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Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: A Catalonia (Spain) case study.

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Abstract

Bisphenol A (BPA) and Di-(2-ethylhexyl) phthalate (DEHP) are two wide spread chemicals classified as endocrine disruptors (ED). The present study aims to estimate the non-dietary (dermal, non-dietary ingestion and inhalation) exposure to BPA and DEHP for a pregnant women cohort. In addition, to assess the prenatal exposure for the fetus, a physiologically based pharmacokinetic (PBPK) model was used. It was adapted for pregnancy in order to assess the internal dosimetry levels of EDs (BPA and DEHP) in the fetus. Estimates of exposure to BPA and DEHP from all pathways along with their relative importance were provided in order to establish which proportion of the total exposure came from diet and which came from non-dietary exposures. In this study, the different oral dosing scenarios (dietary and non-dietary) were considered keeping inhalation as a continuous exposure case. Total non-dietary mean values were 0.002 $\mu g/kg_{bw}$/day (0.000; 0.004 $\mu g/kg_{bw}$/day for 5^{th} and 95^{th} percentile, respectively) for BPA and 0.597 $\mu g/kg_{bw}$/day (0.116 $\mu g/kg_{bw}$/day and 1.506 $\mu g/kg_{bw}$/day for 5^{th} and 95^{th} percentile, respectively) for DEHP. Indoor environments and especially dust ingestion were the main non-dietary contributors to the total exposure of BPA and DEHP with 60% and 81%. However, as expected, diet showed the higher contribution to total exposure with >99.9% for BPA and 63% for DEHP. Although diet was considered the primary source of exposure to BPA and phthalates, it must be taken into account that with non-dietary sources the first-pass metabolism is lacking, so these may be of equal or even higher toxicological relevance than dietary sources.

The present study is in the framework of “Health and environmental-wide associations based on large population surveys” (HEALS) project (FP7-603946).

Keywords: Bisphenol-A; Di-(2-ethylhexyl) phthalate (DEHP); PBPK modeling; exposure assessment.

1. Introduction

Bisphenol A (BPA) and Di-(2-ethylhexyl) phthalate (DEHP) are two high volume industrial chemicals used in a wide variety of consumer products. These compounds are defined as non-persistent Endocrine Disrupters (EDs) and are categorized as chemicals of concern by the World Health Organization (WHO, 2010). The exposure to EDs plays a key role in the epigenome shaping of many aspects of the endocrine function (Casati, 2013; Chen et al., 2018). The evidences present in the literature indicate that EDs can affect the different levels of epigenetic control (Sharma et al., 2017) and in some cases can act transgenerationally, if the exposure to EDs occurs during “critical windows of exposure”, especially, the prenatal and the early life period (Sharma et al., 2016; Volle et al., 2015; Watkins et al., 2017). Furthermore, some studies have shown that exposure to these chemicals in the early period of life may cause functional impairment of development and reproduction (Dodson et al., 2012; Meeker, 2012; Sakhi et al., 2014), increase the risk of allergy/asthma (Robinson and Miller, 2015; Sakhi et al., 2014) and also can develop obesity and type 2 diabetes (Casas et al., 2011; De Cock et al., 2014; Myridakis et al., 2016). It is known that fetal exposure is directly related to the mother’s exposure, due to a bi-directional transfer of chemicals between the placenta and fetal plasma (Sharma et al. 2018). Normally placental barrier is considered protective layer against harmful compounds, however, a recent study has found poor barrier mechanism of placenta against some common EDs (Go et al., 2007; Li et al., 2013; Ribeiro et al., 2017).

Phthalates such as DEHP are industrial chemicals, which are used in polyvinyl chloride (PVC) plastics, found in products such as shoes, gloves and packing materials as well as in building materials, floorings and wall coverings (Giovanoulis et al.,2018). In addition, they are used in pharmaceuticals products, personal care products (PCPs), paints and adhesives (Bao et al., 2015). All of these applications are related to dermal contact, non-dietary ingestion or inhalation exposure sources. Some studies confirm that DEHP is an important contaminant in dust household; people can be exposed to it via dust ingestion, the exposure through this will be higher for workers in PVC industries (Fromme et al., 2004). It is known that babies and young children are the most vulnerable groups with respect to phthalates due to their developmental status (Giovanoulis G et al., 2018; Sathyanarayana et al., 2008; Zhu et al., 2018).

BPA is currently used in polycarbonate plastics, found in materials intended to come into contact with food, like reusable plastic bottles, feeding-bottles, plates, cups, microwave and ovenware (Geens et al., 2009). In addition, we can find BPA in storage containers and epoxy resin linings for food and beverage containers. Furthermore, they are used in thermal papers and paper currencies, medical devices, dental sealants, and PCPs which are related with dermal exposure sources (Geens et al., 2012; Lv et al., 2017). Some studies showed that BPA exposure via dermal route can highly contribute to overall internal exposure (Biedermann et al., 2010; Mielke et al., 2011). Other studies affirm that people who work in offices will be more exposed via dust ingestion or inhalation than others because the levels of BPA in dust offices were almost 5–10 times higher than dust from particular homes (Geens et al., 2009).

The human exposure routes to EDs are multiple (Giulivo et al., 2016). Although the major human route of exposure to BPA and DEHP has been shown by several assessments, including the European Food Safety Authority (EFSA), to be the dietary pathway (EFSA, 2013; Geens et al., 2012; Guo et al., 2013). However, some studies confirm that non-dietary sources need to be more thoroughly characterized (EFSA, 2015; Geens et al., 2012). Estimates of exposure to DEHP and BPA from all pathways

along with their relative importance should be provided in order to establish which proportion of the total exposure comes from diet and which comes from non-dietary exposures. Human exposure to EDs from non-dietary sources, their toxicity, as well as their combined effects, are poorly understood (Larsson et al., 2014).

In this study, occupational risk, lifestyle and the use of different PCPs were considered in order to assess the exposure to different pathways (dermal contact, non-dietary ingestion, and inhalation). Sharma et al., (2018) developed a P-PBPK model for BPA including specific pregnancy physiology and both oral and dermal route of exposure. The simulation results were presented to compare the reported data from different cohorts presuming the collection of samples can be from at different time points, in order to explain the inconsistency in biomonitoring data. Moreover, some authors compared the results obtained between real measurements concentrations levels of EDs in the blood reported and the exposure estimates based on PBPK models (Mielke and Gundert-Remy, 2009); the intake estimated were several orders of magnitude lower than the real values in blood reported in the literature. One way to explain this abnormality could be that in the PBPK model they only considered the dietary source, so this could have led to an underestimation of the exposure to these chemicals through non-dietary routes like dermal, inhalation or dust ingestion. However, there are other contributing factors for this difference such as genetic variability, biomonitoring sampling strategy and contamination of sample during analysis.

The present study aims to estimate the non-dietary (dermal, non-dietary ingestion and inhalation) exposure to BPA and DEHP for a pregnant women cohort. In addition, to assess the prenatal exposure for the fetus, through all routes (diet and non-dietary) a physiologically based pharmacokinetic (PBPK) model was used. The pregnancy PBPK model structure was adapted from Sharma et al., (2018). Previous work has been extended to estimate the aggregate exposure of these EDs to humans to understand the relative importance of non-dietary exposure. Parameters and structure of the models were kept same as our previous publications (Sharma et al., 2018; Martínez et al., 2017), except nondietary routes (inhalation and dermal) were included. The present study is in the framework of “Health and environmental-wide associations based on large population surveys” (HEALS) project (FP7-603946) and part of the study has been completed in MODELBIS project (MINECO funded with ref no AGL2016-78942-R).

2. Materials and methods

2.1. Study population

The study population comprises a cohort of pregnant women and ongoing birth cohort. The pregnant women were recruited during the first trimester of pregnancy as part of the European “HEALS” project. The recruitment of pregnant mothers has started in March 2016 and in the present study 72 mother-child pairs from Reus (Tarragona, Spain) were included. Women were informed of the study during their first visit (12^{th} gestational week) to the University Hospital “Sant Joan de Reus”, in Reus (Catalonia, NE Spain). Women were eligible to participate according to the following inclusion criteria: ≥16 years old, intention to deliver at the reference hospital, and no problems with the communication language. This study was approved by the Ethical Committee of Clinical Research of the Hospital and a written informed consent was obtained from the participants.

2.2. Questionnaires and data acquisition

At 20th gestational weeks (GW), a PCPs frequency questionnaire was filled in a face-to-face interview. Different PCPs were included in the questionnaire: a) makeup (face cream, eyeshadow and liquid foundation), b) lipstick, c) body lotion, d) shampoo, e) shower gel, f) hair conditioner, g) toothpaste, h) deodorant and i) spray perfume. In addition, the questionnaires also included in one hand, general characteristics data of the study population, such as maternal age at delivery, twin pregnancy, maternal body mass index (BMI), maternal education, social economic status, country of origin, and marital status. On the other hand, a set of questions targeting to know other sources of these compounds are included, such as maternal smoking, lifestyle, hours spend outdoors and indoors and occupational risk. A description of the characteristics of the study population is shown in Table 1.

2.3. BPA and DEHP non-dietary assessment

2.3.1. Dermal contact exposure

The assessment of exposure of BPA and DEHP through dermal contact for pregnant women population was calculated according to equation 1. We considered all PCPs previously mentioned.

$$\text{Dermal exposure} = \sum(C_c \times PCP_{fr} \times PCP_a \times ABS \times R_f)/BW_{20GW} \quad \text{Eq. 1}$$

Where C_c is the concentration of BPA or DEHP in PCPs (in µg/g); PCP_{fr} is the frequency application (in application/day); PCP_a is the amount per application (in g/application); ABS is the dermal absorption factor (non-dimensional); R_f is the retention factor for rinse-off products (non-dimensional); and BW_{20GW} is the body weight at 20 gestational weeks (in kg). Dermal exposure is given in µg/kg_{bw}/day. Data used to assess the dermal exposure of BPA and DEHP are summarized in Table 2.

2.3.2. Non-dietary ingestion exposure

Non-dietary ingestion pathways include, on the one hand, dust ingestion that was calculated according to equation 2.a. On the other hand, exposure through PCPs ingestion was considered. Lipstick and toothpaste ingestion was assessed according to equation 2.b.

$$\text{Non} - \text{dietary ingestion exposure } (Dust_{\text{ingestion}}) = (C_c \times I_r)/BW_{20GW} \quad \text{Eq. 2.a.}$$

$$\text{Non} - \text{dietary ingestion exposure } (PCP_{\text{ingestion}}) = (C_c \times PCP_{fr} \times PCP_a \times Ing_f)/BW_{20GW} \quad \text{Eq. 2.b.}$$

Where C_c is the concentration of BPA or DEHP in homes dust (in µg/kg); I_r is the Ingestion rate (in kg/day) and $BW_{20\ GW}$ is the body weight at 20 gestational weeks (in kg). PCP_{fr} is the frequency application (in application/day); PCP_a is the amount per application (in g/application) and Ing_f is the ingestion factor (non-dimensional). The total non-dietary exposure is given in µg/kg_{bw}/day. Table 3 provides data used to assess the non-dietary ingestion exposure of BPA and DEHP.

206

207 2.3.3. Inhalation exposure

208 The exposure assessment of BPA and DEHP through inhalation for pregnant women
209 was calculated according to equation 3. We considered levels of BPA and DEHP in the
210 outdoor and indoor air. In this case, three different scenarios were assessed: sleeping
211 (3.a), indoors (3.b) and outdoors (3.c) scenarios.

212 $$\text{Inhalation exposure}_{\,sleeping} = (C_c^{indoor} \times Ihr_{sleep} \times t_{sleep})/BW_{20GW} \quad \text{Eq. 3.a}$$

213 $$\text{Inhalation exposure}_{\,indoor} = (C_c^{indoor} \times Ihr_{sedentry} \times t_{indoor})/BW_{20GW} \quad \text{Eq.3.b}$$

214 $$\text{Inhalation exposure}_{\,outdoor} = (C_c^{outdoor} \times Ihr_{moderate} \times t_{outdoor})/BW_{20GW} \quad \text{Eq.3.c}$$

215 Where C_c^{indoor} is the concentration of BPA or DEHP in the indoor air (in μg/m^3);
216 $C_c^{outdoor}$ is the concentration of BPA or DEHP in the outdoor air (in μg/m^3); $Ih_{r\ sleep}$ is the
217 inhalation rate during sleep (in m^3/min); $Ih_{r\ sedentary}$ is the inhalation rate while sedentary
218 activities (in m^3/min); $Ih_{r\ moderate}$ is the inhalation rate during moderate activities (in
219 m^3/min); t_{sleep} is the mean of time sleeping (in min); t_{indoor} is the mean of time spending
220 indoor (at work and at home) (in min); $t_{outdoor}$ is the time spending in doing activity
221 outdoor (in min) and BW_{20GW} is the body weight at 20 gestational weeks (in kg). The
222 total inhalation exposure is given in μg/kg$_{bw}$/day. Table 4 contains the data used to
223 assess the inhalation exposure of BPA and DEHP.
224

225 The concentration levels of BPA and DEHP in different PCPs, in dust and air, were
226 taken from the literature with a preference rule of Spanish values> European values>
227 other available data. To deal with variability and uncertainty of parameters used,
228 probabilistic estimation of the dermal, non-dietary ingestion and inhalation exposure
229 was performed in a probabilistic way. Monte-Carlo simulation is a common approach
230 used to incorporate variability and uncertainty of the parameters used into the
231 estimation of human health exposure (Mari et al., 2009; May et al., 2002; Rovira et al.,
232 2016; Schuhmacher et al., 2001). Table 2, 3 and 4 includes the probabilistic distribution
233 of parameters for the calculation of human health exposure. Monte-Carlo simulation
234 was carried out by Oracle Crystal Ball© software. Exposures were calculated based on
235 the propagation variable of variability and uncertainty given by each parameter
236 probability function until 100,000 iterations.

237

238 2.4 Tissue dosimetry model (PBPK).

239 The basic structure of pregnant PBPK model has been adapted from Sharma et al.,
240 (2018) in the current study in order to assess dietary and non-dietary exposure. It
241 comprises plasma, liver, kidneys, fat, brain, skin, placenta, a rest of the body and a
242 fetus compartment. Fetus compartment was subcategorized again into liver, brain, and
243 plasma. All the Physiological parameters during pregnancy are considered to be
244 dynamic parameters that change due to the growth of mother organs (Abduljalil et al.,
245 2012; Gentry et al., 2003; Loccisano et al., 2013). The source of exposure to fetuses
246 was via a free fraction of chemicals into mother's placenta, considering that fetuses'
247 exposure is directly related to mother's exposure. The placental-fetal unit assumes a
248 bidirectional transfer process describing chemical transfer between mothers' placenta
249 to fetuses' plasma and fetuses' plasma to the mothers. Detailed descriptions of

standard and pregnancy-specific model equations are adapted form Sharma et al., (2018). Metabolic kinetic parameters for both mothers and fetuses were previously estimated from in-vitro studies (Martínez et al., 2017; Sharma et al., 2018).

Two different sources of exposure were considered for the current study, dietary exposure and the combination of dietary with non-dietary exposure. The dosing considered being inputs for the PBPK model was estimated using Monte Carlo technique for the exposure assessment. It has been considered the six following exposure scenarios of BPA and DEHP: 5^{th} percentile diet; 5^{th} percentile diet + non-diet; Mean diet; Mean diet+ non-diet; 95^{th} percentile diet, and 95^{th} percentile diet + non-diet. For the current study, the routes of exposure were the following: ingestion and dermal exposure that were divided into three equal doses (with 8 hours of the interval). On the other hand, continuous exposure for inhalation was presumed, considering three different inhalation rates (sleeping time, doing sedentary activities and doing moderate activities).

3. Results and discussion

3.1 Non-dietary (dermal, non-dietary ingestion and inhalation) exposure to BPA and DEHP.

The contribution of dermal contact, non-dietary ingestion, and inhalation to the total non-dietary intake from Reus pregnant mothers' cohort was assessed in a probabilistic way using Monte-Carlo simulation. Figure 1, summarizes the contribution of each non-dietary source to the total exposure of BPA and DEHP.

Regarding BPA (Figure 1), the total non-dietary mean value was 0.002 $\mu g/kg_{bw}/day$ (0.000 and 0.004 $\mu g/kg_{bw}/day$ for 5^{th} and 95^{th} percentile, respectively). Relative mean contributions were 60%, 36% and 4% for non-dietary ingestion, inhalation, and dermal routes, respectively. For DEHP (Figure 1), the total non-dietary mean exposure was 0.597 $\mu g/kg_{bw}/day$ (0.116 $\mu g/kg_{bw}/day$ and 1.506 µg/kg bw/day for 5^{th} and 95^{th} percentile, respectively). The maximum mean contribution was, again, non-dietary ingestion with 81%, followed by dermal route and inhalation with 15% and 4%, respectively.

For both chemicals, BPA and DEHP, non-dietary ingestion was the highest mean relative contributor with 60% and 81%, respectively, of the total non-dietary exposure. These represented a mean non-dietary ingestion exposure of $9.62 \cdot 10^{-4}$ and 0.485 $\mu g/kg_{bw}/day$ for BPA and DEHP, respectively. Non-dietary ingestion route considered the levels of both compounds in homes dust and in PCPs that could be accidentally ingested during their use (lipstick and toothpaste). In both cases, the major contribution (>99.9%) to the total non-dietary ingestion exposure to BPA and DEHP came from home dust ingestion. The average concentration of BPA and DEHP in dust were very high, $2 \cdot 10^{3}$ and $1.20 \cdot 10^{6}$ $\mu g/kg_{dust}$, respectively. BPA levels in dust were obtained from Belgian houses (Geens et al., 2009) and phthalate levels in dust came from different European homes (Wormuth et al., 2006). However, similar BPA and DEHP levels in indoor dust were found worldwide (Das et al., 2014; Fromme et al., 2004; Ginsberg and Belleggia, 2017; Kubwabo et al., 2016; Langer et al., 2014; Loganathan and Kannan, 2011). The high contribution of dust in the total DEHP non-dietary ingestion exposure is due to phthalates, which are used as plasticizers in numerous consumer products, commodities, and building materials. Consequently, phthalates are found in human

residential and occupational environments in high concentrations (Wormuth et al., 2006). As well as DEHP, the high contribution of dust in the total BPA non-dietary ingestion exposure is due to BPA is used in a variety of household applications. Through manufacture and usage, these contaminants can leach into the environment and can be deposited in the indoor dust (Geens et al., 2009). It was assumed that consumers accidentally ingest small amounts of PCPs. So, it was estimated the scenario for non-dietary ingestion using information about the amounts cosmetics ingested daily (Table 3), and the DEHP and BPA concentrations in PCP. No much information was available on how much PCPs are ingested daily and also it was not many literature data about concentration levels of these two EDs in different cosmetic products. Only data regarding DEHP in lipstick and BPA in toothpaste content were found. Therefore, it was only considered the accidental ingestion of these two cosmetics, lipstick and toothpaste, during their use. Results showed that the contribution to this kind of ingestion to the total DEHP and BPA non-dietary ingestion were insignificant (0.07% and 0.01% for BPA and DEHP, respectively) compared to total non-dietary ingestion and also with the dietary total intake. However, more bibliographic data is needed to be able to carry out a good exposure assessment.

According to BPA, inhalation was the second greatest contributor to the total exposure with an exposure of $5.90 \cdot 10^{-4}$ $\mu g/kg_{bw}/day$, that meant the 36% of the total non-dietary exposure. In this case, three different scenarios were assessed: indoor, outdoor and sleeping inhalation exposure that showed a contribution to total BPA inhalation exposure of 37%, 51%, and 12%, respectively. Inhalation exposure was lower than the dust exposure; this can be due to BPA has a comparatively low vapour pressure. As a result, concentrations of BPA in the air can be expected to be low and it will be present mainly in the particulate phase, adsorbed to dust (EFSA, 2013). Finally, dermal contact was the exposure route that contributed the least (4%) to the total mean non-dietary BPA exposure, with a dose of $6.39 \cdot 10^{-5}$ $\mu g/kg_{bw}/day$. Among all the PCPs, face cream (39%), shower gel (20%) and body lotion (18%) have the higher contribution. In Europe, BPA is not allowed as an ingredient in cosmetics (Regulation (EC) no. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products). However, if BPA is present in the packaging (e.g. polycarbonates plastic (PC) packaging), it could migrate into the cosmetic products (EFSA, 2013). It must be taken into account that dermal absorption of BPA can reach 95-100% if BPA is applied dissolved in ethanol, because ethanol may act as a transport mediator for BPA into the skin, thus enhancing the absorption fraction. In addition, this property of dissolving in ethanol can be found in similar compounds in the formulation of creams and body lotions (EFSA, 2013).

Regarding DEHP, dermal contact with a mean value of 0.087 $\mu g/kg_{bw}/day$, was the second greatest contributor to the total non-dietary exposure (15%). In this exposure assessment, perfume and deodorant were the items which contribute more to the total DEHP dermal exposure, with 36% and 33%. The quite high presence of these ED is due to phthalates in general, are added as humectants, emollients, or skin penetration enhancers, which are very common in perfumes and fragrances (Koo and Lee, 2004). Finally, DEHP inhalation (0.025 $\mu g/kg_{bw}/day$) was the item which contributed less (4%) to the DEHP mean non-dietary exposure. Indoor exposure and sleeping inhalation exposure had a relative contribution of 61% and 36%, respectively. Other authors (Wormuth et al., 2006) found that accidental ingestion of PCPs are the major sources of exposure to DEHP in all consumer groups that we estimated. Although the food is the dominating source of exposure to DEHP in all consumer groups (Wormuth et al., 2006).

Indoor environment (home dust ingestion and inhalation (indoor and sleeping)) were the principal source of BPA and DEHP of non-dietary exposure with a relative contribution of 78% and 85%, respectively. PCPs contribute with 4% and 15% to total mean non-dietary exposure of BPA and DEHP, respectively, almost exclusively through dermal contact. Finally, outdoor environment (trough outdoor inhalation) showed a contribution of 18% and <0.1% to total mean non-dietary exposure for BPA and DEHP, respectively.

3.2 Dietary exposure vs non-dietary exposure

Figure 2, shows the comparison between total dietary exposure and non-dietary (dermal, non-dietary ingestion and inhalation) exposure to BPA and DEHP. Data from the dietary exposure was previously estimated using the same cohort population (Martínez et al., 2017).

Regarding BPA, mean dietary daily intake from Reus (Tarragona, Spain) cohort was 0.715 $\mu g/kg_{bw}/day$ (Martínez et al., 2017), and the mean exposure estimated for non-dietary ingestion, inhalation, and dermal contact were $9.62 \cdot 10^{-4}$, $5.90 \cdot 10^{-4}$, $6.39 \cdot 10^{-5}$ $\mu g/kg_{bw}/day$, respectively. In general, in the present study according to non-dietary exposure, the maximum exposure estimated for BPA was 0.0072 $\mu g/kg_{bw}/day$ and the 95% of the population were under 0.0040 $\mu g/kg_{bw}/day$. Non-dietary exposure practically did no contribute to the total exposure (0.2%). In other words, diet was the greatest contributor to the total exposure (99.8%) (Figure 2). However, it is important to know that in this study thermal paper was not considered in dermal exposure estimation, which is considered as a potential exposure source for BPA in the EU by the EFSA, 2015.

BPA is conjugated in the liver by glucuronidation and sulfation, “total BPA” stands for the sum of conjugated and unconjugated forms. For further risk assessment, these two forms need to be distinguished, the unconjugated BPA is more toxicologically relevant. The contribution of dermal and inhalation sources to internal exposure to total BPA is considerably smaller compared to oral sources. However, with dermal and inhalation exposure the first-pass metabolism is lacking, regardless of the small contribution of non-dietary sources to total BPA, their contribution to the plasma concentration levels of unconjugated BPA may be considerable. Kinetic studies have shown that in monkeys only around 1% of orally absorbed BPA becomes systemically bioavailable as unconjugated BPA (Fisher et al., 2011), whereas after dermal absorption, practically all absorbed BPA (around 10% of the external dermal dose, Demierre et al., 2012) initially becomes bioavailable as unconjugated BPA. For that reason, non-dietary sources may be of equal or even higher toxicological relevance than dietary sources (Lu et al., 2017; Völkel et al., 2002; von Goetz et al., 2017). Considering diet and non-diet sources the mean of the total exposure was 0.72 $\mu g/kg_{bw}/day$ and the 5^{th} and 95^{th} percentile of the total exposure were 0.28 and 1.41 $\mu g/kg_{bw}/day$ (Figure 2).

Regarding DEHP, Figure 2 shows that non-dietary sources contribute with 37 % of the total exposure. The mean dietary daily intake of DEHP exposure from Reus cohort was 1.00 $\mu g/kg_{bw}/day$ (Martínez et al., 2017), and the mean exposure estimated for non-dietary ingestion, inhalation, and dermal contact were 0.485, 0.025, 0.087 $\mu g/kg_{bw}/day$ respectively. According to total non-dietary exposure, the maximum dose was 3.86 $\mu g/kg_{bw}/day$ and the 95^{th} percentile was 1.51 $\mu g/kg_{bw}/day$, and mean value was 0.60 $\mu g/kg_{bw}/day$. Considering diet and non-diet sources the mean of the total exposure was 1.60 $\mu g/kg_{bw}/day$ and the 5^{th} and 95^{th} of the total exposure were 0.52 and 3.52 $\mu g/kg_{bw}/day$, respectively (Figure 2).

EFSA published its comprehensive re-evaluation of BPA exposure and toxicity, in January 2015, and established a tolerable daily intake (TDI) of 4 μg/kg_{bw}/day for BPA (EFSA, 2015). On the other hand, EFSA and the European Chemicals Agency (ECHA) established the TDI for DEHP to 50 μg/kg_{bw}/day (ECHA, 2010; EFSA, 2015). Only the non-dietary ingestion estimated data from this study can be compared with this EFSA and ECHA tolerable values because the TDI values are concerned about "daily intake". Therefore, in this study, the maximum value estimated for BPA non-dietary ingestion exposure was 0.0052 μg/kg_{bw}/day and the 95% of the population were below 0.0028 μg/kg_{bw}/day. Whereas, for DEHP, the maximum value estimated for non-dietary ingestion exposure was 3.39 μg/kg_{bw}/day and the 95% of the population were under 1.24 μg/kg_{bw}/day. These values for BPA and DEHP estimated in our study were far away from the tolerable values of the EFSA and ECHA. Although BPA and DEHP non-dietary ingestion exposure assessment values were under the tolerable established, it is important to take into account that non-dietary ingestion and, in general, non-dietary levels must be added to the total dietary exposure assessment, in order to make a good exposure estimation.

3.3 Internal dosimetry

The chemicals' dose inputs considered to run the P-PBPK, were probabilistically estimated by Monte-Carlo simulation (Section 2.4). From probabilistic distribution, six total scenarios were selected for BPA and DEHP: the 5th percentile diet; the 5th percentile diet + non-diet; mean diet; mean diet + non-diet; the 95th percentile diet and the 95th percentile diet + non-diet. The outputs from the model simulation were selected considering the metabolites generated, their toxicity, gestational period and ability to reach the fetus. For this reason, only free BPA and MEHP (a metabolite of DEHP) were considered. The simulation data were taken from pregnant women and fetus for 24 h during the 24th gestational week. This period was selected because at this time fetus organs are more developed and able to incorporate right biological process. This helps us to explain the difference in metabolic processes in mothers and fetuses. Normally, at the early stage of pregnancy, for both BPA and MEHP, fetus plasma concentration level is higher due to low or no metabolic activities in the fetus (Gauderat et al., 2016; Latini et al., 2003). In order to be near to a real scenario, a dietary, and non-dietary (dermal and ingestion) exposure were divided into three equal doses, along with continuous exposure of non-dietary source (inhalation) and were simulated (Figure 3) in the case of BPA. On the other hand, DEHP metabolite MEHP time plasma concentration profile in case of both mother and fetus is showed in Figure 4, the result of single-dose intake of dietary and non-dietary. In this case, inhalation was considered again as continuous exposure, the simulated concentration curves show a sharp peak concentration o within 1 h of intake. It is known that metabolic activity in the fetus is lower compared to mother's metabolism (Heindel et al., 2017). For that reason, concentration levels of both chemicals in the fetus' plasma were higher than in the mother. Therefore, BPA and MEHP stay longer in the fetal body, which may cause higher risk to fetuses and makes the fetus more vulnerable to the exposure. A similar trend has been observed by Sharma et al., (2018).

4. Conclusions

Regarding BPA non-dietary exposure was 0.002 μg/kg_{bw}/day, with the greatest contribution coming from non-dietary ingestion with 60%, followed by inhalation with

36%. Finally, dermal exposure was the one that contributed the least with 4%. However, in this study, the thermal paper was not considered in dermal exposure estimation, which is considered as a potential exposure source for the general population (EFSA, 2015). According to DEHP non-dietary exposure (0.597 $\mu g/kg_{bw}$/day), the maximum contributor was non-dietary ingestion with 81%, followed by dermal contact with 15% and inhalation with 4%. As expected, diet was the main contributor to total exposure to both chemicals. Regarding DEHP, non-dietary sources contribute 37% of the total exposure. The non-dietary exposure to BPA practically did no contribute to the total exposure (0.22%). Indoor environment, dust ingestion, and indoor air inhalation was the main contributor to non-dietary exposure to both ED (78% for BPA and 85% for DEHP) meanwhile PCPs contribute in 4% and 15%, for BPA and DEHP, respectively. However, with dermal absorption that passes the first-pass metabolism, dermal sources may be of equal or even higher toxicological relevance than dietary sources (Völkel et al., 2002; von Goetz et al., 2017). Only the non-dietary ingestion estimated data in combination with other dietary exposure from this study can be comparable with EFSA and ECHA tolerable values because the TDI values are concerned about “daily intake”. Although BPA and DEHP non-dietary ingestion exposure assessment values were under the tolerable established, it is important to take into account that non-dietary exposure levels must be added to the total dietary exposure assessment, in order to make a good exposure estimation.

According to internal dosimetry, six different scenarios were considered in order to run the PBPK model. When the simulation considered diet + non-diet scenarios, the concentration levels of BPA and MEHP (main metabolite of DEHP) increased considerably in plasma. In addition, in fetus’ plasma, the concentration of both chemicals reached levels much higher than those seen previously in mothers. The low metabolic activity in fetus led to maintain a continuous concentration in time. Therefore, this can make the fetus more vulnerable to the exposure compared with their mothers.

The ongoing research is to validate the PBPK model with biological samples from this cohort and demonstrate that this methodology allows the determination of BPA and MEHP for monitoring in biological matrices, such as plasma and urine. Finally, demonstrate that PBPK model can predict the prenatal exposure of the child/fetus to EDs. To conclude, on the one hand, strategies must be presented in order to reduce their exposure. Restrictions must be imposed to regulate the production and use of products related especially with childcare and pregnant women.

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736 Table 1. Characteristics of the study population from Reus cohort, Tarragona (Spain) (n=72).
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Characteristics of the study population (n = 72)	**%**
Maternal age at delivery (years)	
< 20	1
20-29	14
30-39	72
>40	13
Twin pregnancy	8
*Maternal pre-pregnancy BMI**	
Underweight (<19kg/m^2)	6
Normal (19-25 kg/m^2)	50
Overweight (>25 kg/m^2)	25
Obese (>30 kg/m^2)	19
*Maternal pregnancy (20 GW) BMI**	
Underweight (<19kg/m^2)	1
Normal (19-25 kg/m^2)	41
Overweight (>25 kg/m^2)	37
Obese (>30 kg/m^2)	21
Maternal education	
Primary	28
Secondary	31
University	41
Social economic status	
Low level (< 9000-19000€/year)	24
Median level (19000-35000€/year)	49
High level (> 35000 €/year)	27
Maternal country of origin	
Spain	76
Other	24
Marital Status	
Living with the father	99
Not living with the father	1
Maternal smoking	
Never smoke	73
Not during pregnancy	9
During pregnancy	18
**BMI= Body mass index*	

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744 Table 2. Monte-Carlo parameter description to assess the total dermal contribution of BPA and DEHP.

Parameter	Symbol	units	Type	Distribution	Reference
DEHP concentration in	C_{DEHP}	-	-	-	-
Lipstick	-	µg/g	T	1.79 (0-6.45)	Guo and Kannan, 2013
Body lotion	-	µg/g	T	0.96 (0-11.3)	Guo and Kannan, 2013
Face cream	-	µg/g	T	0.4 (0-2.45)	Guo and Kannan, 2013
Shampoo	-	µg/g	T	0.1 (0-1.1)	Esteve et al., 2016
Shower gel	-	µg/g	U	9.53-32.4	Guo et al., 2013
Deodorant	-	µg/g	T	4.98 (0-65.3)	Guo and Kannan, 2013
Hair conditioner	-	µg/g	T	0.18 (0-0.39)	Guo and Kannan, 2013
Spray perfume	-	µg/g	T	15 (7-130)	Wormuth et al., 2006
Eye shadow	-	µg/g	T	0.64 (0-1.46)	Guo and Kannan, 2013
BPA concentration in	C_{BPA}	-	-	-	-
Body lotion	-	µg/g	LN[a]	$3.54 \cdot 10^{-04}$, $1.18 \cdot 10^{-02}$, $1.67 \cdot 10^{-01}$	Liao and Kannan, 2014
Face cream	-	µg/g	LN	0.03 ± 0	Cacho et al., 2013
Liquid foundation	-	µg/g	LN[a]	0,0.02,0.04	Liao and Kannan, 2014
Shampoo	-	µg/g	LN	0.09 ± 0	Cacho et al., 2013
Shower gel	-	µg/g	LN	0.07 ± 0	Cacho et al., 2013
PCP frequency	PCP_{fr}	-	-	-	-
Lipstick	-	Application/day	N	0.18 ± 0.34	Present study
Body lotion	-	Application/day	N	0.78 ± 0.41	Present study
Face cream	-	Application/day	N	0.72 ± 0.44	Present study
Liquid foundation	-	Application/day	N	0.42 ± 0.44	Present study
Shampoo	-	Application/day	N	0.62 ± 0.37	Present study
Shower gel	-	Application/day	N	0.92 ± 0.31	Present study
Deodorant	-	Application/day	N	0.94 ± 0.27	Present study
Hair conditioner	-	Application/day	N	0.35 ± 0.28	Present study
Spray perfume	-	Application/day	N	0.68 ± 0.45	Present study
Eye shadow	-	Application/day	N	0.42 ± 0.44	Present study
PCP amount	PCP_a	-	-	-	-
Lipstick	-	g/application	LN[g]	0.01±3.29	Loretz et al., 2005
Body lotion	-	g/application	LN[g]	3.26 ± 2.25	Loretz et al., 2005
Face cream	-	g/application	LN[g]	0.80 ± 2.55	Loretz et al., 2005

Liquid foundation	-	g/application	LN[g]	0.33 ± 2.99	Loretz et al., 2006
Shampoo	-	g/application	G	0.38,5.79,2.15	Loretz et al., 2006
Shower gel	-	g/application	G	0.67,4.89,2.84	Loretz et al., 2006
Deodorant	-	g/application	LN[g]	0.56 ± 2.41	Loretz et al., 2006
Hair conditioner	-	g/application	LN[g]	10.28 ± 2.20	Loretz et al., 2006
Spray perfume	-	g/application	LN[g]	0.30 ± 3.36	Loretz et al., 2006
Eye shadow	-	g/application	LN[g]	0.01± 3.61	L. J. Loretz et al., 2008
Body weight	BW_{20GW}	kg	LN	71.42 ± 17.15	Present study
Retention factor (rinse off PCP)	R_f	-	-	-	-
Shampoo	-	-	U	0-0.02	EFSA, 2015
Shower gel	-	-	U	0-0.02	EFSA, 2015
Hair conditioner	-	-	U	0-0.02	EFSA, 2015
Ingestion factor lipstick	$1-(Ing_f)$	-	LN	0.20 ± 0.04	Franzen et al., 2016
DEHP dermal absorption factor	$ABS_{(DEHP)}$	-	U	0.05-0.15	EPA, 2011
BPA dermal absorption factor	$ABS_{(BPA)}$	-	U	0.08-0.10	Demierre et al., 2012

LN = Log-normal; T = Triangular; U = Uniform; G = Gamma; N= Normal distribution. Mean, minimum, and maximum values were used for triangular distributions; Mean and standard deviation were used for log-normal distributions; Geometrical mean and geometrical standard deviation were used in log-normal[g] distributions; minimum and maximum values were used for uniform distributions; Percentile 50,95 and maximum were used in log-normal[a] distributions and location, scale and shape were used for gamma distribution.

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746 Table 3. Monte-Carlo parameter description to assess the total non-dietary ingestion contribution of BPA and DEHP.

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Parameter	Symbol	units	Type	Distribution	Reference
DEHP concentration in	C_{DEHP}	-	-		-
Lipstick	-	µg/g	T	1.79 (0-6.45)	Guo and Kannan,2013
Dust indoor	-	µg/kg dust	LN[b]	$1.20 \cdot 10^6$	Wormuth et al., 2006
BPA concentration in	C_{BPA}	-	-		-
Toothpaste	-	µg/g	LN[c]	0.35,0.83	Liao and Kannan,2014
Dust indoor	-	µg/kg dust	LN	$2 \cdot 10^3 \pm 2.1 \cdot 10^3$	Geens et al., 2009
PCP frequency	PCP_{fr}	-	-		-
Lipstick	-	Application/day	N	0.18 ± 0.34	Present study
Toothpaste	-	Application/day	N	1.82 ± 0.76	Present study
PCP amount	PCP_a	-	-	-	-
Lipstick	-	g/application	LN[g]	0.01 ± 3.29	Loretz et al., 2005
Toothpaste	-	g/application	U	0.79-1.20	McNamara et al., 2007
Dust ingestion rate	I_r	kg/day	N	$3 \cdot 10^{-5} \pm 3 \cdot 10^{-6}$	EPA, 2011
Ingestion factor	Ing_f	-	-	-	-
Lipstick	-	-	LN	0.20 ± 0.04	Franzen et al., 2016
Toothpaste	-	-	U	0-0.10	Angerer et al., 2010
Body weight	BW_{20GW}	kg	LN	71.42 ± 17.15	Present study

LN = Log-normal; T = Triangular; U = Uniform. Mean, minimum, and maximum values were used for triangular distributions; Mean and standard deviation were used for log-normal distributions; Geometrical mean and geometrical standard deviation were used in log-normal[g] distributions; minimum and maximum values were used for uniform distributions; Mean and P95 were used for log-normal[b] distributions; Percentile 50 and 95 were used in log-normal[c] distributions.

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752 Table 4. Monte-Carlo parameter description to assess the total inhalation contribution of BPA and DEHP.
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Parameter	Symbol	units	Type	Distribution	Reference
DEHP concentration in	C_{DEHP}	-	-	-	-
Air indoor	-	µg/m^3	T	0.3 (0.05-0.62)	Wormuth et al., 2006
Air outdoor	-	µg/m^3	T	0.01 (0-0.05)	Wormuth et al., 2006
BPA concentration in	C_{BPA}	-	-	-	-
Air indoor	-	µg/m^3	T	0 (0-0.01)	EFSA, 2015
Air outdoor	-	µg/m^3	LN	0.01 ± 0.01	Salapasidou et al.,2011
Inhalation rate					
sleeping	$Ih_{r\ sleep}$	m^3/min	LN[b]	0,0.01	EPA, 2011
sedentary activity	$Ih_{r\ sedentary}$	m^3/min	LN[b]	0,0.01	EPA, 2011
moderate activity	$Ih_{r\ moderate}$	m^3/min	LN[b]	0.02,0.03	EPA, 2011
Time sleeping	t_{sleep}	min	N	521 ± 52.10	IEC, 2012
Time outdoor	$t_{outdoor}$	min	N	106 ± 10.60	IEC, 2012
Time indoor	t_{indoor}	min	-	1440	-
Body weight	BW_{20GW}	kg	LN	71.42 ± 17.15	Present study

Time indoor= 24 hours – (T_{sleep} + $T_{outdoor}$). LN = Log-normal; T = Triangular. Mean, minimum, and maximum values were used for triangular distributions; Mean and standard deviation were used for log-normal distributions; Mean and P95 were used for log-normal[b] distributions.

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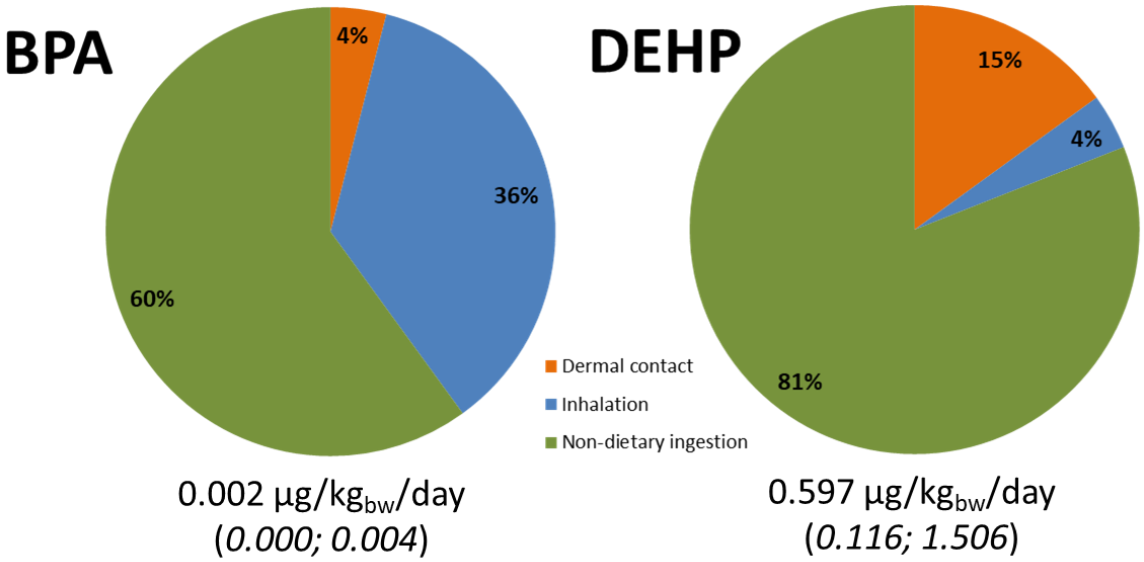


Figure 1. Non-dietary exposure (dermal contact, non-dietary ingestion and inhalation) Reus (Tarragona, Spain) pregnant women cohort exposure to BPA and DEHP exposure. Results are given in mean (*5th; 95th percentile*).

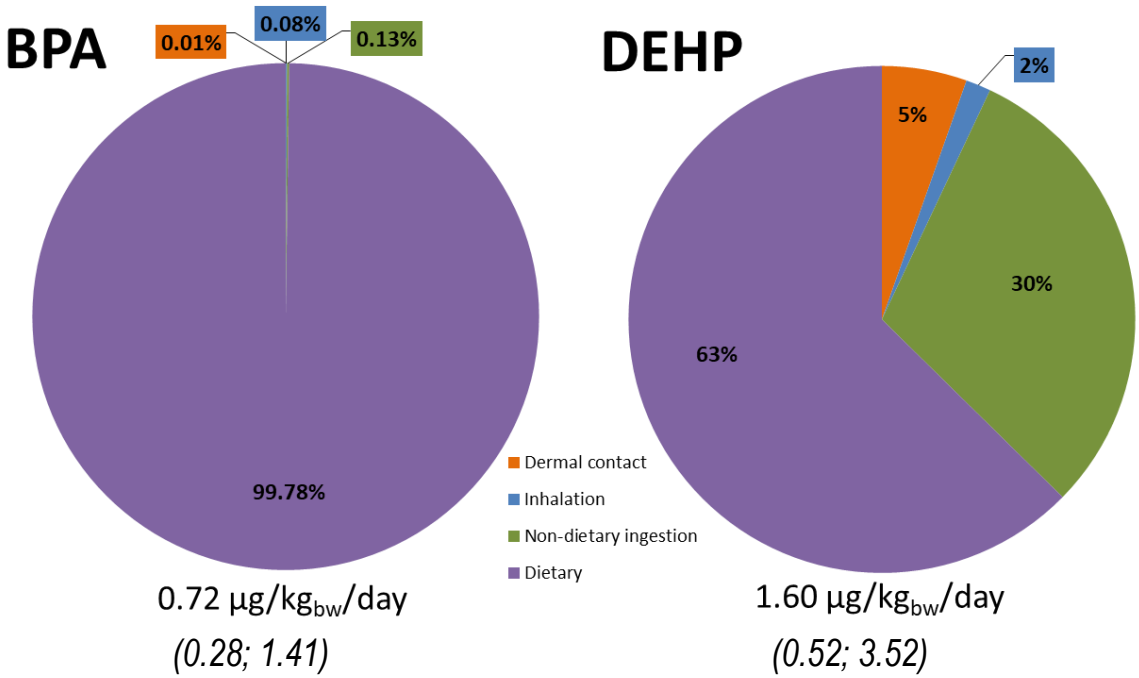


Figure 2. Total mean exposure dietary (Martínez et al., 2017) and non-dietary (dermal, non-dietary ingestion and inhalation) to BPA and DEHP for Reus pregnant women cohort. Results are given in mean (*5th; 95th percentile*).

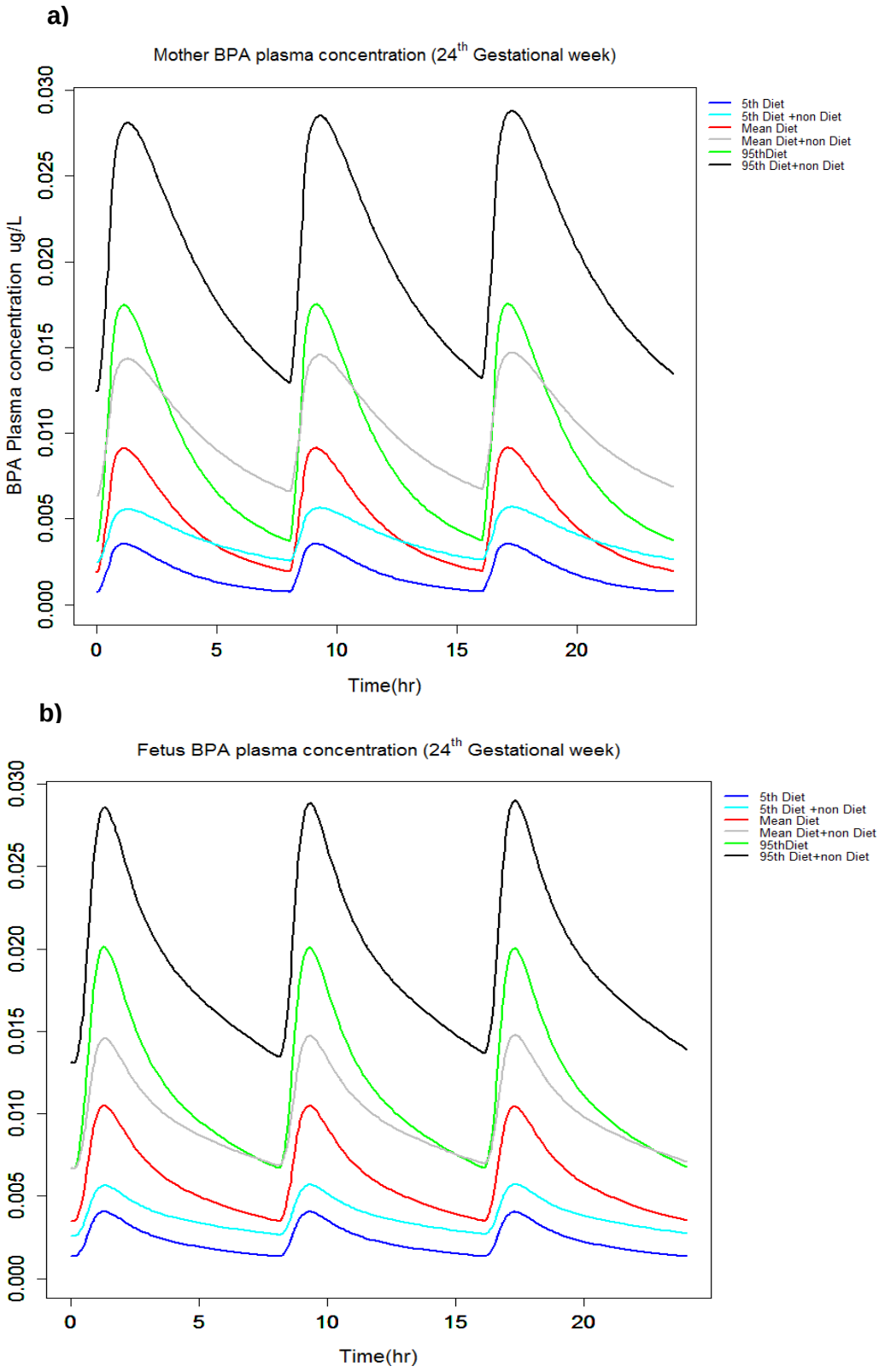
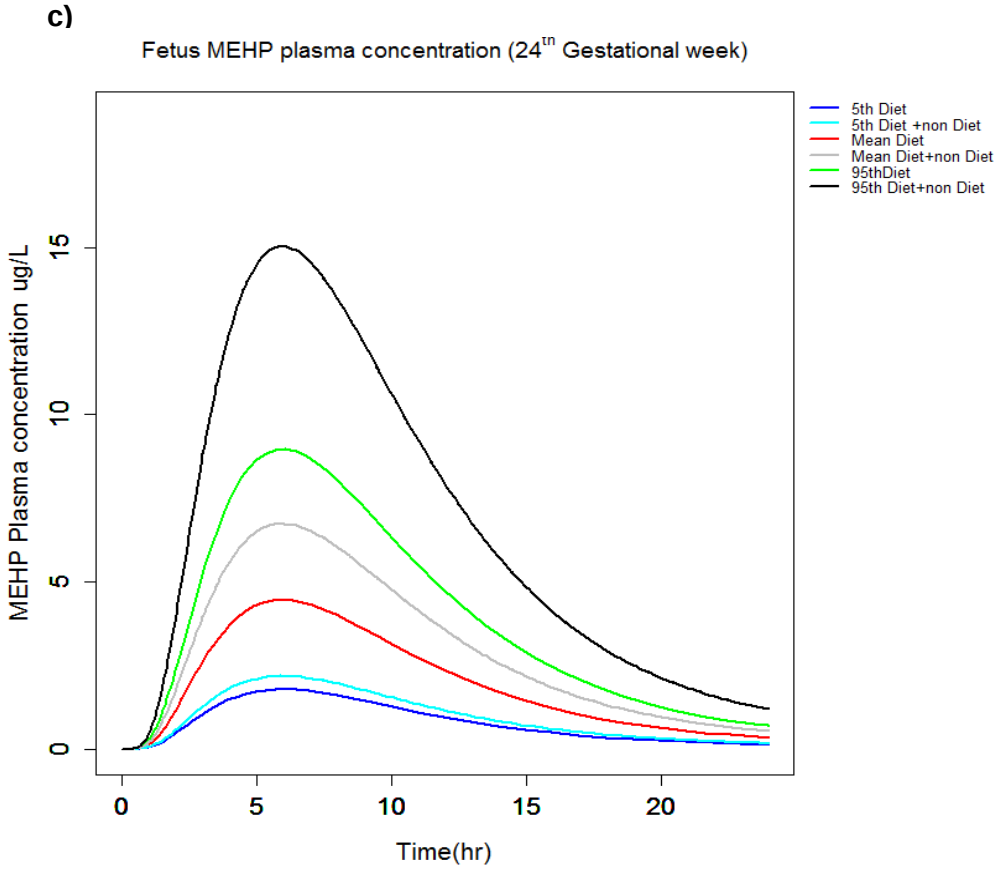


Figure 3. Time versus BPA plasma concentration for mothers a), and fetuses b), considering six different exposure scenarios (the 5th percentile diet; the 5th percentile diet + non-diet; mean diet; mean diet + non-diet; the 95th percentile diet and the 95th percentile diet + non-diet). It was considered three-food intake dose for diet and non-diet (dermal and dust ingestion) keeping inhalation as a continuous exposure.



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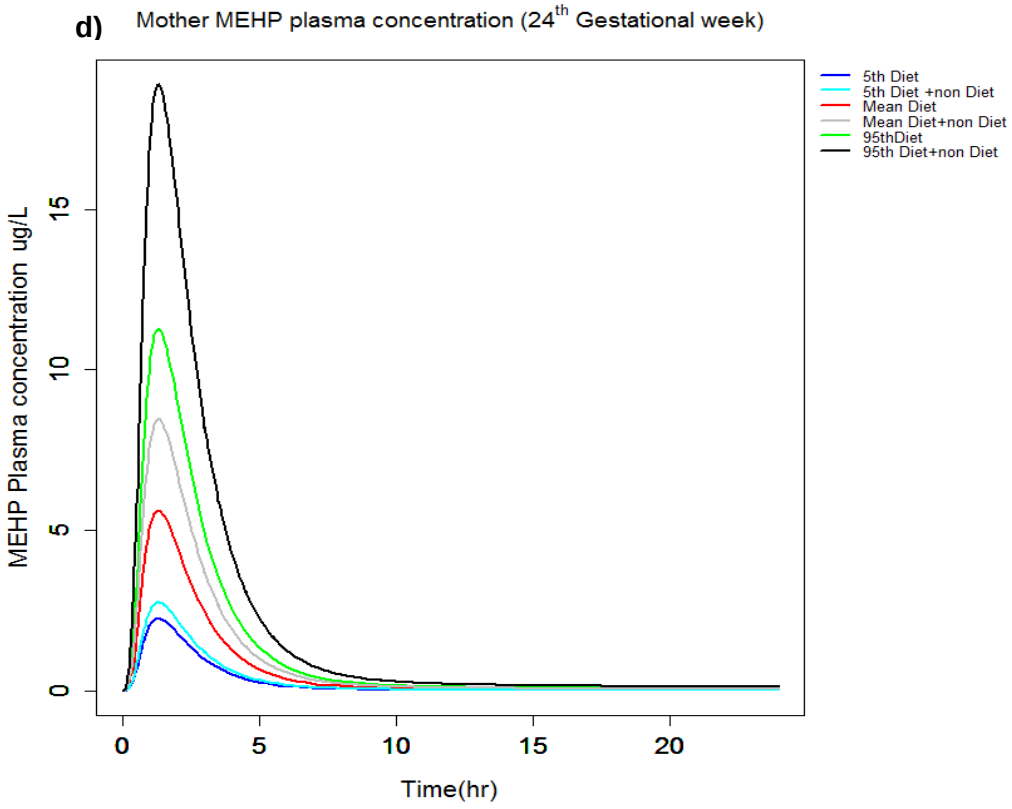

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775 **Figure 4.** Time versus MEHP plasma concentration for mothers c) and fetuses d), considering
776 six different exposure scenarios (the 5th percentile diet; the 5th percentile diet + non-diet; mean
777 diet; mean diet + non-diet; the 95th percentile diet and the 95th percentile diet + non-diet). It was
778 considered one-food intake dose for diet and non-diet (dermal and dust ingestion) keeping
779 inhalation as a continuous exposure.