Comments to the EFSA Public consultation on the draft protocol for hazard assessment of BPA

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Commenting as a private individual

September 2017

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Selection of experts

- The draft protocol does not specify how experts will be selected to participate in conducting the assessment
  - EFSA has existing procedures for this but it would add transparency if these were outlined in the protocol

- The protocol involves elicitation of expert judgements but does not specify how experts will be selected to participate in that
  - Structured procedures for selecting experts for elicitation are included in EFSA's 2014 Guidance on Expert Knowledge Elicitation

Consideration of excluded evidence

- Section 4.2.1 states that publications in languages other than English will be excluded, and acknowledges that this may be a source of uncertainty
- Later sections describe further criteria for including or excluding evidence at later stages of the assessment
- This focussing of assessment on the most relevant and reliable evidence is necessary, but introduces uncertainty regarding the contribution that evidence could have made
- The protocol should state explicitly that this will be taken into account as part of the uncertainty analysis at the end of the assessment
  - As recommended in EFSA's Prometheus approach and EFSA's Guidance on Weight of Evidence Assessment

Combining ordinal rating scores (1)

- Ordinal scales such as those used proposed for Quality and Risk of Bias are useful aids when evaluating evidence
- However, combining ordinal scales using matrices of the type shown in Table 12 is subject to serious weaknesses, discussed in appendix B.3 of EFSA's draft Guidance on Uncertainty

		Quality rating		
		Reliable without restrictions	Reliable with restrictions	Not reliable
Risk of Bias rating	Low RoB	Tier 1	Tier 2	Not further considered
	Medium RoB	Tier 2	Tier 3	Not further considered
	High RoB	Tier 3	Not further considered	Not further considered

Combining ordinal rating scores (2)

- If such matrices will be used, then the protocol should state clearly the justification for the rules implied by the matrix
  - e.g. why are studies rated high risk of bias and 'reliable without restrictions' assigned to Tier 3, while studies rated low risk of bias and 'not reliable' are 'not further considered' – which implicitly gives more weight to quality than risk of bias?

		Quality rating		
		Reliable without restrictions	**Reliable with restrictions**	**Not reliable**
Risk of Bias rating	**Low RoB**	Tier 1	Tier 2	Not further considered
	Medium RoB	Tier 2	Tier 3	Not further considered
	High RoB	Tier 3	Not further considered	Not further considered

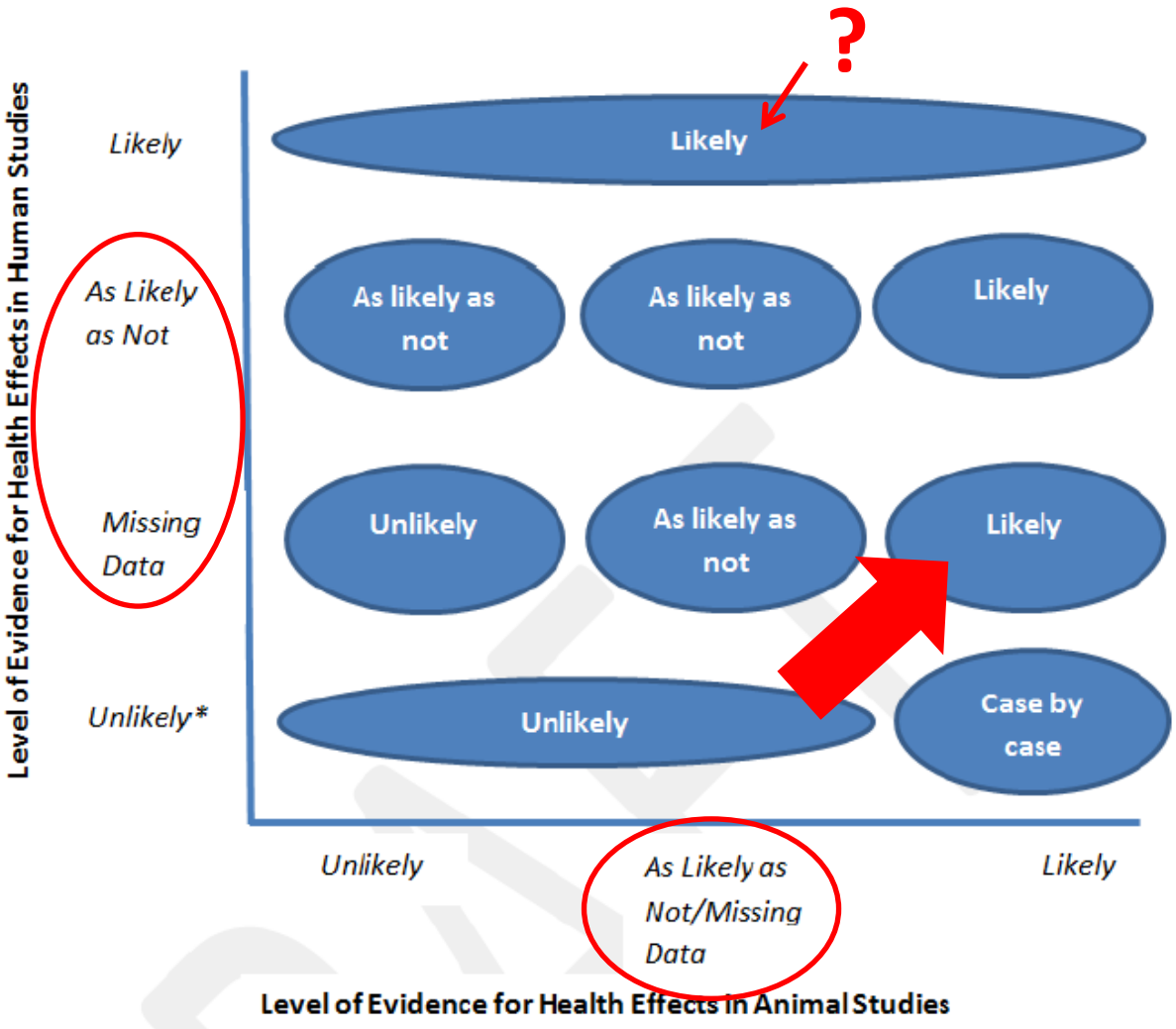
Combining ordinal rating scores (3)

- Also, avoid the issues described by Cox (2008) for risk matrices, which apply also to matrices for uncertainty and evidence quality
  - e.g. is it reasonable that, for borderline cases, a small decrease in risk of bias and a small increase in reliability can lead to a 2-category difference in Tier assignment?

		Quality rating		
		Reliable without restrictions	**Reliable with restrictions**	**Not reliable**
Risk of Bias rating	**Low RoB**	Tier 1	Tier 2	Not further considered
	Medium RoB	Tier 2	Tier 3	t further considered
	High RoB	Tier 3	Not further considered	Not further considered

Combining ordinal rating scores (4)

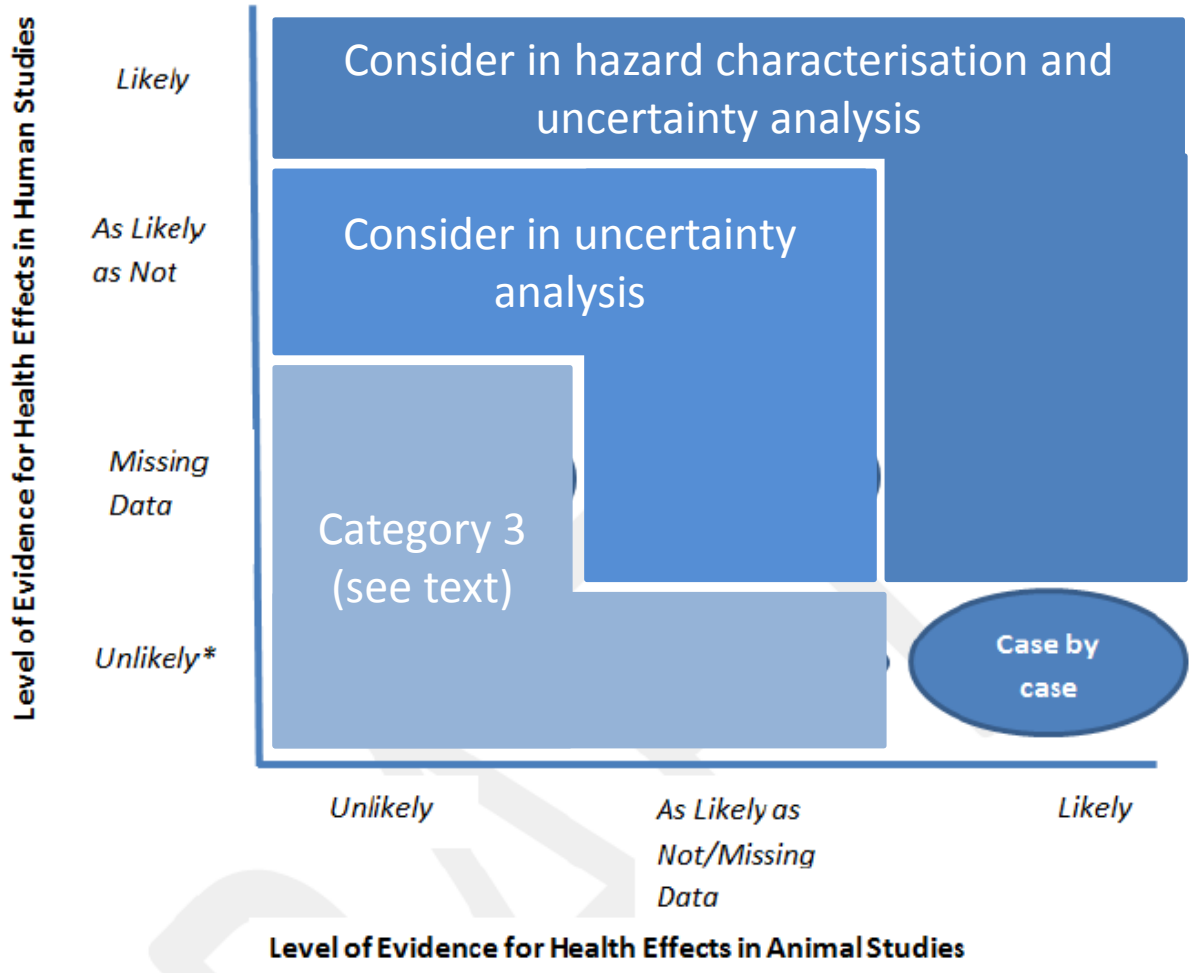
- Same issues apply here
- What is the logic of the scales and combinations?
  - E.g. why is missing data equated to 'as likely as not' for animal studies, but less likely for humans?
  - Is it appropriate that small changes have large consequences?
  - To what outcome do the resulting likelihoods refer?



Combining ordinal rating scores (5)

- Might be better to present it as a decision rule, since this is how EFSA proposes to use these scales in the assessment

- Category 3 should not be completely excluded but recalled at the end of the assessment (see slide 3)

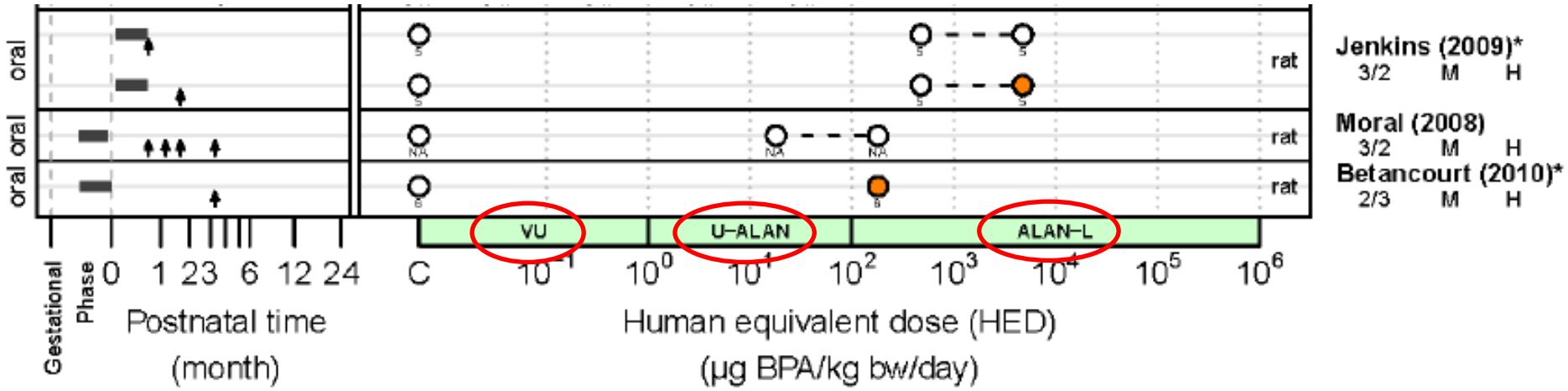


Human relevance and adversity

- The protocol states that the justification for judgements on relevance and adversity will be documented
- It is also important to assess and take account of the uncertainty of these judgements
- This could be done in a similar way to the 2015 BPA opinion, where experts expressed their judgements about the human relevance and adversity of each effect using the likelihood scale
- These could then be combined with the likelihood of each type of effect in animals, providing a logic model for the likelihood of adverse effects in humans, to support expert judgements on the overall conclusions (see later)

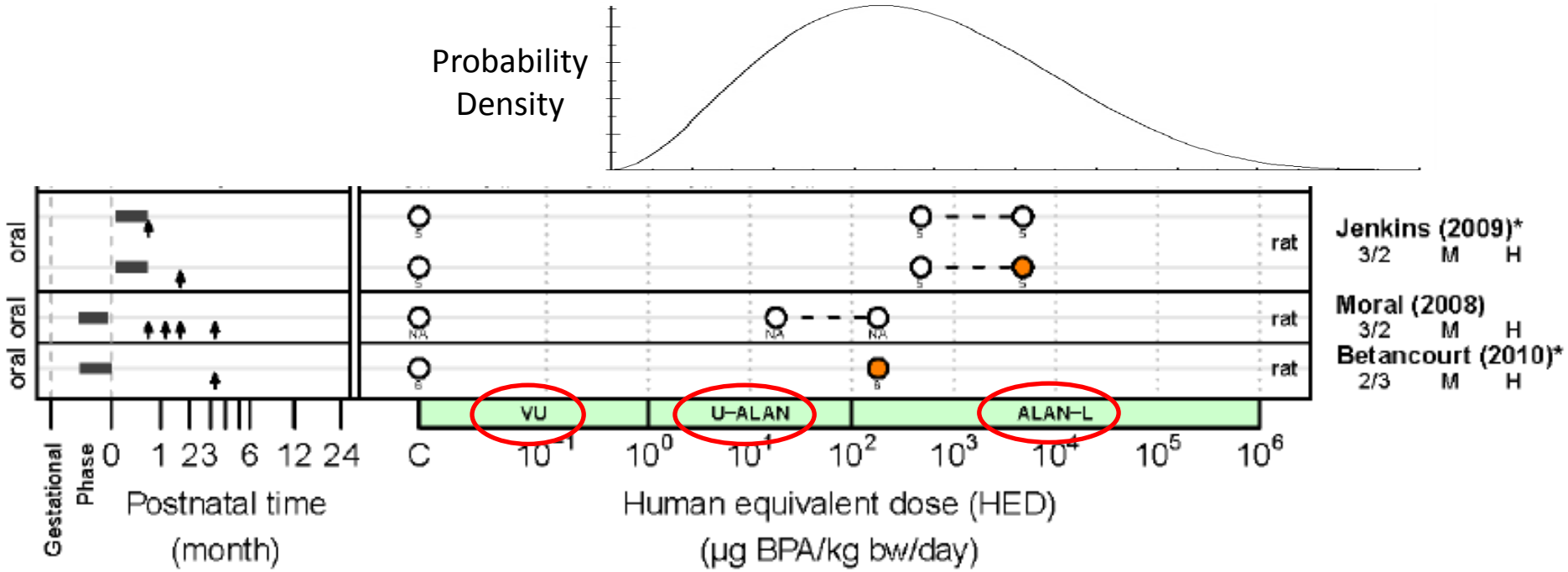
Uncertainty analysis for hazard characterisation (1)

- Lines 776-779 imply a similar approach to the 2015 opinion (☺)
- Evidence for each effect was summarised graphically
- The likelihood of the effect in each dose range was assessed
- These were used with the likelihoods for human relevance and adversity, to make an overall judgement about the likelihood of *any* relevant and adverse effect in humans in each dose range
- This helped decide what size of uncertainty factor was needed to account for the possibility of these effects at doses below the reference point



Uncertainty analysis for hazard characterisation (2)

- I suggest that approach could made better and easier by eliciting probability *distributions* for the dose at which a critical effect size would be reached (conceptually analogous to a BMD) rather than probabilities for each dose interval



Uncertainty analysis for hazard characterisation (3)

- I also suggest the Panel consider defining a logical model to combine the likelihoods for occurrence, human relevance and adversity of the different effects
- This would provide a *calculated* probability for the probability of any relevant adverse effect as a function of dose
- This could support (not replace) expert judgement of the overall conclusion, helping the experts to take account of how the different probabilities combine - which is difficult to do by judgement alone

Uncertainty analysis

- I support the proposed approach to addressing uncertainties
- I suggest that rather than conduct all the expert judgements by a minimal 'informal' approach, the working group consider a tiered approach
  - Start by eliciting all judgements in a simple way
  - Identify which judgements have most influence on the overall conclusions
  - Revise the most critical judgements using a more formal elicitation procedure
- This is analogous to the 'minimal assessment' procedure described in EFSA's (2014) guidance on expert knowledge elicitation, and would increase the rigour of the assessment as a whole