ANNEX E: EXPERT REVIEW OF EPIDEMIOLOGICAL STUDIES DESCRIBED IN THE ANSES 2013 REPORT ON HARMONIZED CLASSIFICATION AND LABELLING OF BISHPENOL A

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Review of the epidemiology studies described in the ANSES 2013 report on harmonized classification and labeling of Bisphenol A

Summary

This document reviews the epidemiologic literature in the ANSES CLH report on Bisphenol A and is a response to the invitation from ECHA for public comments. It is divided into two sections, parallel to the ANSES report, on 1: the female reproductive system and 2: the male reproductive tract. The concern about the poor quality of many studies expressed in the report on page 10 is shared. Most importantly, nearly all the studies rely upon a spot serum or urine sample with which to determine exposure. Given the short half-life of BPA, a single sample is not representative for general exposure, a concern also raised by a joint committee of FAO/WHO (2010) and by Teeguarden et al (1). Further with few exceptions, none of the samples was collected during the etiologic relevant period for disease. The population-based studies did not collect any information from the subjects to distinguish any dietary or other behaviors and to confirm the observed BPA concentrations. Most of the studies employ a cross sectional design which can only demonstrate a mathematical correlation of the observed data and not temporal association or causal connection. After a thorough review of the epidemiology studies included in the ANSES report, we conclude that the inconsistent results, in combination with the poor quality, do not provide additional evidence for BPA toxicity. The inconsistency, null findings, doubtful results and contradictory findings in the 20 epidemiology studies are best compatible with a situation where there is no biologically plausible relationship that can be established. Consequently, the presence of any robust adverse health effects caused by BPA can be excluded. .

The female reproductive system

The study by Cobellis et al (page 76 of the ANSES document) has many shortcomings including the ones described by ANSES (2). In addition it was noted that in the 11 controls neither BPA, nor BPB could be detected in serum, which makes it doubtful that the very small control group used in this study is representative of the population from which the cases were derived. The control group consisted of women suspected of having endometriosis who had symptoms and complaints compatible with it. The control group may have included women with dysmenorrhea and other pelvic diseases. In addition, no blinding during the analytical phase of the projects seems to be applied. Perhaps the most striking feature of this study is that the reported BPA serum levels in endometriotic women are very similar to those measured in healthy populations reported in other studies as reviewed by Dekant and Volkel (3). The lack of association between BPA levels and endometriosis reported by Itoh et al (4) sheds more doubt on the results reported by Cobellis et al.

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As to claims made around exposure, e.g., blood or urine BPA and/or BPA-glucuronide measurements, such as those presented by Cobellis et al. (2009), serious attention must be paid to analytical challenges in measuring BPA, especially the weak estrogenic aglycone (free BPA). Given that the determination trace level quantitation of free (aglycone) and/or total (aglycone + conjugates) ^{12}C-BPA (< 1 ng/mL) in human blood and urine is very challenging, the following recommendations are presented as guidance to ensure accurate and precise data. Methods used to determine free and total ^{12}C-BPA must strive to eliminate and continually monitor for background contamination from all sources (collection to analysis) with the appropriate blanks, controls and fortified controls. The method must demonstrate and monitor method performance using matrix spikes fortified with ^{12}C-BPA-G at the method quantitation limit (MQL). In addition, the use of a surrogate analyte, in this case ^{13}C-BPA-G is also strongly recommended, provides valuable information on method performance and aids in method troubleshooting as it is not affected by exogenous ^{12}C-BPA. The total BPA method should verify enzyme hydrolysis efficiency at relevant concentrations with the target conjugates and in the study matrix. The method should analyze replicate samples or replicate matrix spikes to evaluate reproducibility. The method should employ state of the art HPLC/MS/MS instrumentation to ensure the desired sensitivity and selectivity can be routinely achieved. Finally, if only free ^{12}C-BPA is being reported, the method must demonstrate that only free ^{12}C-BPA is being measured by demonstrating the major metabolite of ^{12}C-BPA (^{12}C-BPA-G) is stable (no hydrolysis to free ^{12}C-BPA) when subjected to all the method elements from sample collection to analysis. For these reasons, the exposure evidence claimed by epidemiological studies, especially for BPA aglycone, is suspect. Furthermore, due to our knowledge around the toxicokinetics of of BPA, the claim of measured BPA aglycone concentrations in blood is not credible:

> *...aglycone BPA levels reported in human blood in the ng/ml range from routine sample collections are implausible and could represent sample contamination artifacts; ....Unfortunately, until more critical assessments of analytical methodology, pharmacokinetics, and biomonitoring are included in study design, funding, conduct and peer review of BPA biomonitoring studies, the data will be difficult to evaluate for use in risk assesment.* (5)

On page 77 the very recent study by Ehrlich (6) is described as reporting an association between BPA concentrations in urine and implantation failure undergoing in vitro fertilization. However, no statistically significant differences between the first, second and third BPA level quartile were noted. The only statistically significant findings reported were the differences between the lowest quartile and the highest quartile. This difference became attenuated and non-statistically significant after controlling for other risk factors. The reported findings could be a chance finding rather than an actual association. The authors themselves describe the results of their study as a preliminary finding (page 983, Ehrlich et. al. 2012). In addition, the most relevant hypothesis tested in this study was the possible association between BPA levels and the success of the fertility treatment. Although these data were collected, the analyses were not reported in the paper. We propose that the lack of

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statistical significance and the statement made by the authors themselves about the preliminary status of the findings be added to the text of the ANSES report.

The description on pages 77 and 78 of the case-control study on recurrent miscarriage and BPA conducted by Sugiura-Ogasawara (7) is incomplete. It should be noted that the authors did not present any information on the timing or number of samples taken or how the samples related to the time of miscarriage. In addition the distribution of BPA concentrations were extremely skewed and for this reason a non-parametric mode of testing is preferred. The ANSES report describes the difference in mean BPA concentrations but this difference is clearly the result of several outliers. As a result, the median is preferred over the arithmetic mean in this case. Indicatively, the median BPA concentration did not differ between cases and controls. The statistical analysis was inadequate given no adjustments were made for potentially confounding factors. In fact, a later letter to the editor stated that the study provided no support for an association with BPA. In contrast, the levels reported for the controls are much lower than those reported as background levels by others (3). The paper by Sugiura-Ogasawara does not provide details on how the controls were selected, other than they were medical co-workers. Medical co-workers may imply co-workers of the researchers and laboratory personnel of the institute were recruited for the control group. Such a control group is unacceptable in an epidemiologic study since it *a priori*, is not representative, and is not a proper comparison group for women who have had four miscarriages or more. The ANSES report should have addressed these shortcomings and should also have noted that the authors themselves describe the study as preliminary.

The study by Cantonwine, described on page 78, is of a questionable quality and the ANSES report correctly questions the value of a single sample to determine exposure to a compound with such a short half-life (8). This concern has also been expressed by WHO, as they stated that a single sample is insufficient (9) (page viii). In addition, no reason is given why women who delivered in week 37 of gestation were switched from the case group to the control group. With the original classification of cases and controls, no statistically significant difference was noted. In fact, had the authors not changed the classification the difference between cases and controls would have been minimal and very well explainable by a few outliers. No association for urinary BPA and gestation age for a much larger group of births (n = 339) was reported for the US Children's environmental Health Study (10). The ANSES report should have mentioned that the authors designate the study as preliminary and the findings have not been replicated.

On page 78, a study on 84 women attending an IVF clinic is described (11). As mentioned in the ANSES report one of the key weaknesses of this study is the BPA exposure determination was based on a one or two samples, taken at a moment not relevant for the follicular maturation. The paper by Mok-Lin (11) also suffers from a methodological shortcoming very common among similar papers: an extensive battery of statistical analyses is performed, including a range of sophisticated statistical modeling techniques, but only a very limited sample of the outcomes of

these analyses are presented. This is a clear violation of the well accepted STROBE guidelines for reporting the results of observational epidemiology studies (12). Poisson regression models using generalized estimating equation techniques are notoriously unstable when applied to small datasets such as this study. The research design of this study contains a methodological pitfall not addressed by the authors. For women who produced fewer oocytes in the first cycle and continued on the IVF program for a second cycle, the measures of BPA exposure consisted of the geometric mean of the two samples.. Given the skewed distribution of the BPA concentrations, the mean of two samples would be higher than one of the measurements. As a result the BPA levels of women producing fewer oocytes, and being treated for more cycles, would have a higher mean BPA level compared to the women producing many oocytes with a single BPA measurement. In addition, it is noteworthy that the BPA urine levels in the total group of 84 women attending the infertility clinic are comparable to that of the total US population (see page 8 first paragraph). This implies that the study population has BPA levels similar to background, a conclusion not compatible with an association between BPA levels and infertility. The research described in the publication by Mok-Lin et al (11) is viewed in the ANSES report as a high quality study (page 10) and seen as a critical piece of evidence. It is notable that the women in this study are also part of the analyses reported by Ehrlich et al., (6). The ANSES report fails to recognize that the subjects reported by Bloom et al., (13), with higher BPA levels, showed no association between BPA and the number of oocytes. We conclude that Mok-Lin et al. (9) is limited by serious weaknesses, both regarding the study methodology as well as how it is reported, and the findings are in conflict with another epidemiology study conducted by Bloom et al (13).

On page 79, the study conducted by Fujimoto et al (14) is described as indicator for an association between a single BPA measurement and in vitro fertilization success. However the authors found NO association between oocyte maturation and BPA concentration in the total study group (page 1817 Fujimoto et al 2011). The authors state on page 1817: “There was no association between BPA and oocyte maturation when all cases were considered”. Only after having restricted the total population of 44 women to 26 couples who underwent ICSI did the researchers find associations with BPA. The only proper way to interpret such an analysis is that the study overall showed no association. The authors do not give any plausible explanation why they only presented the finding for the ICSI group.

The description of the study by Bloom et al (13) lacks several aspects of the paper. First the authors stress that the findings are preliminary. Second, the researchers use very sophisticated statistical modeling techniques, which become very unstable in cases where the study sample is limited, which is the case here also. Another questionable decision made by the investigators was the retention of three women who had previously initiated a single canceled IVF cycle. Was inclusion of these women necessary to reach a statistically significant result? The study did not find an association between BPA and the number of oocytes retrieved and it can be assumed that this was the primary hypothesis being tested. The authors describe their study as preliminary and note that the results need confirmation.

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The study by Takeuchi et al (15) is described on page 79 of the ANSESas a study with results difficult to interpret and has several shortcomings. There is no description of how, where and when the study subjects were recruited for the study population. Any mention of review by a medical ethical committee is lacking, and the sample is so small that reliable conclusions cannot be drawn, particularly given the large number of statistical significance tests performed. With the large number of statistical tests performed the p value should have been smaller than the conventional 0.05 in order to decrease the probability of false positive findings. It is common understanding in epidemiology that is p value of 0.05 is appropriate only if a single or a limited number of significance tests are done. If multiple testing is done the p value should be adjusted and a smaller value should be taken, e.g 0.01 or 0.005, in order to avoid drawing wrong conclusions

A study by Kandaraki (16) is described on page 79 of the ANSES report. Apart from the problem with the analytical methodology, there is an issue about the direction of the relationship, if one exists. BPA levels were determined AFTER PCOS diagnosis. It is common knowledge that the prevalence of thyroid dysfunction is very high among PCOS patients (see for example Garelli et al (17)). Poor thyroid function will result in slower metabolism, which could be a more likely explanation for differences in BPA levels in these patients. The study by Wolff et al (18) did not find any association between BPA levels and the onset of puberty. This study had the largest sample size of all human studies cited in the ANSES report.

In the summary evaluation on page 81, it is stated that the findings of Mok-Lin were confirmed by Fujimoto et al. This is not correct. The study conducted by Fujimoto essentially is negative. This is confirmed on page 1817 of the paper where the authors state: “There was no association between BPA and oocyte maturation when all cases were considered”.

The male reproductive tract

On page 106 of the ANSES report the study conducted by Galloway is quoted as having found a highly significant association between the daily BPA excretion and total testosterone levels (19). The quote is incorrect. Galloway stated that their study suggests that low levels of environmental BPA MAY be associated with a modest reduction in free testosterone markers. Perhaps more importantly, the investigators did not find any consistent associations between BPA levels and semen quality parameters, which was the hypothesis they originally set out to test.

The ANSES report is quite critical of the study conducted by Li et al (20-22). Apart from the comments made on this study an additional number of shortcomings are identified: Questionnaire data on sexual behavior are notoriously unreliable. The difference in participation rate between exposed and non-exposed raises more doubts about the validity. Moreover, the study is reported to be a cohort study. However, no description of the process of how former workers were identified or

how the follow-up was conducted is given. This study is more likely a cross-sectional study and not a cohort study. Perhaps the design aspect with the highest concern is that the investigators included 120 spouses whose wives were selected as unexposed controls. Including about one third of the control group from a completely different population source makes the study design flawed and no valid conclusions can be drawn from this study. The second publication by Li (21) suffers from the same serious shortcomings. Again, the third publication by Li et al (22) suffers from the same design flaws and should be entirely ignored. The flawed design and its consequences demonstrate the importance of replication by independent researchers. In this case there is a substantial difference with the findings reported by Mendiola et al (23), who essentially found no association between BPA levels and sperm parameters.

The study by Meeker (24) on BPA exposure and semen quality is described in the ANSES report as having found an inverse association between urinary BPA concentrations and semen quality in 190 men recruited through an infertility clinic. The ANSES report states page 107: "But a link between BPA exposure and impaired sperm quality was also established". However, after careful inspection of the results in the publication by Meeker et al (24) it is necessary to draw another conclusion. In Table 4 of the Meeker publication (page 535) none of the 16 described Odds Ratios reach a level of statistical significance at $p < 0.05$ and 6 of the 16 presented Odds Ratios are below 1, indicating a positive effect of BPA on sperm quality rather than a negative effect. The results presented in Table 4 are compatible with a situation where no association between urinary BPA and sperm quality exists. Similarly in Table 5, page 536 in Meeker et al (24) only 5 of the 40 β-coefficients presented have a p value below 0.05 and 21 of the 40 β-coefficients are negative indicating an inverse effect as expected. Overall, the findings in Table 5 are best interpreted as being more compatible with no association with. The best the authors can make of their data is that they conclude that confirmatory studies are needed. This should be acknowledged in the ANSES report and it should have been concluded that a link with BPA exposure was not established by the data presented by Meeker et al. (24).

On page 107, the discrepancy between the results of Meeker et al (25) and Hanoaka et al (26) is noted in the ANSES report, and the contradictory findings are attributed to the fact that the study populations are not the same. Importantly, the study populations indeed are not the same, but this is the scientific method for replication and independent confirmation of results. It is the consistency between the studies that support an association. The two studies showed opposite associations, which is evidence against the existence of an association. However, it must be stated that both studies have their shortcomings in terms of sample size, exposure measurement and robustness.

The study by Bloom et al (27) described on page 107 has a small sample size and it can be questioned whether any prior sample size calculations were made. It should also be considered that in the statistical analysis all embryos were treated as independent. The authors should have carried out a multi-level analysis instead of the GEE analyses and the potential interdependence should have been adjusted for. Again, despite the over sophisticated statistical analyses and the multiple

testing approaches, overall, no statistically significant association emerged. Only after stratification by sex, an association was reported for the BPA levels in men, but not for the women.

On page 108 the study by Miao et al (28) on anogenital distance (AGD) and BPA exposure is described. There are several critical shortcomings in the Miao study. First, since this study used the populations assembled by Li et al it suffers from the same flaws discovered in those publications. Again, it is unclear how the populations were assembled. Next the researchers did not take into account that the workers included in the exposed group, were also exposed to other compounds. Although the researchers claim to have conducted in-person interviews by trained interviewers, none of the information collected was used in the statistical analysis. The only parameters which they controlled for were age and weight. Height however, was not included in the model because Swan et al (29) had reported that weight was the factor related to AGD. It is indeed correct that Swan found that weight played a role in AGD, but in that study it was also concluded that AGD by itself was not the proper outcome measure and AGD divided by weight (AGI) was the parameter of choice. Miao provides no justification why they only partly followed the recommendations made by Swan and did not use AGI instead of AGD as propagated by Swan. Miao et al describe their findings as preliminary and in need of further confirmation, a fact the ANSES report fails to mention.

The ANSES report erroneously concludes on page 109 that “all studies point out a correlation between higher BPA levels and different sexual parameters and strengthen the plausibility of causality”. A more concise summary of the epidemiology studies on male fertility is: The severe weaknesses and limitations of the epidemiology studies on male fertility make it difficult, if not impossible to derive conclusions on causal inference. However, if a causal association between BPA and male fertility parameters exists, there should have been a more consistent pattern of results between the relatively large numbers of studies that have been conducted.

Overall conclusion

Of the over 20 reviewed epidemiology studies, 7 report no association between BPA levels and the primary outcome under investigation. In four studies, the authors describe their findings as preliminary and in need of further confirmation. Most studies suffer from shortcomings, with 5 studies having serious flaws in their research design. No, free of serious methodological shortcomings reports a positive finding with regards to the *a priori* hypothesis under investigation. Perhaps the most striking overall conclusion is that these 20 studies, representing a large body of data, have not yielded any finding that has been independently confirmed in another study. This conclusion is reflected in a recent review of the evidence published by Cantonwine et al.(30)

> *While there is a growing body of literature suggesting adverse relationships with fertility and birth outcomes in relation to BPA exposure, human studies remain extremely limited and highlights the need for more epidemiological research. The*

often contradictory findings for the effects of BPA on fertility, adverse pregnancy and birth outcomes may reflect analytical differences, study populations and methodological issues related to exposure assessment or study design. The majority of the epidemiological studies reviewed here relied upon a single time point measure of BPA which failed to address the temporal relationship between toxicant exposure and pregnancy outcomes.

Although the poor quality of the research conducted with frequently occurring serious flaws hampers drawing firm conclusions, the lack of confirmatory results demonstrates that BPA is not a reproductive risk in humans. As a whole, the epidemiology studies weaken rather than strengthen the plausibility of a causal association. It also further questions the human relevance of the findings of animal studies.

With respect to regulation EC 1272/2008 Table 3.7.1(a) " Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans" it is concluded based on the review of the human data that no such evidence is forthcoming and therefore the placing of BPA in Category 1 is inappropriate and unsupportable.

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