EFSA Workshop on bisphenol A (BPA) hazard assessment protocol

Brussels, September 14

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Agenda

- Introduction
- Specific topics
  - *Time span of evidence search* - US NTP/FDA CLARITY-Study
  - WoE should include all relevant data - “positive” and “negative”
  - Exposure characterisation in human studies - potential misclassification
  - Internal study validity - high RoB studies should be excluded from WoE

Introduction

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- The global PC/BPA Group acknowledges that **scientific criteria** concerning the selection of the new scientific studies **are laid down in advance of the re-evaluation** which will result in **a transparent, comprehensible process.**

- We consider the CEF Panel draft BPA **hazard assessment protocol generally as very thorough, transparent, and comprehensible.**

- Potentially eligible studies will be **evaluated for relevance to the assessment by two independent reviewers**. We agree that the evaluation by more than one scientist is crucial.

- **In case of disagreement**, the two independent reviewers will discuss the paper in order to find a solution to solve it. In case an agreement between the two reviewers cannot be found, **the paper will be discussed by the Working Group for a final decision**. In our view, this process is comprehensive and transparent.

US NTP/FDA CLARITY-Study

- The CEF Panel draft BPA hazard assessment protocol specifies that the re-evaluation will deal with new evidence available since 1 January 2013 and indicates *"The proposed ending date is 31/12/2017 unless the publication of the NTP/FDA study is delayed."*

Since this study will be a major additional building block for the overall assessment of BPA, we consider the flexible ending date essential to ensure that the ongoing comprehensive CLARITY study will be included into this re-evaluation.

US NTP/FDA CLARITY-Study
Study design – core study I

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- Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA)
- *Large group size*
- *Appropriate statistics*
- *Multiple BPA doses; low to high doses*
- *2 l*evels of the reference estrogen *ethinyl estradiol* (EE2)

Table 1
Number of animals/treatment group assigned to the interim (1 year) and terminal (2 year) sacrifices of the core chronic BPA toxicity study.[a]

Group	Arm (Continuous/Stop)	1 Year		2 Year	
		Male	Female	Male	Female
Vehicle	Continuous	22	23	50	50
	Stop	20	20	50	50 (49)[b]
2.5 BPA	Continuous	22	22	48	48
	Stop	20	22	48	50
25 BPA	Continuous	20	22	48	46
	Stop	20	20	48	48
250 BPA	Continuous	24	24	50	50
	Stop	20	22	50	50
2500 BPA	Continuous	20	20	50	50
	Stop	20	20	50	50
25,000 BPA	Continuous	22	24	46	46
	Stop	22	22	46	46
0.05 EE_2	Continuous	26	26	26	26
0.50 EE_2	Continuous	26	26	26	26

[a] Animals were allocated to the interim or terminal sacrifice of the continuous or stop dose arms of the study at weaning. There were no same sex litter mates in any treatment group. The original protocol indicated 26 animals/sex/treatment group for the interim sacrifice and 50 animals/sex/BPA treatment group (26 for EE_2 groups) for the terminal sacrifice. A shortfall in the number of pups available for the specialty studies resulted in a change such that 20–26 animals/sex/treatment being allocated to the interim sacrifice and any extra pups were allocated to specialty studies.
[b] In this group, one animal assigned was found to have been incorrectly sexed and was discarded on the day of allocation.

Heindel, et al. 2015. NIEHS/FDA CLARITY-BPA research program update. Reproductive Toxicology. 58:33-44.
http://www.sciencedirect.com/science/article/pii/S0890623815300071

US NTP/FDA CLARITY-Study
Study design – core study II

- NCTR/NTP 90-day subchronic toxicity study (Delclos 2014) provided information on the dose level.
- *Core GLP study at NCTR/NTP*
- 13 academic researchers, were provided with animals and/or tissues or serum from animals taken from the core chronic study for exploratory research to addresses questions from earlier exploratory studies.

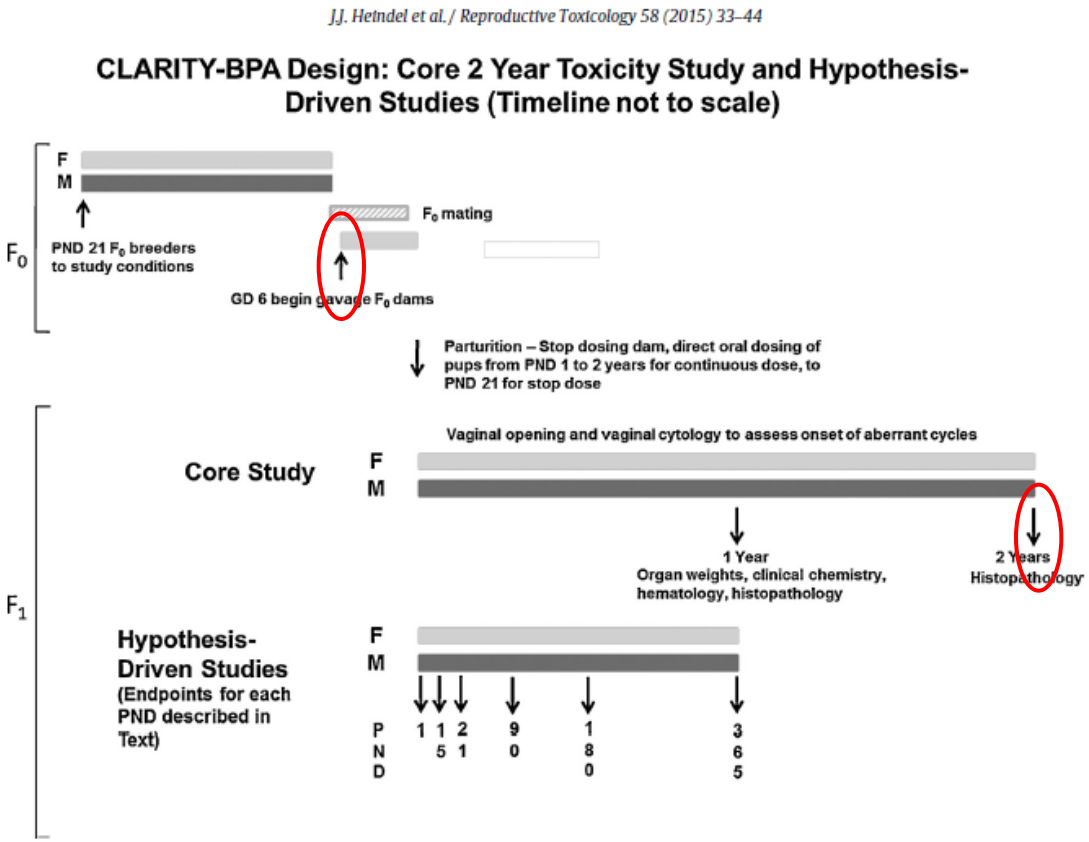


Fig. 1. Schematic representation of the study design as described in the text. The planned animal assessment times for core chronic and specialty studies are indicated; continuous and stop dose arms are not depicted.

Heindel, et al. 2015. NIEHS/FDA CLARITY-BPA research program update. Reproductive Toxicology. 58:33-44.
http://www.sciencedirect.com/science/article/pii/S0890623815300071

US NTP/FDA CLARITY-Study
Available data I

- Core study data
  - Initial data are expected later in 2017

- Hypothesis driven studies from extramural grantees
  - Initial data by some researchers report "s*ome", "limited" , "non-consistent" or "estrogen receptor-independent"* effects (Rebuli 2015, Johnson 2016, Arambula 2016, Patel 2017, Gear 2017).

Hypothesis driven studies have to be set into perspective with the core study data to derive overall conclusions on "apical" and "intermediate" endpoints mentioned in the EFSA hazard assessment protocol.

Given the nature of the comprehensive CLARITY Study and the information the core NCTR/NTP study will provide for the overall assessment of BPA, we support the CEF Panel considerations and timeline indicated in the draft protocol.

Rebuli et al. 2015. Toxicological Sciences. 148(2):341-354, Johnson et al. 2016. Hormones and Behavior. 80:139-148, Arambula et al. 2016. Endocrinology. 157(10):3856-3872, Patel et al. 2017. Endocrinology. 158(6):1727-1738, Gear et al 2017. Toxicology Letters. 275:123-135.

WoE should include all relevant information; “positive” and “negative”

- **For a true Weight of Evidence (WoE) approach, it is important to include both “positive” and “negative” results.**

- The draft protocol clearly describes the inclusion criteria for studies
- The CEF Panel intends to do an initial "first pass" screening for eligible studies based on titles and abstracts.
- However, sometimes studies examining multiple chemicals do not discuss the chemicals with “null” results in the abstract.

These “null’ results represent an important aspect of a true WoE approach. It is in our point of view therefore important that the Panel does not exclude studies if BPA is not mentioned in the study’s title or abstract.

WoE should cover all parameters reported in a study

- potentially eligible studies will be further evaluated for relevance to the assessment by two independent reviewers. We agree that the evaluation by more than one scientist is crucial.

- Endpoints without a measured effect are sometimes mentioned only in Material and Methods and/or only briefly mentioned in the result chapter without detailed discussion (e.g. *“data not shown”*).

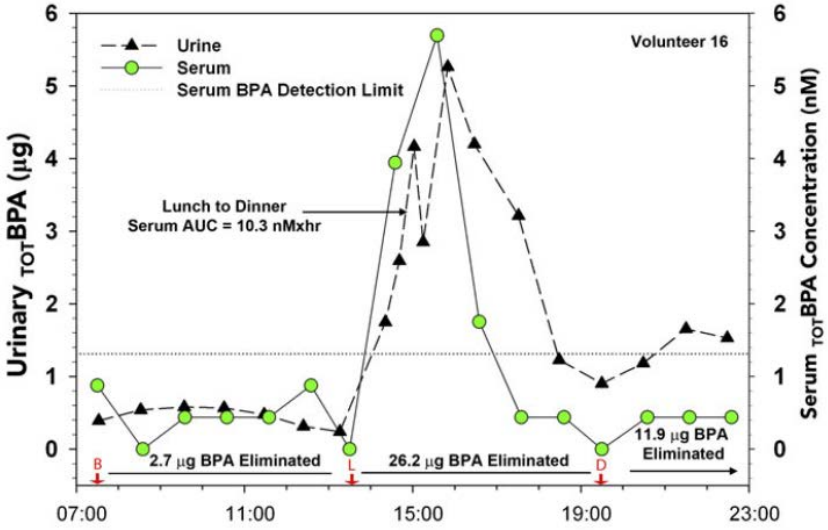
We consider it important that the Panel ascertains that this evaluation covers all parameters and endpoints measured in a study, including “null” observations.

Exposure characterization in human studies – intra day variability

- For human studies, quality evaluation criteria are adapted from the NTP OHAT Risk of Bias (RoB) system.

- While the CEF Panel's quality system in our view is generally thorough and includes many important epidemiology quality issues, it does not include an explicit requirement to consider BPA-specific limitations in exposure characterization.

- BPA has a short half-life of 4-5 hours after oral ingestion and studies have shown that BPA levels in urine are highly variable **within one day**



Teeguarden et al. 2011. Toxicological Sciences. 123(1):48-57.

Exposure characterization in human studies – inter day variability

- Lassen 2013 (Environmental Research. 126:164-170): 24 h urinary BPA level investigated at days 1, 4, 44 or 87. *"The considerable variability of phenol urinary excretion over time within one person, **in particular for BPA (ICCs ranging from 0.10 to 0.42**), hampers exposure classification in epidemiological studies and potentially **leads to misclassification when the exposure measures are intended to reflect exposure through a longer period of time than just the hours immediately prior to urine sampling**."*

- Townsend 2013 (Environmental Health.12:80): two spot urine samples, 1 to 3 years apart. *"In all samples, as well as first-morning urine samples, we observed high within-person variability relative to total variability of BPA (**ICC = 0.14 and 0.15, respectively**) …"Conclusions Overall, our observation of **low reproducibility of urinary BPA excretion over 1 to 3 years indicates evaluation of associations with disease risk in epidemiologic studies may be challenging** when only a single spot urine measurement is available."*

Intraclass correlation coefficient (ICC): value between 0 and 1; reflects the relationships between the within- and between-person variances (calculated by dividing the estimated between-person variance by the total variance). For example, an ICC of 0.55 means that 55% of the observed variation in the measurements is due to between-person variation and 45% is due to within- person variation.

Exposure characterization in human studies: potential misclassification

- Overall, it would be beneficial if the CEF Panel modifies question 1 of the quality analysis

  "Can we be confident in the exposure characterisation?“

  to explicitly take into account potential exposure misclassification and the impact on the interpretation of epidemiology studies, especially if chronic effects are being evaluated.

Internal study validity: criteria are transparent

- The Panel combines the study quality and risk-of-bias (RoB) ratings to reach an overall rating of a study's internal validity, classifying studies into three tiers, from 1 to 3 corresponding to decreasing levels of internal validity, or removing studies from the WoE evaluation

Table 12: Internal validity

		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

We support this general approach to define study specific validity criteria and to exclude studies rated as “Not reliable” from the WoE evaluation. In particular the exclusion of studies determined to be unreliable is important to an accurate WoE evaluation.

High RoB studies should be excluded from WoE

- If a study has been performed with reliable methods, but has substantial bias in its results (high RoB), it is not appropriate to use such a study for either hazard or risk assessment; thus we recommend that such a study should not be relied upon further for integration of evidence.

Table 12: Internal validity

		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

High RoB studies should be excluded from WoE

- RoB categories: (“Definitely low RoB (++)”, “Probably low RoB (+)”, “**Probably high RoB (-)”, “Definitely high RoB (--)”).**

- High RoB; **human studies:**
  - One key question is scored with ***-/--***

    or
  - **Any non-key** question is scored with **--**

- High RoB; **animal studies:**
  - **One key question** is scored with ***-/--***

    or
  - **More than two non-key questions** are scored with **--**

- Example questions:
  - Key question human studies: ***“Did selection of study participants result in appropriate comparison groups?”***
  - Non-key question animal studies: ***“Were experimental conditions identical across study groups?”***

Summary

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Overall, we consider the CEF Panel draft BPA hazard assessment protocol generally as very thorough and transparent.

We appreciate the opportunity to participate in this process and to share our suggestions on areas that could be clarified or improved.

Thank you!