Uncertainty analysis for genotoxicity including results

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12. The purpose of the uncertainty analysis for genotoxicity was to assess the degree of certainty for the conclusion on whether BPA presents a genotoxic hazard by a direct mechanism (direct interaction with DNA), taking into account the available evidence and also the associated uncertainties. This overall question was divided into two sub-questions, which were assessed by three WG members with specialist expertise in genotoxicity assessment:

Sub-question 1: What is your probability (%) that there is a genotoxic hazard in humans from BPA?

Sub-question 2: If there would be a genotoxic hazard in humans from BPA, what is your probability that its causes include a direct mechanism?

13. When assessing the two sub-questions, the experts considered all the data they had reviewed for the genotoxicity assessment, including results from in vitro studies and animal models, taking into account their relevance to humans; the available data from human studies were considered not relevant.
14. The experts' judgements were elicited by the structured procedure described below:

15. The word 'include' in sub-question 2 was introduced to accommodate the possibility that both direct and indirect mechanisms could operate together.

16. The experts were provided with guidance on how to assess and express their probability judgements for the two questions. They were asked to consider all the data they had reviewed for the genotoxicity assessment, including results from in vitro studies and animal models, taking into account their relevance to humans; the available human data were considered not relevant.

17. The three experts first worked on the questions independently, based on the evidence they had already reviewed and evaluated for the opinion, and recorded their probabilities and the reasoning for their judgements in an excel template similar to that which was used for Question 1 in the uncertainty analysis for non-genotoxic endpoints. This was followed by a facilitated meeting, where the three experts presented their judgements and reasoning and discussed them together with the WG Chair. After the meeting, the three experts were invited to review and, if they wished, revise their judgements and reasoning in the light of the discussion.

18. Each expert's revised probabilities for the two sub-questions were multiplied to provide a probability for the overall question. This is appropriate because the second question is conditional on the first. The first sub-question provides a probability for BPA presenting a genotoxic hazard; the second question provides a conditional probability that, if BPA presents a genotoxic hazard, there is a direct mechanism. So the product of these is a probability that both are true: that BPA does present a genotoxic hazard and that there is a direct mechanism. As the experts' probabilities were approximate (ranges), the calculation is done by interval arithmetic and the resulting probabilities are also approximate.

19. The three experts presented and discussed their revised judgements and reasoning in a facilitated meeting with the full WG. The WG discussed the results

of the calculations combining the experts' probabilities for the two questions and expressed the conclusion of the WG both as a probability range and using verbal likelihood terms from the approximate probability scale, which is recommended by EFSA (EFSA Scientific Committee, 2018) for harmonised use in EFSA assessments. Finally, the WG discussed the implications of their conclusion for whether a TDI could be set for BPA or whether a Margin of Exposure approach was required.

20. Table 1 shows the revised judgements provided by the three experts together after sharing and discussing their initial judgements and reasoning. The third row of Table 1 shows their probabilities for the overall question, which were obtained by multiplying each expert's probabilities for the two sub- questions. These are their probabilities that BPA does present a genotoxic hazard and that there is a direct mechanism. The bottom row of Table 1 shows the complement of the probabilities in the third row, obtained by subtracting each probability from 100%. These are the experts' probabilities for the opposite outcome: that BPA does not present a genotoxic hazard by a direct mechanism. The fifth column of Table 1 shows the 'envelope' of the probabilities for the three experts, obtained by taking the lowest and highest probabilities in each row. These express the range of opinion across the three experts.

Table 1 Results of the uncertainty analysis for the genotoxicity assessment.

	Expert A	**Expert B**	**Expert C**	**Envelope of three experts**	**Assessment (rounded values)***
Experts' probabilities that BPA presents a genotoxic hazard in humans (sub-questions 1)	70-90%	66-90%	70-90%	66-90%	66-90%

Experts' probabilities that, if BPA is genotoxic, there is a direct mechanism (sub-question 2)	10-33%	10-33%	20-30%	10-33%	10-33%
Calculated probabilities that BPA is genotoxic by a direct mechanism ((sub-question 1) x (sub-question 2)	7-29.7%	6.6-29.7%	14.27%	6.6-29.7%	5-30%
Calculated probabilities that BPA is not genotoxic by a direct mechanism (100% minus row above)	70.3%-93%	70.3%-93.4%	73-86%	70.3-93.4	70-95%

*The calculated probabilities were rounded to the nearest 5%. The experts probabilities of 33% and 66% were not changed because they correspond approximately to a 1 in 3 chance and a 2 in 3 chance, respectively.

Source: Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs, EFSA, (2021).

21. The results in Table 1 and the reasoning of the three experts were presented and discussed in detail at a facilitated meeting with the full WG. It was agreed to take the envelope of the 3 experts' results as the consensus of the WG, taking account of the available evidence and associated uncertainties. The WG also agreed that their consensus probability that BPA is genotoxic by a direct mechanism should be rounded to 5 – 30%, as shown in the right-hand column of Table 1, to take account that it is based on expert judgement and avoid the implied precision of the calculated values. Similarly, the WG rounded their consensus probability that BPA is not genotoxic by a direct mechanism to 70 – 95%.

22. The width of the consensus probability range for BPA not being genotoxic by a direct mechanism, reflects the uncertainty of the three experts and the other WG members about the judgements on sub- questions 1 and 2. The WG discussed in more detail which lines of evidence tended to support probabilities in the lower end of this range, and which tended to support the upper end of the range (Table 2).

Table 2. Summary of lines of evidence supporting either lower or higher probabilities that BPA does not present a genotoxic hazard by a direct mechanism, within the range assessed by the WG (70-95%).

Evidence supporting probabilities closer to 95 %	• Consistent negative Ames tests • Indications of carcinogenic effects of BPA do not indicate direct genotoxic mechanism because only at very low doses and not higher doses (non monotonic), only after development exposure (up to weaning) and only in one target tissue • Reactive non-conjugated metabolites of BPA are observed in animals but not in humans • Effects only from repeated exposure, so might be secondly • Evidence for several indirect mechanisms
Evidence supporting probabilities closer to 70%	• Presence of uncharacterised DNA adducts • Mutational spectrum from whole genome assessment

Source: Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs, EFSA, (2021).

23. It was concluded that it is Unlikely to Very Unlikely (5 – 30% probability) that BPA presents a genotoxic hazard, the causes of which include a direct mechanism (combining subquestion 1 and 2, see third row of Table 1). Accordingly, it was concluded that it is Likely to Very Likely (70 - 95% probability) that BPA either presents a genotoxic hazard only through indirect mechanism(s) or is not genotoxic. The likelihood terms used in these conclusions are taken from the

approximate probability scale, which is recommended by EFSA (Table 2 in EFSA Scientific Committee, 2018) for harmonised use in EFSA assessments.

24. EFSA Scientific Committee (2017) has advised that, where the overall evaluation of genotoxicity for a substance leaves no concerns for genotoxicity, HBGVs may be established. However, if concerns for genotoxicity remain, establishing a HBGV is not considered appropriate and a Margin of Exposure (MoE) approach should be followed.

25. Considering the WoE for probabilities closer to either 70% or 95% that BPA does not present a genotoxic hazard by a direct mechanism (Table 2), the CEP Panel concluded that probabilities close to 95% are more strongly supported by the evidence than probabilities close to 70% and, therefore, the balance of evidence allows a HBGV to be established.