nothing is known about the potential adverse impact of BP mixtures including possible interactions among single bisphenols.

CONCLUSION

Bisphenol A and its analogues, bisphenols B, F, S, Z and AF, were measured in sow urine on an actual pig farm. The results showed that BPB was the predominant pollutant among the six analysed bisphenols. At the same time, the urinary concentration of BPB was the highest, followed by BPA, BPS, BPZ, BPAF and BPF. Estimated oral daily intake as well as hazard quotients of all the bisphenols were far below the threshold levels recommended

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for humans, however, the possible long-term effect of low doses of bisphenols on the health status or performance of lactating sows cannot be ruled out. Therefore, elimination or reduction of the incidence of BPA and its analogues from the pig farming sector is desirable for ensuring healthy and safe animal products as well as the welfare of the pigs. The results of the present study might contribute to knowledge of the occurrence and distribution of bisphenols in actual pig farms.

Conflict of interest

The authors declare no conflict of interest.

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