Meeting

Final minutes of the extraordinary meeting on BPA 10th February 2022

Meeting of the Committee at 10:00 on the 10th of February 2022 on Microsoft Teams

Present

Chair	Professor Alan Boobis

COT Members:	Dr Phil Botham
	Ms Jane Case
	Dr Stella Cochrane
	Dr Rene Crevel
	Professor Gary Hutchison
	Dr Sarah Judge
	Dr Gunter Kuhnle
	Dr David Lovell
	Dr Mac Provan
	Dr Michael Routledge
	Dr Cheryl Scudamore
	Dr Natalie Thatcher
	Professor Thorhallur Ingi Halldórsson
	Professor Shirley Price
	Dr Simon Wilkinson
	Professor Matthew Wright

Prof Paul Haggarty	SACN Liaison
Prof John O’Brien	Science Council Liaison

Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland	FSA Scientific Secretary
	Ms Claire Potter	
	Mr Barry Maycock	
	Dr Barbara Doerr	
	Dr Alex Cooper	
	Dr Olivia Osborne	
	Ms Emma French	
	Dr Joseph Shavila	
	Ms Rhoda Aminu	
	Ms Sabrina Thomas	
	Dr Gail Drummond	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
	Ms Cleanncy Hoppie	
	Ms Jocelyn Frimpong-Manso	
	Ms Sophy Wells	
	Dr Gaetana Spedalieri	
	Mr Thomas Hornsby	
	Mr Lawrence Finn	
	Dr Emily Hudson	
	Dr David Kovacic	
	Dr David Gott	
	Mr Shaddad Saleh	

UK HSA Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
FCM JEG Members:	Dr Sibylle Ermler	Joint Expert Group for Food Contact Materials
	Dr Emma Bradley	
	Dr Gill Clare	
	Dr Jenny Odum	
COM Members :	Professor Gareth Jenkins	Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
	Dr Paul Fowler	
	Dr Andy Povey	
	Dr Carol Beevers	
	Professor David Harrison	
	Dr George Johnson	
COC Members :	Dr Lesley Rushton	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
	Dr Neil Pearce	
	Professor David Harrison	
Invited Experts and Contractors:	Dr Sarah Bull	Institute for Environment and Health
Invited Experts and Contractors:	Ms Frances Hill	Department for Business, Energy and Industrial Strategy (BEIS)
Assessors	Mr Ian Martin	Environment Agency
	Ms Susannah Brown	Department of Health and Social Care (DHSC)
	Ms Louise Dearsley	Health and Safety Executive (HSE)

External Observers	Dr Stephen Ruckman	TSG consulting
	Ms Judith Giernoth	Covestro
	Dr Kevin Sondenheimer	Covestro
	Ms Marion May	Food and Drink Federation
	Professor Ian Kimber	University of Manchester / Consultant American Chemistry Council
FSA and other Officials:	Mr Josh Hunt	FSA
	Mr Tim Chandler	FSA
	Mr Vincent Greenwood	FSA
	Dr Amie Adkin	FSA
	Dr Ovnair Sepai	UKHSA
	Dr Tim Marczylo	UKHSA
	Ms Krystle Boss	Food Standards Scotland (FSS)
	Ms Lucy Smythe	FSS
	Dr Helen McGarry	HSE

Contents

2	Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Overview, methods and weight of evidence.	5
3	Benchmark dose modelling (including uncertainty analysis and derivation of the HBGV)	17
4	Immunotoxicity	39
5	Reproductive and developmental toxicity	50
6	Neurotoxicity and Developmental Neurotoxicity	60
7	Genotoxicity	69
8	Toxicokinetics and other endpoints – approach to epidemiology, metabolic effects, cardiotoxicity, and carcinogenicity	75
9	Summary & discussion	76
10	Next steps	82
	Date of the next meeting	29th March 2022

Announcements

1. The Chair welcomed Members and other attendees.

2. It was noted that the aim of the meeting was to discuss the draft opinion and agree any comments to be sent back to EFSA and if necessary to

agree any next steps. There was no intention to conduct a risk assessment for Bisphenol A. A document had been set up in the COT teams site to allow Members to add minor comments or any additional comments following the meeting.

Interests

3. The Chair reminded those attending the meeting to declare any commercial or other interests they might have. Professor Thorhallur Ingi Halldórsson of the Committee and Dr David Gott of the Secretariat were Members of the EFSA CEP panel and BPA Working Group. They were able to answer questions and provide clarification but could not take part in the discussion. Professor Matthew Wright is an EFSA panel Member but was not involved in the BPA evaluation and was able to take part. Dr Stella Cochrane and Dr Natalie Thatcher declared non personal specific interests, as their employers would have an interest in the use of BPA in packaging.

Item 1: Apologies for absence

4. Apologies were received from COT Members Dr James Coulson, Dr Caroline Harris, Professor Maged Younes, Ms Juliet Rix and Professor Phillippe Wilson. Apologies were also received from Mr Michael Dickinson of the Secretariat.

Item 2: Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Overview, methods and weight of evidence (TOX/2022/11)

5. In December 2021, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) published a draft opinion re-evaluating the health risks arising from the presence of bisphenol A (BPA) in food. The panel proposed a significant reduction to the current temporary Tolerable Daily Intake (TDI) of 4 µg/kg body weight (bw) to 0.04 ng/kg bw. This reduction would mean that both mean and high level consumers for all age groups would exceed the new TDI by 2-4 orders of magnitude.

6. Paper TOX/2022/11 considered the methods used by the EFSA CEP panel to conduct the evaluation and covered the Health Outcome Category

(HOC)/cluster approach, the study selection, the weight of evidence evaluation, and the integration of the human and animal streams of evidence. The views of the Joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence subgroup (SETE) were also compared to the approach taken by the EFSA panel.

7. The Committee agreed that EFSA had approached the subject in a methodical and structured way. However, due to the amount of detail and the structure used to manage it, the Committee found it difficult to find critical information and draw overall conclusions. The Committee noted that there was no in-depth consideration of studies used in the previous (2015 EFSA) opinion. There was a large body of data missing and so the new opinion did not transparently encompass the totality of the available evidence.

8. The Committee discussed the epidemiological evidence and how it had been assessed using the scoring and weight of evidence (WoE) approach. Members noted that this was a standard approach in epidemiological studies but one which tended to be conservative and produce negative conclusions.

9. Members discussed the key endpoints that had been identified by EFSA and highlighted the use of the increase in Th17 cells as an area of concern. The Committee noted that the supporting epidemiological evidence was not strong and the use of the intermediate animal endpoint was conservative. Based on the evidence the Committee were not convinced that EFSA had reached an appropriate conclusion (immunotoxicity is discussed further below) on an appropriate reference point.

10. The Committee then considered the reproductive toxicity HOC and the change in follicle ratios that was used as an endpoint for Benchmark dose modelling, which, the EFSA panel noted, would also have resulted in a TDI that the population were significantly exceeding. The Committee highlighted that this choice was based on a Tier 2 study when a Tier 1 study had not shown an effect but had not been fully considered as it was a single dose study. This suggested that inconsistent data had not been fully considered and this reduced confidence in the way the data had been treated. Emphasis was placed on immunological studies (e.g. the O'Brien study) with hypersensitivity effects shown, but the allergic inflammation data appeared to have been ignored, leading to positive bias.

11. Members noted that there might be some errors in the tier ratings listed in the main opinion compared to those given in Annex G. (Post meeting note-

there are some errors but some studies have a different tier rating depending on the endpoint considered).

12. Members discussed the weighting of the studies and agreed that there was more discussion of the positive than the negative animal studies, suggesting that the studies may not have been weighted appropriately. EFSA also tended to focus on data that could be modelled, potentially ignoring other relevant information.

13. The Committee discussed the use of the term “as likely as not” (ALAN) and considered the usefulness of this term. It was noted that in epidemiological studies, ALAN is used frequently as a standard term where balance of evidence neither supported nor contradicted a putative causal relationship between an effect and a stressor with any confidence, with the focus on positive evidence. It was suggested that guidance was needed because it was difficult to determine how EFSA came to their scientific judgment when this term was used.

14. The Committee discussed the approach taken regarding the assessment of genotoxicity and the expert elicitation used in the uncertainty analysis. It was explained that initially, experts in the area were involved and further elicitation was carried out by all Members of the working group. This gave a numerical probability and likelihood, which was then subjected to mathematical modelling. The Committee concluded that whilst the modelling itself was quantitative, the output was ultimately subjective. Members queried if the method was quality assured as the data were extremely variable and could lead to uncertainty. The Committee were informed that there were attempts to standardise the interpretation by the experts to reach a final consensus; however, it was noted by Members that this could have introduced elements of bias. The Committee were informed that the process was conducted in R and, although available, the code was not easy to follow.

15. Members thought it surprising that there was not a deeper scrutiny of the justification given for the dramatic change in the TDI, and questioned how much it was scrutinised. Members also had great difficulty in determining from the draft opinion how EFSA came to their decision.

16. The way in which the data had been assessed as individual endpoints in different exposure periods made it difficult to see the whole picture and also to assess individual studies in their entirety.

Item 3: Benchmark dose modelling (including uncertainty analysis and derivation of the HBGV) (TOX/2022/13)

17. A summary of the BMD modelling approach that EFSA had used in its hazard characterisation of BPA to establish the new TDI of 0.04 ng/kg bw was presented by a COT Member.

18. The presentation concentrated on the 0.06 µg/kg bw per day BMDL that EFSA had used in its approach based on analysis of the Luo *et al.* (2016) study, as this was the measure used to establish the new TDI. It was noted that there was evidence of randomisation with respect to the dams and their offspring used in the study, which reduced the risk of bias being introduced. However, specific details of how data on the numbers of Th17 cells were collected were limited.

19. A standard analysis of variance had been performed and the data appeared to be suitable for dose-response modelling. Members noted that the values of the BMDL (termed CEDLs in the figures produced by the EFSA PROAST software) for the female post-natal day 21 (FPND21) group ranged from 0.045 to 0.056 µg/kg bw per day for the various models used. The BMDL value produced by model averaging was 0.06 µg/kg bw per for the FPND21 group.

20. The Member presenting pointed out that the BMDL values for the male groups were 5-6 times higher than that for the FPND21 group. However, only the FPND21 group value of 0.06 ug/kg bw per day was subsequently used in EFSA's determination of the TDI.

21. It was pointed out that effectively three choices were made by EFSA in their use of the data to establish the TDI. Firstly, a study with some of the lowest BMDL values was selected for calculation of the TDI (it was argued that in the 'uncertainty study' it was 90 % probable that no other endpoint was more sensitive than the Th17 cells study). Secondly, the lowest BMDL was chosen from the results of the four groups in the Luo *et al.* (2016) study. Thirdly, a critical effect size (CES) of 20 % was chosen, rather than the default CES value of 5 % recommended in the EFSA guidance for continuous data. It was noted, however, that the guidance suggests that biological significance and variability should also be considered when choosing the CES.

22. It was noted that when the default CES value of 5% is used, the BMDL of 0.06 µg/kg bw per day for the FPND21 group decreases to 0.0004 µg/kg bw per

day (that is, by approximately two orders of magnitude).

23. The Member presenting went on to explain that analysis of the FPND21 group using the US EPA's BMDS 3.2 software produced estimates of BMDL values appreciably higher than the PROAST values (in some cases, by two orders of magnitude). The two packages have different criteria for deciding if model fits are acceptable for use and there were disagreements with this data set.

24. It was added that modelling software packages such as PROAST and BMDS make assumptions about the data, which in some cases differ. These assumptions can affect the results of the modelling. The mathematical models fit dose-response curves to the data but the parameters that are estimated have only a limited biological interpretation. Models may differ, for instance, on how they describe responses at high doses. In some cases, effects at high doses may not be relevant to the interpretation of effects at low doses. Re-analysis - excluding the top dose in this study - reduces the BMDL values appreciably.

25. Consequently, it was explained, there can be appreciable uncertainty around the value of the BMDL used to estimate the TDI as a result of the choice of software and underlying assumptions. It was also pointed out that there are now a number of additional BMD software packages available. Methods such as Bayesian Model Averaging, recommended by the World Health Organisation (WHO) which differs from the model averaging used by EFSA, may add to the diversity of values that are obtained.

26. Members asked whether, when the presentation was put together, any consideration had been given to the uncertainty surrounding the EFSA’s flow cytometry data. It was explained that this had not been examined, only the mean values included in EFSA’s report were available. It was noted that the raw data had been made available to EFSA, but it was not included in the publicly available material.

27. Members highlighted several additional sources of uncertainty in EFSA’s modelling approach. These included the exposure, the manual gating in flow cytometry, the small percentages used and the dose metric; in one of the main studies that EFSA had used, BPA was administered to mice in drinking water, with a mark on the side of the bottle used to determine daily consumption. In this same study, the researchers only measured the baseline levels of BPA to ensure it was below analytical levels in the tap water. Furthermore, it was noted that there were no data to confirm the dosing in the water bottles, how this might change over time, or whether there might be BPA exposure from other sources such as

food.

28. One Member also identified uncertainties with respect to the EFSA's flow cytometry analysis and the setting of the 20 % CES – specifically with the way the 20 % CES had been used when taking mouse spleen cells gated on CD4 and IL-17 to adult human serum samples, gated on CD161 (a different marker). It was noted that trying to set a 20 % CES based on this (and to extrapolate across to changes in developmental stages) was problematic.

29. Other Members expressed the view that the use of the 20 % CES was not necessarily unreasonable, since the BMD guidance produced by most authorities is that this may be appropriate - provided it is justified by the dataset and does not involve extrapolating too far beyond the lowest observed response.

30. Members noted that the human equivalent dose factor (HEDF) used by EFSA (0.00155) had changed from the 2015 version and took account of three human studies. In these studies, BPA was administered either in hard gelatine capsules, in cookies (100 µg/kg) or in soup (30 µg/kg) in order to evaluate buccal absorption. It has been recognised in the scientific literature that very little difference in BPA exposure occurred between these studies after taking into account the administered BPA dose, which Members commented gives little basis for concluding that there is buccal BPA absorption.

31. The data EFSA considered was based on a study in ewes, where BPA was administered via feed or via a nose tube. From this, EFSA concluded that there was a difference between the two methods of exposure in terms of BPA absorption, which they used to suggest that in human studies there was also likely to be a difference in absorption via the mouth. Since substances absorbed buccally pass directly into the systemic circulation without first-pass metabolism, Members concluded that this was likely to be why EFSA had added up all of the metabolites. However, the Committee considered that this was very conservative as there will be at least some first pass metabolism of BPA following oral exposure.

32. It was recognised that EFSA had apparently used the sheep data to help interpret the human data but as Members noted, there was much debate in the literature over this approach.

33. It was considered that dietary BPA exposure is unlikely to lead to disproportionate buccal absorption, due to the relatively small buccal surface area and the duration for which the substance is in contact with the buccal

mucosa compared with the intestinal mucosa. It was also noted that buccal exposure was likely to be associated with a late peak in absorption, which had not been observed. Members considered this to represent an additional source of uncertainty in EFSA's BMD modelling analysis.

34. Members acknowledged another apparent inconsistency in the human studies looking at buccal BPA absorption, also recognised by EFSA, which is that absorption from the cookies should theoretically have been higher than from soup, due to mastication. However, this does not appear to have been the case when the administered dose is considered.

35. Overall, Members had reservations about the endpoint and choice of studies used by EFSA to establish the new HBGV for BPA of 0.04 ng/kg bw. Members also had reservations over the BMD analysis, including the way EFSA had presented it and the uncertainty surrounding the BMDL identified.

36. No views were expressed with respect to the methods and outcomes of the uncertainty analysis that EFSA had undertaken.

37. It was asked whether a 20 % increase in Th17 cells was truly adverse. It was agreed to return to this question, and also to return to the data that EFSA had used to derive the 20 % CES value and the complexities surrounding this in the discussion on immunotoxicity.

Item 4: Immunotoxicity (TOX/2022/14)

38. Human and laboratory animal studies indicated that BPA had adverse immunological effects, but these were not taken forward by EFSA in 2015 due to shortcomings in the available data. A subsequent evaluation of two additional studies in 2016 did not changes EFSA's initial view that the data were not sufficiently robust for a risk characterisation. The current evaluation is in line with the earlier indications of potential effects on the immune system, but according to EFSA, there was now more definitive evidence with respect to adverse outcomes on the immune system, notably effects on cellular immunity, and parameters indicating allergic lung inflammation. While the mechanisms for the effect of BPA on the immune system are not clear, the studies shed some light on the factors involved.

39. The immune system parameters investigated mainly comprised intermediate endpoints (e.g. interleukins, mast cell mediators, specific antibodies related to allergy), and indications for inflammation were noted; disease

endpoints were investigated in only a small number of studies. EFSA therefore considered these studies to indicate an effect but did not judge the studies to be of high quality. An inflammatory effect was also seen in the epididymis, which may be mediated by similar mechanisms. While an effect on innate immunity was considered ALAN by EFSA, the increased number of antigen-resenting (dendritic) cells observed underscored the effect of BPA on homeostasis of the immune system.

40. Overall, EFSA considered BPA to have an adverse effect on the immune system, and that exposure may result most likely in inflammatory reactions, depending on the dose. Whereas the developing immune system is generally considered more vulnerable, effects were noted following exposure during development and during adulthood. Hence, EFSA concluded that BPA affected the immune system throughout different life-stages and using a WoE approach, considered BPA-induced effects on Th17 cells, neutrophils in epididymis, eosinophils in bronchoalveolar lavage “likely” and effects on serum-OVA-specific IgE “very likely”. Therefore, these endpoints underwent BMD analysis and a TDI of 0.04 ng/kg bw was established, based on the increase of Th17 cells as the critical effect.

41. The COT noted that one of the difficulties was the time frame of the literature search. This is a general issue that scientific opinions face but was highlighted here by the availability of follow-up studies published after 2018 showing different results to the critical effect reported in the study used in the EFSA assessment.

42. Discussing the animal data, Members had general reservations about using Th17 cells as an endpoint. An effect on Th17 cells was considered to be an intermediate effect rather than an adverse outcome of immunotoxicity and there was reasonable evidence demonstrating an increase in Th17 cells was a natural response of the immune system, e.g. when fighting infections. Hence, it was not clear whether an increase in Th17 cells is a pathological effect in its own right. Members acknowledged the evidence associated with BPA for a change in Th17 cell numbers in mice but considered that there was a significant data gap which did not allow extrapolation to adverse effects in humans. This was further supported by the observation that the change in Th17 cells and its associated effects was not reflected in the other clusters investigated by EFSA, other animal studies, or in the epidemiological data.

43. It was noted that while often described or assumed to be a homogeneous cell population, Th17 cells were quite diverse, especially in species

other than the mouse, and Th17 cells in the mouse do not mirror the effects of Th17 cells in humans. A study published after the cut-off point for EFSA's literature review indicated as much, and used the same concentrations of BPA as in the critical effect study. Other studies seem to confirm that variation in Th17 cells observed in humans are more likely associated with autoimmune and intestinal inflammation than (severe) asthma.

44. Members questioned the toxicological relevance of the 20% change in Th17 cell levels in general, but also given that other studies indicated lower ranges in Th17 cell levels. This could be due to differences in methodology, and Members noted issues with the methodology used in the critical effect study used by EFSA, for example, the conduct of the flow cytometry, a limited data set, and the data were based on percentages and not actual numbers.

45. In early life-stages, while the immune system is still developing, changes in immune system parameters are fairly common. Hence, Members questioned whether an effect such as a change in Th17 cells would result in an adverse outcome later in life. Studies from 2012 showed a similar effect in early life stages, however the effect was not translated/visible throughout the life stages into adulthood.

46. Members agreed that although BPA appears to cause a change in the number of Th17 cells, they were uncertain as to whether it was as strong an effect as EFSA had concluded, especially given the effects reported in the mouse study were not mirrored in the other clusters on immunotoxicity. Overall, Members would have liked to see a wider consideration of the database. Immune response is not straightforward but consists of a number of feedback loops; there are numerous models available which EFSA could have used to further consider other areas, such as autoimmune diseases that are exacerbated by Th17 cells.

47. Based on epidemiological data, EFSA considered an effect of BPA on the immune system to be "ALAN". The COT noted that while there was some evidence, overall it was not conclusive and did not indicate a need to further explore the biological effects experimentally. Assigning the epidemiological effects to be "ALAN" challenged the strength of the conclusion and it was not entirely clear from EFSA's assessment, given some of the other factors that might have caused the association in the epidemiological studies, why EFSA chose to then single out the mouse study on Th17 cells as their critical endpoint.

48. Members questioned the reasoning for the increase in Th17 cells to be selected as the critical effect for BMD modelling. The COT considered that it was

inappropriate to use the quantitative estimate in cell change in this mouse study to extrapolate to human effects, and raised concerns as to whether the selected study was robust enough to derive a HBGV.

Item 5: Reproductive and developmental toxicity (TOX/2022/15)

49. The CEP panel reviewed the available human and animal data on reproductive and developmental toxicity. Findings from the human studies were judged to be “Not Likely” or “ALAN”.

50. However, a number of endpoints from the animal studies were considered “Likely” and taken forward for BMD analysis. Most notably, for the female reproductive toxicity HOC this included changes in follicle ratios observed in the Tier 2 mouse study by Hu et al., (2018). The EFSA panel had noted that this would have provided the second most sensitive endpoint on which to base the reference point. However, the same effect was not seen in a mouse study by Moore-Abriz et al (2015) using a single but comparable dose.

51. Members considered the Secretariat’s report to be an accurate summary of the EFSA Opinion on BPA. Members noted the range of endpoints assessed in the extensive evaluation but had some reservations. The Committee agreed that the human data did not indicate that BPA had “likely” effects on the endpoints assessed. However, Members considered that discussion of the animal models was not balanced between the rodent and sheep studies, given sheep ovary is a better comparator for human ovarian activity and cycle than rodent ovary; while it was helpful to have the information on rodents it was limited. Effects on the endpoints were correlated but Members did not consider a causal effect had been demonstrated. Members concluded that there was a range of different results; some studies showed impacts on sperm, follicles, and possible implantation, but there was no outcome that showed an effect on overall fertility.

52. The Committee noted that the hormones evaluated had not been affected by BPA. There was a lot of information available, particularly for thyroid hormone levels, but there was nothing to indicate a causal effect as the results of the evaluated studies were not interconnected.

53. It was noted that there was much emphasis on the Hu et al 2016 paper, particularly around the follicular changes. However, it was very difficult to interpretate the data and there was lack of understanding of the mechanism

behind the follicular changes. It was suggested that data on follicle numbers instead of ratios may have helped to elucidate the mechanism. The mechanism was unclear and the measurements of related hormones showed little effect.

54. There was insufficient information on the experimental design of some studies, for example, at what stage of the oestrous cycle were the ovaries collected in the Hu et al (2016) study and there was no real evidence of hormonal changes that would support the results. Members concluded that too much emphasis was given to a very small number of papers and many questions can be asked regarding the results of these studies.

55. Members pointed out that some of the information was very difficult to assess as historical data were not presented in the studies reviewed by EFSA.

56. Members agreed that some studies of similar quality used comparable doses, for example the Hu et al (2016) paper and Moore-Ambriz et al (2015) study, but showed different effects; it was not clear whether these discrepancies had been fully taken into account and they had not been explained. The EFSA strategy was that once an effect was identified, the most sensitive study was selected and used for dose-response assessment. However, it appeared that this was sometimes done regardless of the reliability of the study concerned.

57. Members agreed there was lack of clarity on the final conclusions and that the Opinion could benefit from a summary report to explain more clearly and at high level the conclusions on the key endpoints bringing all the strands of evidence together.

Item 6: Neurotoxicity and Developmental Neurotoxicity (TOX/2022/16)

58. In the 2015 EFSA opinion, a likelihood level of “ALAN” was assigned to neurological, neurodevelopmental and neuroendocrine effects of BPA in a WoE approach.

59. However, newly available literature indicated that the central nervous system was a target for BPA toxicity. Within the HOC “Neurotoxicity and developmental neurotoxicity”, the evaluation of the human data considered endpoints from the cluster neurodevelopment. In the animal studies, three clusters of endpoints were identified: neuromorphology, nervous system functionality and behaviour.

60. Based on the human data, it was concluded that the evidence for an association between BPA exposure and impaired neurodevelopment was “Not Likely” and based on the animal data, all three neurotoxicity clusters showed effects that were judged as Likely.

61. It was noted that for the human data there was only one cluster covering a large number of endpoints, approximately 16 from 14 longitudinal studies. Members expressed concern that this could replicate endpoints, for example, there were 5 separate behaviour endpoints. The Committee agreed that there was no overall effect of BPA exposure on these endpoints and agreed with the WoE based on the human data.

62. The Committee noted that the doses used in the animal studies associated with adverse neurological effects were much higher than those where immunotoxicity was reported.

63. Members agreed that the grouping of endpoints in the animal studies was better than for the human studies and the weight of evidence assessment was more convincing than for the human data. However, they expressed concern over how the data had been integrated. Based on the conclusion that the human data had shown BPA had no effect, whereas animal data did show an effect, the EFSA panel’s overall conclusion was that BPA was likely to have an effect but it was unclear how this conclusion had been arrived at, based on integration of the human and animal data.

64. Overall, the Committee were satisfied with how EFSA had analysed the data, but were not convinced by the final integration and conclusions.

Item 7: Genotoxicity (TOX/2022/12)

65. The summary paper produced by the Secretariat was circulated to COM Members, some of whom were also present in the meeting.

66. The 2015 EFSA opinion on BPA had concluded that BPA was not mutagenic (in bacteria or mammalian cells), or clastogenic (micronuclei and chromosomal aberrations). It was considered that the potential of BPA to produce aneuploidy *in vitro* was not expressed *in vivo*. The positive findings in the post labelling assays *in vitro* and *in vivo* were judged unlikely to be of concern, given the lack of mutagenicity and clastogenicity of BPA *in vitro* and *in vivo*.

67. In 2015, 15 papers were discussed and assessed. In the newly found literature (up until July 2021) another 80 studies were found of varying quality. Members considered that EFSA had assessed the studies well and deficient studies were clearly identified.

68. The Committee noted that there were some unidentified adducts (spots) in a P-32 labelling study, but other studies, not discussed in the Opinion, had identified the nature of the BPA adducts.

69. Members considered that the studies appeared to have been integrated using an incremental approach rather than looking at the totality of the data but that this did not affect the final conclusion.

70. The Committee concurred with the EFSA evaluation that BPA was not directly genotoxic and agreed that any observed effects were most likely related to the production of reactive oxygen species rather than direct genotoxicity.

Item 8: Toxicokinetics and other endpoints – approach to epidemiology, metabolic effects, cardiotoxicity, carcinogenicity.

71. Members had no comments on other sections of the evaluation.

Item 9: Summary & discussion

72. The Committee considered the implications for future chemical risk assessments, given that the HBGV was determined using an extremely sensitive intermediate endpoint and a hazard characterisation approach. Using the BMDL20 for immunotoxicity as an endpoint would suggest that whole population would be at risk, as all food consumption would lead to BPA exposures orders of magnitude above the recommended level and hence would be at risk of adverse effects. However, this did not seem to be supported by the available human data.

73. BPA is one of the most intensively investigated chemicals in the world, and it is not clear how a positive result could be addressed by further research. The approach adopted by EFSA appeared to consider the results of any study without obvious flaws as equally informative. This ignores the importance of replication in science. Expert elicitation with the possibility of group think cannot overcome this. Despite the extensive guideline studies supported by the US authorities under CLARITY, individual publications still raise questions, and hence

no obvious resolution is apparent. This has clear implications for the risk assessment of chemicals in general.

74. It was suggested that given the profound implications reached in this draft opinion, a wider group of toxicologists should therefore meet to discuss interpretation of the critical findings in a situation analogous to a pathology peer review.

75. The Committee considered that the approach taken when using intermediate endpoints was essentially the same as when using functional/apical endpoints, but if intermediate endpoints are to be used in the future, then current approaches may not be appropriate.

76. The Committee suggested that an up to date exposure assessment would have been useful, however, it was noted the that mandate from the European Commission specifically did not request another exposure assessment to be performed for this re-evaluation paper so the 2015 estimates had been used. The Committee considered that without an updated assessment, it was not possible to fully understand the vulnerability of specific groups or to determine what the implications would be for risk management.

77. It was noted that the revised HBGV also had profound implications for REACH, as BPA alternatives would need to be sought that may be less well characterised.

Item 10: Next steps

78. The deadline for the Secretariat to provide final comments to EFSA is the 22nd of February, 2022. Therefore, Members were requested to send any additional comments to the Secretariat by 17th of February, and asked to include section numbers and line numbers where possible.

Date of next meeting

79. The next meeting of the Committee will be at 10:00 on the 29th of March 2022 via Skype and Teams.