FOOD INGREDIENTS AND PACKAGING UNIT

Scientific Panel on Food Contact Materials, Enzymes and Processing Aids (CEP)

MINUTES OF THE 31st PLENARY MEETING

Held on 25-27 October 2022, by Teleconference

Meeting open for Observers

(Open session: 25-26 October 2022, from 14:00 to 16:00 the last day)

(Agreed on 25/11/2022)[1]

Participants

- Panel Members:

  José Manuel Barat Baviera, Claudia Bolognesi, Andrew Chesson, Pier Sandro Cocconcelli, Riccardo Crebelli, David Michael Gott, Konrad Grob, Claude Lambré (Chair), Evgenia Lampi, Marcel Mengelers, Alicja Mortensen, Gilles Rivière, Inger-Lise Steffensen, Henk Van Loveren, Laurence Vernis and Holger Zorn

  European Commission: Catherine Evrevin, Jonathan Briggs

- Hearing experts: Andrew Hart and Laurence Castle
- ECHA: Evelin Fabjan, Francesca Pellizzato, Vessela Vitcheva
- EFSA: Edward Bray, Cinzia Percivaldi, Munoz Gallardo Irene Pilar

  Food Ingredients and Packaging (FIP) Unit: Jaime Aguilera, Zainab Al Harraq, Magdalena Andryszkiewicz, Kyriaki Apergi, Matilde Benedettini, Laura Cabo Sanmartin, Daniele Cavanna, Daniele Comandella, Cristina Croera, Valeriu Curtui, Chantra Eskes, Natalia Kovalkovicova, Alexandros Lioupis, Yi Liu, Simone Lunardi, Remigio Marano, Silvia Peluso, Francesco Pesce, Sandra Rainieri, Elisa Savini, Vasiliki Sfika, Emmanouil Tsochatzis, Katharina Volk.

- Others:
- Observers: Attending via web-streaming:

  Acar Hasan Salih, Adler Katharina (Bundesministerium für Ernährung und Landwirtschaft), Almeida Costa Sofia (Institute of Public Health of University of Porto), Arnardottir Hronn (ORF Genetics), Aungst Jason (US FDA), Bang-Lauritsen Louise (Danish Medicines Agency), Bedford Charlotte (Crown Packaging), Bird Jasmin (Plastics Europe), Boix Estefania (Chemours), Brendler-Schwaab Susanne (Federal Institute for Drugs and Medical Devices, BfArM), Camacho Luisa (US FDA/NCTR), Cariou Ronan (Oniris), Cerqueira Renata (Cargill), Cogalniceanu Elena (EAS

1 Adopted by written procedure

Strategies), Costa Sofia Almeida (Instituto de Saúde Pública da Universidade do Porto), Delfosse Thomas (ExxonMobil), Delgado Juan Manuel (Spanish Food Safety and Nutrition Agency), Dominguez Maria (Finnish Food Authority), Domínguez Anayancy (Cafés de Especialidad de Chiapas, CAFESCA), Figueiras Rita (EFSA), Flores Rosalía Amgen (Consulting SL), Garcia Monica (GRUPO VALL COMPANYS), Gestermann Sven (Covestro), Giernoth Judith (Covestro Deutschland AG), Giusto Elisa (Law firm), Goodman Julie (Gradient), Gruszecka-Kosowska Agnieszka (AGH University of Science and Technology), Guazzotti Valeria (Fraunhofer-Institute), Haixia Sui (China national center for food safety risk assessment), Hamelton Anne-Marie (Metal Packaging Europe), Hannon Joe (Food Safety Authority of Ireland), Hessel Ellen (RIVM), Heyvaert Els (FPS Health, Food Chain Safety and Environment Belgium), Hoesl Tanja Ramona (Cflex), Hooper Jeremy (Effem), Hoxha Gerard (Albanian National Food Authority), Huang James (The Coca-Cola Company), Jensen Victoria (Danish Medicines Agency), Katerelos Nikolaos (Hellenic Food Authority, EFET), Komoda Takashi (Polycarbonate Resin Manufacturers Group), Lacourt Charlene (Danone), Lawson Jane (Croda International PLC), Lea Linda (AkzoNobel), Lomastro Francesca (EQS), Lorenz Claudia (BfR), Lorenz Kristin (Bundesinstitut für Risikobewertung, German Federal Institute for Risk Assessment), Marras Marco (Kraft Heinz Company), Martin Ana (Cefic), Masset Dominique (ANSM), Mastrantonio Michela (Cefic - European Plasticisers), Monneraye Véronique (MASSILLY HOLDING), Nehring Ulrich (NEHRING Consultants GmbH), Nikodinoska Ivana, Nilsson Marie-Louise (Swedish Food Agency), O'Hagan Sue (PepsiCo International), Oldring Peter (Sherwin williams), Otter Rainer (BASF SE), Pinter Elisabeth (OFI - Austrian Research Institute for Chemistry and Technology), Ponzano Stefano (EMA), Prieto Arranz Miguel Angel (Cefic), Puzniak Jakub (Metal Packaging Europe, MPE), Ranjan Ravi (EcoBlue Limited), Regaudie Emmanuel (Ball Packaging EMEA), Schmidt Marianne (Danish Medicinal Agency), Siewert Katherina (German Federal Institute for Risk Assessment), Soncin Silvia (Thegbfoods), Sondenheimer Kevin (Covestro Deutschland AG), Soviero Giovanna, Sullivan Kathryn (PPG INDUSTRIAL COATINGS), Sütçü Kürşat (The Ministry of Agriculture and Forestry), Svensson Kettil (Swedish Food Agency), Tarnow Patrick (German Federal Institute for Risk Assesssment, BfR), Teste Bruno (ANSES), Toptancı İsra (Engineer), Ukkonen Anne (Biosafe Ltd), Van Aerts Leon (Medicines Evaluation Board), Van de Ven Bianca (RIVM), Van Malderen Karen (European Medicines Agency Network), Vasconcelo Ana (AIMPLAS), Vey Domitille (UFC Que Choisir), Weel Koen (The Coca-Cola Company), Whitaker Richard (Crown Holdiings), Zappacosta Saverio (EFSA)

OPEN SESSION

1. Welcome and apologies for absence

The Chair welcomed the participants to the meeting. Apologies were received from: Christina Tlustos for the entire Plenary, Konrad Grob on 25th October.

2. Guidelines for observers attending the open session

The CEP Panel coordinators introduced the rules for Observers to be followed during and after the open Plenary meeting as well as some tips for the smooth running of the virtual meeting. Observers were given the possibility to send questions when submitting their registration and these questions

would be answered in a dedicated session at the meeting. Observers were also informed that the Chair would grant opportunity for additional questions at the end of each discussion topic.

3. Adoption of the Agenda

The agenda was adopted without changes.

4. Declarations of Interest of Scientific Panel members

In accordance with EFSA's Policy on Independence[2] and the Decision of the Executive Director on Competing Interest Management[3], EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

5. Agreement of the minutes of the 30th Plenary meeting held on 13-15 September 2022

The minutes of the 30th Plenary meeting held on 13-15 September 2022 were agreed by written procedure on 29 September 2022[4].

6. Report on written procedures since 30th Plenary meeting

No scientific outputs were adopted by written procedure since the last plenary meeting.

8. Feedback from the Scientific Committee/Panel(s), EFSA, European Commission

8.1 CEP Panel Working Groups /Task Forces

8.1.1. CEP WG on Food Contact Materials

No additional issues were brought to the attention of the CEP Panel further to what is already recorded in the **minutes of the WG**.

8.1.2. CEP WG on Recycling Plastic

No additional issues were brought to the attention of the CEP Panel further to what is already recorded in the **minutes of the WG**.

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[3] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf
[4] https://www.efsa.europa.eu/sites/default/files/2022-07/070722-m.pdf

8.1.3. CEP WG on Enzymes

No additional issues were brought to the attention of the CEP Panel further to what is already recorded in the **minutes of the WG**.

8.1.4. CEP WG on BPA re-evaluation

No additional issues were brought to the attention of the CEP Panel further to what is already recorded in the **minutes of the WG**.

8.1.5. CEP WG on preparation for re-evaluation of phthalates, structurally similar substances and replacement substances

No additional issues were brought to the attention of the CEP Panel further to what is already recorded in the **minutes of the WG**.

7. Scientific outputs submitted for discussion and possible adoption

7.1. Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs (EFSA-2016-00635)

Parts of the draft opinion on the re-evaluation of the risks to public health related to the presence of BPA in foodstuffs were presented to the members of the CEP Panel. The presented parts of the draft opinion were endorsed by the Panel subject to incorporation of changes as suggested during the meeting. The remaining parts of the draft opinion will be presented for discussion and possible final adoption at the December CEP Panel meeting.

Questions from and answers to Observers (in application of the guidelines for Observers)

The Panel coordinators reported the question(s) received from Observers in advance to the plenary as follows:

Q1a. In the report on the public consultation on the BPA hazard assessment protocol EFSA clearly states that due to time and resources a cut-off date (01/01/2013 – onwards) was determined. This is in clear contradiction to EFSA's guidance on Weight of Evidence. Here, it is stated that "In principle, all evidence identified as potentially relevant in step 1 should be taken into account, but limitations on time and resources may require the assessment to focus primarily on the most relevant and/or most reliable evidence." This means the only criteria for limitation are relevance and reliability, not the evaluation time period. Please comment in detail on this inconsistency.

Q1b. Please explain in detail how you considered reliable and relevant evidence from before 2013 in the Weight of Evidence assessment for the evaluated HOCs?

A1a-b. Due to the similarity of the two questions, they were answered together. It was clarified that according to the Terms of Reference (ToR) of the mandate, the European Commission (EC) asked EFSA to:

"(…) -re-evaluate the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. In particular, the re-evaluation should take into consideration new data available from the results of the US NTP/ FDA study due in 2017 as well as all other new available information not previously evaluated by EFSA, and which fulfil the criteria laid down in an established protocol. This re-evaluation should seek to clarify the remaining uncertainties concerning the toxicological endpoints of BPA, especially those concerning the mammary gland, reproductive, metabolic, neurobehavioral and immune systems and to establish a full tolerable daily intake (TDI) on the basis of the new information available."

According to the ToR, the TDI was set based on the available data starting from 2013 up to October 2018, when the CLARITY NTP chronic study became available.

It was highlighted that performing a safety assessment using a systematic approach implies necessarily a predefined cut-off date for the literature to be considered and consequently the production of a data-gap in the evaluation.

It was also pointed out that, in spite of this, additional literature published after 2018 was taken into account and referred to, where appropriate, in the response to the comments received during the public consultation (PC) that will be published in a specific Annex of the opinion. Furthermore, specific literature published after 2018 was referred to in the revised opinion for improving the description of the clusters and endpoints grouping and mechanistic issues.

It was also remarked that already in the draft opinion submitted to the PC, for each health outcome category (HOC), the conclusions on the Weight of Evidence (WoE) from the 2015 EFSA opinion on BPA (EFSA CEF Panel, 2015) (evaluating the literature published before 2013) and from the 2016 EFSA Statement on Immunotoxicity (EFSA CEF Panel, 2016) were considered in the conclusive Sections of the hazard identification of the opinion. Additionally, more details on how such conclusions were considered are provided in the revised opinion.

Q2. Neurotoxicity/Reproductive toxicity: Please explain how you integrated the effects (shown in table 20) for these 2 HOCs into the overall evidence with respect to former guideline studies (i.e. Stump et al., 2015; Ema et al., 2001 and Tyl et al., 2002; Tyl et al., 2008; Ema et al., 2001, respectively) and how you weighed this evidence.

A2. Regarding neurotoxicity, it was highlighted that in the 2015 EFSA opinion, neurological, neurodevelopmental and neuroendocrine effects of BPA at low doses were judged in a WoE approach to be ALAN, considering inconsistent results for anxiety-like behaviour, learning and memory, social behaviour and sensorimotor function. The results of the current assessment extended the previous database, and animal studies indicating possible effects of BPA during development and in adulthood mainly on anxiety and depression-related behaviours, learning and memory, as well as on dendritic spine density and AChE activity in the hippocampus and the prefrontal cortex.

Regarding reprotoxicity, it was noted that in the 2015 EFSA opinion, the CEF Panel concluded that although the evidence was not sufficient to infer a causal link between BPA exposure and reproductive and developmental effects in humans, BPA was re-confirmed to be a reproductive toxicant in experimental animal studies at high doses. The CEF Panel then assigned a likelihood level of ALAN to reproductive and developmental effects of BPA in animals at low doses.

In the current evaluation, it was pointed out that new evidence emerged, including evidence on new endpoints and on endpoints not previously assessed at all doses (EFSA CEP Panel, 2015), which strengthens the evidence for adverse effects on reproduction observed at low doses.

Q3. How can you conclude that effects reported in a low-quality study are supported by the weight of evidence for immune effects in general for the proposed TDI without consistent support for that specific MoA? Same for other endpoints.

A3. Regarding the Luo et al. (2016) study, the CEP Panel did not consider it to be a low-quality study. On the contrary, following a thorough systematic appraisal conducted by independent assessors, the study was considered of high quality (Tier 1). The effects observed in the Luo et al. (2016) study were reproduced in a separate study by the same authors. In addition, studies from other groups of researchers also reported similar immunotoxic effects from BPA.

Regarding the mechanism of action, although knowledge on a clear mechanism is helpful to substantiate effects, it is not necessary for using the available data and come to a conclusion. As such, the opinion is not mechanism driven. Although the precise mechanism of BPA effects on the immune system is not fully understood, the CEP Panel has further elaborated in the revised opinion on the data shedding light on this mechanism.

Q4. Please answer in detail the questions below regarding Th17 cells:

- Is there any evidence that BPA exposure would lead to increased Th17 cells in any other species than the mouse, importantly in humans?
- What is the toxicological and biological relevance of increased Th17 cell levels in the spleen for mice and importantly for humans?
- Is there compelling evidence that small changes in the percentage of Th17 cells in the spleen of mice would translate into lung inflammation or enhanced inflammatory reactions in humans?
- Does human evidence suggest that BPA exposure is associated with allergy or asthma and most importantly that Th17 cells play a role in this process?

A4. Additional considerations on the previously reported human studies regarding a possible association between post-natal BPA exposure and asthma were included in the revised opinion. However, no data on the measurement of Th17 cells following BPA exposure in human are currently available.

The effect observed on Th17 cell percentage was not considered small by the CEP Panel. Although it is true that the proportion of Th17 cells within the lymphocyte population is relatively small, i.e. less than 2%, this is apparently enough for them to play their physiological role. An almost doubling of the population, as assessed by the CEP Panel in the opinion, can therefore not be judged as minor. In addition, not only the Th17 cell percentage changed following BPA exposure in the study of Luo et al. (2016), but also their activity, as demonstrated by serum increase in IL-17 and IL-21. Finally, the relevance of Th17 cell changes, its adversity and relevance to humans, is further supported by other studies, including studies published after 2018 period as detailed in the Annex addressing the comments to the PC.

In the revised opinion, further mechanistic clarifications are given on the link between the reference point (Th17 cells) and immune mediated adverse conditions, as well as on the link between BPA and immune-mediated disorders. Furthermore, it was acknowledged that there is more variability in the human population than in animals and, taking also into account the plasticity of the immune system, it was decided to raise the benchmark response (BMR) used. Finally, it was highlighted that the conclusions are not based on one single study, but on a WoE assessment of a number of clusters of endpoints for a certain HOC (e.g., allergic lung inflammation, cellular immunity and inflammation). Furthermore, it was pointed out that besides the immunotoxicity study, also studies in other HOCs, i.e. in reproductive and developmental toxicity (ratio of primordial and total follicles, sperm motility) and metabolic effects (uric acid), were noted at doses that are within 7 fold compared to the effects

observed on Th17 cells. The effect on Th17 cells was the most sensitive endpoint observed, even if the differences in doses with the other effects were relatively small.

Q5. We would like to reiterate that there is no valid association between Th17 cells and IgE production. The toxicological importance of the increased numbers of Th17 cells in mice, with no information on any functional consequences thereof, is still questioned. We are asking additional clarification of the scientific grounds for the EFSA position related to this aspect.

A5. It is acknowledged that some parts of the text of the draft opinion submitted for public consultation could have given the impression that there was a direct link of Th17 cells with IgE. This has been amended where appropriate in the revised opinion and it was clarified that Th17 cells and their interleukins are involved in inflammatory responses and autoimmunity. Antibodies targeting Th17 cells are therapeutically used in several autoimmune conditions. In asthma, in particular neutrophil asthma, there is also a clear role for Th17 cells. It has also been shown that in the course of neutrophil asthma, there is increased specific IgE production. In the studies evaluated, there is evidence of increased proportions of Th17 cells, as well as of increased specific IgE production.

Q6a. I want to know the health based guidance value of BPA in the final report and the endpoint it is based?

Q6b. What is the current status of the HBGV?

A6a-b. Due to the similarity of the two questions, they were answered together. It was acknowledged that for the endpoint Th17 cells, there is more variability in the human population than in the animals and taking also into account the plasticity of the immune system, it was decided to raise the BMR. Based on this and on the established uncertainty factors, the established TDI is still in the range of ng BPA/kg bw per day.

Q7. How can EFSA justify the proposed TDI considering its extremely large safety margin when comparing the estimated BPA plasma concentration to the exposure levels where the adverse effects are seen in vivo and LOEC in vitro of BPA? At which level of exposure (external dose or plasma concentration) does the EFSA consider an actual risk would be anticipated? We would suggest the low level of the TDI is reconsidered in the light of its missing biological plausibility and should not be set merely on methodological and mathematical grounds.

A7. It was clarified that any TDI should ensure that life-time exposure up to the TDI value does not lead to appreciable adverse health effects in the general population. Exceeding a TDI does not automatically lead to an adverse health effect, and whether or not such effects occur, depends on several factors, such as the magnitude and the time of the exceedance. It was also noted that, as for any TDI, it cannot be predicted how severe those effects will be.

Q8. Why didn't EFSA consider whether a 100,000x decrease of the TDI made sense in terms of real-world risks?

A8. Calculation of the TDI was done following the recommendations of the methodologies described in various EFSA guidance documents (EFSA Scientific Committee, 2017a[5], 2017b[6], 2018a[7], 2018b[8]). It was highlighted that exposure to the TDI is not supposed to produce any adverse effect as, by definition, it is an exposure to an amount of substance that can be taken in daily over a lifetime without producing appreciable health effect.

Q9. Is it possible that reported low dose effects are not adverse, but part of homeostasis, and that is why there are no apical low-dose effects in robust animal studies?

A9. It was clarified that the assessment presented in this opinion identified an intermediate endpoint, the increase in Th17 cell percentage, as the reference point for establishing a TDI for BPA. For an intermediate endpoint to be appropriately used in risk assessment, the CEP Panel noted that it needs to have a clear causal relationship with an adverse outcome. The information reviewed in this opinion, as well as the still increasing information, clearly indicates that an increment in Th17 cell percentage, and their cytokine IL-17, is linked to inflammation occurring e.g. in autoimmune diseases and certain asthmatic conditions. Hence, this intermediate endpoint adheres to the EFSA definition of adversity. However, as the increase in Th17 cells is an upstream event to a potential adverse outcome, adversity needs not necessarily be evident right away or occur at the same dose.

In general terms, guidance on how to use intermediate endpoints in risk assessments is lacking. It was remarked that the outcome of this assessment is based on the data available and the current knowledge, applying the currently existing guidance.

Q10. Is 1 study with an effect at a low, but not high, dose sufficient to support an NMDR, or should you see similar effects consistently across studies and species with a similar pattern of effect to be accepted as plausible in humans?

A10. It was clarified that the conclusions of the opinion are not based on one single study, but on a WoE assessment of a number of clusters of endpoints for a certain HOC (e.g., allergic lung inflammation, cellular immunity and inflammation). See also response to Q4. With regard to the NMDRs, EFSA published in 2021 an "Opinion on the impact of non-monotonic dose responses on EFSA's human health risk assessments" and the recommendations made in the opinion were taken into consideration when evaluating NMDR in the assessment.

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[5] EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Aerts M, Bodin L, Davis A, Edler L, Gundert-Remy U, Sand S, Slob W, Bottex B, Cortiñas Abrahantes J, Court Marques D, Kass G and Schlatter J, 2017a. Update: use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. doi:10.2903/j.efsa.2017.4658.

[6] EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter J, Silano V, Solecki R, Turck D, Benfenati E, Chaudhry Q, Craig P, Frampton G, Greiner M, Hart A, Hogstrand C, Lambre C, Luttik R, Makowski D, Siani A, Wahlstroem H, Aguilera J, Dorne J, Fernandez Dumont A, Hempen M, Valtuena Martínez S, Martino L, Smeraldi C, Terron A, Georgiadis N and Younes M, 2017b. Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. doi:10.2903/j.efsa.2017.4971.

[7] EFSA Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter J, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Martino L, Merten C, Mosbach-Schulz O and Hardy A, 2018a. Guidance on uncertainty analysis in scientific assessments. EFSA Journal 2018;16(1):e05123, 39 pp. doi:10.2903/j.efsa.2018.5123.

[8] EFSA Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Germini A, Martino L, Merten C, Mosbach-Schulz O, Smith A and Hard' A, 2018b. The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment. EFSA Journal 2018;16(1):e05122, 235 pp. doi:10.2903/j.efsa.2018.5122.

Q11. Taking the uncertainty regarding the biological plausibility and the issues regarding toxicokinetic properties of mice vs humans into account for establishing the HEDF and considering the shortcomings of the Luo et al. (2016) study, the appropriateness of the study to derive an overly conservative TDI using the BMD approach is questioned and further clarification is requested.

A11. It was clarified that the HED factors (HEDFs) that account for the toxicokinetic differences between a given animal species and humans have been derived in the 2015 EFSA opinion for mouse, rat and monkey. Already in the public consultation to the 2014 draft opinion, the derivation of the HEDF from the study of Doerge et al. (2011) was critically commented. The CEP Panel had therefore revised the calculation of the AUC, which resulted in a higher value compared to what was then used for the published opinion in 2015. After the publication of the 2015 opinion, no further comments were raised. The HEDFs were not reconsidered in the current re-assessment but used as published in 2015. However, the high uncertainty surrounding the HEDF for mouse was addressed in the section on the uncertainties stating that the uncertainty of the HEDF for mouse is high and providing additional explanation.

Q12. What the committee did with all the input in the PC on the HBGV?

A12. It was clarified that all comments received have been addressed within a dedicated Annex to the revised opinion (to be published together with the opinion), and that the opinion has been revised accordingly, where applicable.

Q13. Will the meeting minutes and presentation materials used in scientific meetings be made available later?

A13. It was clarified that the plenary meeting minutes will be published in due time. However, presentation material will not be made available to observers.

Q14. Is there any intention to evaluate preparation for reuse stations and practices, considering the fact that expected reuse targets to be established by the Packaging Waste legislation will trigger a shift to reuse with huge implications for the food contact and hygiene issues?

A14. It was highlighted that this question is outside the remit of the present assessment. If necessary, the question can be addressed to the European Commission by e-mail.

During the Plenary, the following questions were received from Observers and answered as follows:

Q15. Do the most conservative experts in this type of uncertainty exercise drive the BMDL downward? That implies you are always led by the most conservative ones.

A15. No, this is not the case. It was clarified that the outcome of the uncertainty analysis reflects the judgements of all the experts and is not determined solely by the most conservative experts. Furthermore, the final conclusion of the uncertainty analysis and the additional uncertainty factor were based on the averaged judgements of all 16 experts.

Q16. From the Uncertainty analysis, it seems that at least one expert for immunotoxicology did not come to the same conclusion as the other experts for immunotoxicology. Did you reflect this discrepancy in some way also in the hazard assessment and characterisation?

A16. It was clarified that all individual assessments were reported, discussed and taken into account in the revised opinion. The final judgements of every expert on each question are tabulated in an Annex and were all included in the final hazard assessment and characterisation reported in the Opinion. The final conclusion of the uncertainty analysis and the additional uncertainty factor were based on the averaged judgements of all 16 experts, giving equal weight to every expert. The wide range of opinion between experts regarding the assessment was highlighted in the text and shown graphically. Furthermore, the differences in judgement between experts was listed as an additional source of uncertainty and taken into account in the final assessment of overall uncertainty, which contributed to the definition of the need for an additional uncertainty factor when establishing the TDI.

Q17. You have described that there is no guidance to establish the extrapolation factor from an intermediate endpoint to an apical adverse outcome. A guidance for that will be developed but is expected earliest in 2025. What is your comment to the conclusion that in consequence the currently proposed value for the TDI can only be seen draft and is not suitable to base any regulatory measure on?

A17. It was highlighted that there are other examples where EFSA has established TDIs based on intermediate endpoints. Furthermore, any TDI might be revised in future based upon availability of new scientific evidence. That does not mean that a TDI identified based on all evidence available represents a draft TDI. The outcome of the current assessment of BPA is based on the data available and the current knowledge, applying the currently existing guidance, and its uncertainty has been characterised.

Q18. You mentioned in the uncertainty analysis that in the O'Brien study an effect on lung inflammation (apical endpoint) was only seen at the highest dose in males. You should clarify that the highest BPA dose led to a decrease in inflammatory score in mice and therefore, this study provides no evidence that BPA exposure would lead to lung inflammation in mice.

A18. The study by O'Brien et al. (2014) reports effects on the production of pro-inflammatory mediators and specific IgE in mice exposed prenatally to BPA. BPA exposure was not observed to worsen pulmonary inflammation (inflammatory score decreased only in males, only at highest dose) following allergen challenge, but it stimulated the markers of inflammation after challenge. However, since this parameter can be triggered by different stimuli, including physiological stimuli, and it is not considered very close to the apical endpoint of allergic lung inflammation, it was decided not to bring this endpoint forward for BMD analysis. This was taken into account in the uncertainty analysis. It was included among the considerations of the experts supporting high estimates for Question 2 for the cluster allergic lung inflammation (Question 2: If one or more endpoints in the WoE table for this cluster occurs in animals tested with BPA and is both relevant and adverse for humans, what is your prediction for the lowest BMD of those endpoints, expressed as HED?).

Q19. If no adverse outcome pathway has been identified for Th17, would it be appropriate to include a statement that it is possible this effect may be adaptive or part of homeostasis, rather than an upstream event to a potential unknown adverse outcome?

A19. The question was answered already in Q9. Furthermore, uncertainty related to the use of Th17 cells has been taken into consideration in the uncertainty analysis.

Q20. Is it not premature to use the approach using intermediate endpoints for establishing the TDI given the knowledge gap on how to use them? How are risk assessors supposed to address the knowledge gap in practice?

A20. It was pointed out that it is not premature to use this approach, because based on the data available, the current knowledge and applying the currently existing guidance, it was possible to establish a full TDI. The second question regards risk management that is out of the remit of EFSA.

Q21. In order to ensure that packaging materials for foodstuffs that contain, for example, lacquers with low levels of BPA are below the limit value, it is necessary to analyse them. Which analytical method can be used to detect the low limit value of BPA in packaging materials? Or can the new development be seen as a future general ban on BPA in packaging materials?

A21. Although it is correct that with conventional instrumentation, such low levels of LOQs could not be achieved, with new technologies, such as high capability LC-MS/MS analysis, with pre-concentration and applying controlled environmental conditions with regard to BPA presence, such a LOQ could be measured in simple matrices. Although it may take some time for analytical laboratories to adjust their methods and overcome possible issues regarding sample matrix and environmental contamination, this could in principle be achieved. When setting limits, the EC might take into account issues related to the detection limits.

Regarding the question on general ban, this is a risk management decision, which is outside the remit of the present assessment.

Q22. How is this decrease in TDI going to affect the specific migration limit of BPA? Will there be a direct correlation? How can you calculate this?

A22. It was clarified that this issue is outside the remit of the present assessment.

Q23. In light of the uncertainties regarding use of intermediary biomarkers in terms of adversity and the use of an extrapolation factor to account for the uncertainty (e.g. lower than 1), will the EFSA assessment of BPA and the low TDI be re-evaluated (and potentially be adjusted) when more experience is available?

A23. It was highlighted as this issue has been already addressed in earlier questions (e.g. Q20). The CEP Panel remarked that health-based guidance values are not everlasting.

Q24. Luo study: considered polycarbonate cage exposure was negligible. What about water and food?

A24. It was highlighted that potential background contamination (of e.g. BPA, phytoestrogens, others), is well known, and even under the most carefully controlled conditions it may occur. It should be noted that background exposure would apply to both treated and control animals. However, in the Luo et al. (2016) study, treatment effects were not only noted, but also showed a clear dose-response. Even if it is not known whether background exposure affected the Th17 cells, again controls were treated similarly as the test animals. The uncertainty of the dose at which the effect occurs was taken into consideration in the uncertainty analysis section of the revised opinion.

7.2. Phthalates task 2b: Protocol for the hazard assessment as part of the safety assessment of phthalates, structurally similar substances and replacement

substances potentially used as plasticisers in materials and articles intended to come into contact with food (EFSA-Q-2021-00593)

The draft protocol for the hazard assessment as part of the safety assessment of phthalates, structurally similar substances and replacement substances potentially used as plasticisers in materials and articles intended to come into contact with food was presented to the members of the CEP Panel together with the main points for discussion. The draft protocol was unanimously endorsed by the Panel subject to incorporation of changes as suggested during the meeting.

Questions from and answers to Observers (in application of the guidelines for Observers)

The Panel coordinators reported the question(s) received from Observers in advance to the plenary as follows:

Q25. With respect to hazard identification it is very important to include a definition of "adverse effect" – as this is the basis for defining a hazard. Will a definition of adverse effect be included in the revised EFSA hazard document (e.g. WHO definition)?

A25. The observer acknowledged that the question had already been addressed by explanations given during the discussion of the output, where it was indicated that indeed a reference to a definition of 'adverse effect' has been added to the protocol.

Q26. When reviewing the available data it is very important to conduct a robust weight of evidence evaluation of the data, in particular to consider the quality of the studies. Key criteria for assessing studies to determine hazard properties are included in the CLP regulation. Will reference to weight of evidence and the key criteria be included in the revised EFSA hazard document?

A26. The observer acknowledged that the question had already been addressed by explanations given during the discussion of the output: as regards the weight of evidence evaluation, the approach described in the protocol is based on the respective guidance from the EFSA Scientific Committee (2017), where relevance (including biological relevance), reliability and consistency are considered as the three basic steps of weight of evidence assessment. This was considered to also be compatible with the criteria described in the ECHA CLP guidance.

Q27. How does EFSA want to evaluate academic studies that used substances which are provided by dealers or even self-synthesized test substances that definitively are not comparable to chemicals that are produced in strictly controlled industrial processes?

The above-mentioned publications might lack data on purity and substance characterization.

A27. As explained during the discussion of the output, the approach for appraising the studies (and specifically the exposure characterisation) was changed in a way that rather than focus on purity alone, information on the composition (identification and quantification) will be considered when assessing the internal validity of a study. It could be envisioned that albeit not produced in strictly controlled industrial processes, data characterising the substance used in a study should be reported. If such information is not available, this will then be taken into account when assessing the level of internal validity of the study in question.

CLOSED SESSION

7.3. Recycling process rPET Aviv Shalam (Starlinger iV+ technology) (EFSA-Q-2021-00468)

The CEP Panel discussed all parts of the draft opinion. The Panel identified a missing detail that needed to be requested and provided by the applicant. Therefore, the draft opinion could not be adopted during the meeting.

7.4. Recycling process Duy Tan Plastic (Starlinger iV+ technology) (EFSA-Q-2021-00626)

The CEP Panel discussed all parts of the draft opinion. The Panel identified a missing detail that needed to be requested and provided by the applicant. Therefore, the draft opinion could not be adopted during the meeting.

7.5. Recycling process Alef Recycling (Starlinger iV+ technology) (EFSA-Q-2022-00191)

The CEP Panel discussed all parts of the draft opinion. The Panel identified a missing detail that needed to be requested and provided by the applicant. Therefore, the draft opinion could not be adopted during the meeting.

7.6. Recycling process EcoBlue (PET direct iV+ technology) (EFSA-Q-2021-00686)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

7.7. Recycling process Poly Recycling (VACUNITE technology) (EFSA-Q-2021-00301)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

7.8. Animal rennet and "Présure" from young *Bos primigenius* (cattle), young *Capra aegagrus hircus* (goat) and young *Ovis aries* (sheep) (EFSA-Q2022-00180)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

7.9. Use of the non-GM *Hamamotoa singularis* (YIT 10047) as a source of β-galactosidase (EFSA-Q-2016-00529)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

7.10. Polygalacturonase and beta-glucanase from the non-genetically modified *A. aculeatus* (strain NZYM-RE) (EFSA-Q-2014-00200/00201)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

7.11. Recycling process Ester Industries (recoSTAR PET FG technology) (EFSA-Q-2021-00396)

The CEP Panel discussed all parts of the draft opinion. The opinion was unanimously adopted, subject to the incorporation of changes as suggested during the meeting and editorial changes.

8. Feedback from the Scientific Committee/Panel(s), EFSA, European Commission

8.2 Scientific Committee/Panel(s) including their Working Groups

The Chair reported the main points discussed during the 110th Scientific Committee Plenary, held on 21st-22nd September 2022.

8.2. EFSA

None.

8.3. European Commission

None.

9. New mandates

9.1. New questions received since the 30th CEP Plenary

The following 6 new mandates have been received since the 30th CEP Plenary meeting.

Food Sector	EFSA-Q-Number	Subject	Reception date
ENZ	EFSA-Q-2022-00595	Leucyl aminopeptidase from Aspergillus oryzae (strain AE-MB)	28/09/2022
ENZ	EFSA-Q-2022-00600	Triacylglycerol lipase from Candida cylindracea (strain AE-LAYH)	03/10/2022
ENZ	EFSA-Q-2022-00603	Glucan 1,4-α-maltohydrolase from Bacillus subtilis strain MAM	30/09/2022
REC	EFSA-Q-2022-00580	Recinpra_Vacurema Advanced	20/09/2022

REC	EFSA-Q-2022-00612	Shangrao Bisource Technology Co., Ltd._Vacurema Prime	04/10/2022
REC	EFSA-Q-2022-00616	Reliance Industries Limited_OHL Super-Clean Technology	05/10/2022

9.2. Valid questions since the 30th CEP Plenary:

The following 6 new mandates have been validated since the 30th CEP Plenary meeting.

Food Sector	EFSA-Q-Number	Subject	Validity date
REC	EFSA-Q-2021-00401	Concept Plastics Packaging_(Gneuss 2)	05/10/2022
REC	EFSA-Q-2022-00014	Battenfeld-Cincinnati_BattenfeldProcess	05/10/2022
REC	EFSA-Q-2022-00434	TANRIKULU_Starlinger iV+	04/10/2022
REC	EFSA-Q-2022-00456	Dialog_Starlinger iV+	06/10/2022
REC	EFSA-Q-2022-00471	Arcoplastica_BanderaPURe15	07/10/2022
REC	EFSA-Q-2022-00473	Umincorp Polymers BV_NGR	06/10/2022

9.3. Withdrawn questions since the 30th CEP Plenary:

None.

10. Other scientific topics for information and/or discussion

None.

11. Any Other business

None.