Epidemiology - (BPA) in foodstuffs – Reproductive and Developmental Toxicity

In this guide

Epidemiology

2. A total of 47 epidemiology studies were considered. Details of their appraisal for internal validity is set out in Annex B to the EFSA opinion. The studies are listed alphabetically and may cover more than one endpoint. All epidemiology studies were considered to be tier 3, mainly because of low confidence in the exposure assessment.

3. Weight of evidence analysis was conducted on the following clusters and endpoints (see section 2.3.2 of the main opinion for further information on HOCs etc). The main information extracted from the studies is summarised in section C5 of Annex C to the opinion. The outcome of the weight of the evidence is described in the text of the opinion (and summarised below) and presented in a tabulated format in section D4 of Annex D to the opinion.

• C: Fetal and post-natal growth – Exp: Adulthood.

• C: Prematurity – Exp: Pregnancy.

• C: Pre-eclampsia – Exp: Adulthood.

• C: Male fertility – Exp: Adulthood.

• C: Female fertility – Exp: Adulthood.

Cluster Fetal and post-natal growth - Exposure during pregnancy

4. A total of 13 studies reported results on indices of fetal growth (Burstyn et al., 2013; Philippat et al., 2014; Smarr et al.2015; Veiga-Lopez et al., 2015; Birks et al., 2016; Casas et al., 2016; Ferguson et al., 2016; Huang YF et al., 2017a; Pinney et al., 2017; Woods et al., 2017; Lee YM et al., 2018; Lester et al., 2018; Mustieles et al., 2018b. Of these, two studies examined associations with measures of growth *in utero* based on ultrasound measures and two studies (Philippat et al., 2014; Lee YM et al., 2018) examined associations between maternal pregnancy BPA concentrations in urine with measures of post-natal growth up to 3 and 6 years of age. Overall, no consistent associations with birth weight, birth length, head circumference or other indices measured *in utero* or at birth were observed. In most cases the effect estimates were centred around the NULL with wide confidence intervals, but significant associations were observed in

a few studies. As an example, the panel noted a study by Lee YM et al. (2018) which reported a significant increase in birth weight with higher maternal exposure while a significant decrease in femoral length *in utero* was observed. A second study by Mustieles et al. (2018) examined associations with birthweight among 346 subjects who were having their fertility status examined. In this study a significant inverse association between maternal pre-pregnancy urinary BPA concentration and birth weight was observed [~79 g decrease (95%CI: −153, −5) for ~3-fold increase in BPA exposure]. For maternal samples collected during pregnancy this association was in the same direction but non-significant [−38 g (95%CI: −101, 25)]. Although interesting, the panel considered that this inverse association for maternal pre-pregnancy BPA concentration would need to be replicated in another study before any robust conclusions can be drawn.

5. In terms of possible high exposures, Birks et al. (2016) used individual data from 13 European birth cohorts to identify pregnant women who had been occupationally exposed (based on self-report) to BPA during pregnancy. Of 133,957 individuals a total of 59 women with occupational exposure were identified. Mean birth weight among these exposed women was not significantly different from unexposed women. The few studies that examined more clinically relevant birth outcomes such as small for gestational age and low birth weight (Burstyn et al., 2013; Lester et al., 2018) did not find any association with maternal BPA exposure. However, only the case–control study by Burstyn et al. (2013) had sufficient statistical power to evaluate this outcome with some accuracy. Concerning post-natal growth, the study by Lee YM et al. (2018) also reported some significant associations between maternal concentrations of BPA in pregnancy and weight and weight for length from age 3 to 6 years of age. In contrast, no association with weight or length up to 3 years of age was observed in the study by Philippat et al. (2014).

Overall conclusions

6. On the basis of the above studies, the CEP Panel concluded that an association between maternal BPA exposure and impaired pre-natal and post-natal growth is **Not Likely.**

Cluster Prematurity - Exposure during pregnancy

7. A total of seven studies examined the association between maternal BPA concentrations and length of gestation or preterm delivery (Weinberger et al., 2014; Cantonwine et al., 2015; Smarr et al., 2015; Veiga-Lopez et al., 2015;

Birks et al., 2016; Casas et al., 2016; Pinney et al., 2017. In a study of a cohort of 72 pregnant women, Weinberger et al. (2014) reported a significant inverse association between total BPA concentration in urine and length of gestation (approximately 1-day shorter gestation for each interquartile increase in exposure). In contrast, a relatively large case–control study sampling 130 preterm cases and 352 random controls taken from a larger birth cohort (n = 2246) did not find any association between maternal urinary BPA exposure (samples collected minimum three times during pregnancy) and preterm delivery (Cantonwine et al., 2015. In other studies looking at length of gestation, no association was consistently observed. In studies examining associations with length of gestation no associations were observed (Smarr et al., 2015 ; Veiga-Lopez et al., 2015; Casas et al., 2016; Pinney et al., 2017).

8. In terms of possible high exposures Birks et al. (2016) reported a slightly longer gestation period (approximately 4 days) among 59 women that were likely to have been occupationally exposed to BPA (based on self-report) compared with unexposed women (n = 116,358).

Overall conclusions

9. On the basis of these studies, the CEP Panel concluded an association between BPA exposure and shorter duration of gestation or increased risk of preterm delivery is **Not Likely**.

Cluster Pre-eclampsia - Exposure during adulthood

10. Two case–control studies, Ye et al. (2017) n = 173 (73 cases, 99 controls) and Cantonwine et al. (2016), n = 481 (50 cases, 431 controls) for a total number of cases of 123, assessed the association between BPA exposure measured in spot urine (n = 1) or serum (n = 1) samples in pregnancy and endpoints related to pre-eclampsia (onset and/or severity).

11. The detailed description and risk of bias assessment related to these studies are provided in Annexes C and D to the opinion respectively. The study by Cantonwine et al., (2016) was conducted in the US and did not report an association with pre-eclampsia: HR (95% CI), 10 weeks 1.53 (1.04–2.25), 18 weeks 1.12 (0.61–2.07), 26 weeks 0.68 (0.43–1.07), average 1.14 (0.73–1.79). The study by Ye et al., (2017) was conducted in China with similar endpoint definitions. In this study, BPA exposure (continuous and per tertile) was statistically significantly associated with pre-eclampsia Odds ratio (OR) (95% CI),

continuous BPA, 1.39 (1.19–1.63); OR (95% CI), categorical BPA, medium 2.15 (0.98–4.75), high 16.46 (5.42–49.95), pre-eclampsia onset OR (95% CI), continuous BPA, mild severity 1.42 (1.21–1.67), severe 1.35 (1.14–1.60) and pre-eclampsia severity (OR (95% CI), continuous BPA, early onset 1.33 (1.07–1.66), late onset 1.41 (1.20–1.66) 20–1.66).

Overall conclusions

12. On the basis of the above, the CEP Panel concluded that the evidence for a positive association between BPA exposure and pre-eclampsia is **ALAN.**

Cluster Male fertility - Exposure during adulthood

13. A total of five studies (Buck Louis et al., 2014; Bae et al., 2015; Dodge et al., 2015; Goldstone et al., 2015; Buck Louis et al., 2018) in three different cohorts examined the relationship between urinary BPA concentrations and fertility in both males and females.

14. Among couples (n = 218) seeking fertility treatment, Dodge et al. (2015) found no association between urinary BPA concentrations in men and fertilisation or live birth following in vitro fertilisation or insemination. Similarly, Buck Louis et al. (2014) examined associations between urinary concentrations in both male and female couples (n = 501) with fecundability. No association was observed for urinary BPA concentrations in males and females.

15. In a later study of 339 males from the same cohort (Buck Louis et al., 2018) no association was observed between BPA concentrations in seminal plasma and fecundity.

16. These findings are in line with a study by Goldstone et al. (2015) where no association was observed between urinary BPA concentrations and semen quality (total count, concentration or morphology) in 418 males.

17. Finally, Bae et al. (2015) reported an association between paternal BPA exposure and fewer male births (lower male to female sex ratio). (Relative risk of male birth. per standard deviation change in the log- transformed maternal urinary BPA concentration. RR 1.16 (95% CI 1.03–1.31). The model was adjusted for paternal concentration, urinary creatinine, research site, maternal age, difference in couples' ages, annual income and maternal parity). The panel noted that as no other studies have reported on this outcome and in the light of the fact that none of the other studies found consistent associations with live birth rate,

fecundability or other fertility outcomes, a chance finding seems plausible.

Overall conclusions

18. On the basis of the above, the CEP Panel concluded that an association between exposure to BPA measured in spot urine and reduced fertility is considered **Not Likely.**

Cluster female fertility- Exposure during adulthood

19. A total of 11 studies examined the association between exposure to BPA during adult life with fertility in females (Souter et al., 2013; Buck Louis et al., 2014; Lathi et al., 2014; Bae et al., 2015; Minguez-Alarcon et al., 2015; Chavarro et al., 2016; Jukic et al., 2016; Minguez-Alarcon et al., 2016; Chin et al., 2018; Pollack et al., 2018; Wang B et al., 2018). These included associations between BPA exposures during pregnancy with fecundability and miscarriage and offspring sex ratio in the more general population (Buck Louis et al., 2014; Lathi et al., 2014; Bae et al., 2015; Jukic et al., 2016; Chin et al., 2018; Wang B et al., 2018) or associations with fertility outcomes in a more selective group of women seeking fertility treatment (Souter et al., 2013; Minguez-Alarcon et al., 2015; Minguez-Alarcon et al., 2016.

20. For the studies among the general population, associations with fecundability were inconsistent, with three studies reporting no association (Buck Louis et al., 2014; Jukic et al., 2016; Chin et al., 2018. One study (Wang B et al., 2018) reported associations between maternal BPA exposure and decreased fecundability (OR 95% CI: 0.87 (0.78, 0.98) for ~3-fold increase in exposure]. OR < 1 reflects longer time to pregnancy. A study by Lathi et al. (2014) also reported a significant positive association between BPA and aneuploid pregnancy and risk of miscarriage (Association between BPA and aneuploid pregnancy risk ratio and respective 95% CI for every quartiles of BPA exposure (1st quartile as reference) 1Q–2Q: RR = 1.18 (95% CI: 0.57–2.45) 2Q to 3Q: RR = 1.63 (95% CI: 0.86–3.09) >3Q: RR = 1.97 (95% CI: 1.08–3.59) $p < 0.05$ Association between BPA and miscarriages. Risk ratio and respective CI for every quartiles of BPA exposure (3Q: RR = 1.83 (95% CI: 1.14–2.96) $p < 0.05$).

21. In a group of selected women seeking fertility treatment, Chavarro et al. (2016) reported a significant decrease in live births among strata of women who did not consume soy (n = 100), while no such association were observed among majority of study participants that did consume soy (n = 247). As women who

seek treatment may change their dietary habits before treatment it is possible that women who did not consume soy in a group of selected women may have underlying different fertility compared with those who reported to consume soy. The context of the study was that animal studies had shown that soy could ameliorate the effects of BPA, so the aim was to establish if this was the case in humans. Similarly, in a group of selected women Minguez-Alarcon et al., (2016) reported decreased probability of implantation and clinical pregnancies with higher BPA exposures.

Overall conclusions

22. Overall, the results from these studies conducted in both selected and more unselected group of women are inconsistent and an association between BPA exposure in adult life and reduced fertility was judged as **ALAN.**

Cluster Pubertal/endocrine - Exposure during pregnancy

23. Watkins et al. (2017a) examined the association between exposure to BPA during pregnancy and pubertal development in 109 male offspring aged 8 to 14 years. In a separate publication based on the same cohort, associations with pubertal development were also examined in 120–129 female offspring aged 8 to 13 years (Watkins et al., 2014 ; Watkins et al., 2017b). No associations with markers of pubertal development were observed in either of the studies.

24. Similarly, no association between exposure to BPA in pregnancy and markers of puberty was observed in 112 boys in a study by Ferguson KK et al. (2014). However, a study by Berger et al. (2018) examining the relation between maternal BPA exposure and pubertal development in 179 female and 159 male offspring at age 9 to 13 years found associations with later and earlier pubertal development in female and male offspring, respectively. Association between BPA exposure and thelarche onset in females (mean change in months with 95% CI). All girls: 3.0 (95% CI, 0.9–5.1); normal weight: 4.7 (95% CI, 2.5–7.0); overweight: 1.6 (95% CI, −1.6–4.8), inverse association between maternal BPA concentrations and pubarche onset in boys. Mean shift in months −3.1 (95% CI: −5.1 to −1.0) Inverse association between BPA exposure and gonadarche onset in boys. Mean shift in months −4.1 (95% CI: −6.6 to −1.6).

25. Finally, three studies reported associations with anogenital distance (Barrett et al., 2017; Arbuckle et al., 2018; Sun et al., 2018, an outcome that is often used as a predictor for later reproductive disorders. Overall, despite a few significant findings being observed the findings from these three studies were

inconsistent.

26. On the basis of these studies, the CEP Panel concluded that an association between BPA exposure during pregnancy and pubertal development is considered as **ALAN.**

Cluster Pubertal/endocrine - Exposure during childhood

27. A total of five prospective studies examined associations between exposure to BPA measured in urine during childhood and pubertal development (Lee et al., 2013; Wolff et al., 2015; Kasper-Sonnenberg et al., 2017; Wolff et al., 2017; Binder et al., 2018. However, two of these studies were conducted in the same study population but with different lengths of follow-up (Wolff et al., 2015; Wolff et al., 2017). Overall, no association between childhood exposures to BPA and pubertal development were observed in these studies.

28. On the basis of these studies, the CEP Panel concluded that an association between BPA exposure during childhood and pubertal development is considered **Not Likely**.

Overall conclusions

29. On the basis of these studies, the CEP Panel concluded that an association between BPA exposure and pubertal development is **ALAN.**

Cross sectional studies

30. A number of cross-sectional studies were considered for each endpoint as described above (p181-182 of the opinion). In general, these did not add to the assessment and have not been considered further in this document. Some findings of interest are:

- Leclerc et al., 2014 found no statistical significance between maternal exposure and pre-eclampsia, analysing levels in maternal and fetal serum and placenta. In placental tissue, concentrations of BPA were higher in preeclamptic women compared with normotensive pregnant women (p-value = 0.04).
- 15 cross-sectional studies considered BPA and male fertility, assessing a number of different parameters. It was noted that although, the associations were not entirely consistent in terms of directionality, findings from some individual studies could be interpreted as being adverse for male reproductive function. However this was not supported by other lines of

evidence – prospective studies and animal studies.

- Similarly, a number of cross-sectional studies reported associations between BPA concentrations and adverse effects in female fertility. It was noted that the measured BPA concentrations reflected exposure during the previous few hours and as such, in the absence of further evidence, are unlikely to reflect past exposure that may have led to development of the underlying disease condition. Differences in lifestyle factors that may affect exposure to BPA or rate of uptake or excretion among cases may equally explain the observed findings, particularly in the absence of similar findings from prospective studies.