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Montevil et al., 2020*'s assessment of non-monotonicity effects of BPA in developing mammary gland of rats - limited methodology and questionable results

Summary: The authors claim to have found several non-monotonic dose response relationships for the mammary gland. For the "traditional" methods as applied in this study, no effects were observed. The description of the novel exploratory measuring technique is extremely limited. The authors´ conclusion on evidence for non-monotonic dose response, often referred to as low dose effects, from BPA therefore appears highly questionable.

Montevil et al., 2020, is one of the grantee studies assigned in context of the academic research elements of the CLARITY-BPA program and the 90-day pilot-study (Delclos et al., 2014). Montevil et al. 2020 compared the outcome of well-established toxicologically relevant endpoints (referred to in the study as semi-quantitative method) with the results of the application of novel measuring techniques (referred to as automatic and non-automatic quantitative methods). In the "traditional" part of their investigations of respective tissues received from the CLARITY core study the authors did not observe effects on the animals´ mammary glands at the investigated points in time and dose levels. The novel measuring technique is described as automatic and non-automatic quantitative 2D/3D measurements.

Claimed non-monotonic effects on mammary gland not supported by results of established semi-quantitative methods both in the author´s own study and in the CLARITY-BPA core chronic study

Only when applying the novel quantitative measuring techniques, the authors claim to have found several non-monotonic dose response relationships (NMDR) for the mammary gland. For the established "semi-quantitative" methods which were also applied in this study, *no effects* were observed by the authors when investigating validated, toxicologically relevant endpoints in the CLARITY-BPA data[1].

This finding is consistent with the respective conclusions in the CLARITY-BPA Core study: In their Research Report on this endpoint in the CLARITY-BPA Core study, the conclusion of the US National Toxicology Program (NTP), an interagency program run by the US Dept of Health and Human Services (NIEHS) is that, based on biological plausibility, the *"Evaluation of the totality of the evidence regarding the elevated incidence of mammary adenocarcinomas or combined adenomas and adenocarcinomas in the stop-dose females exposed to 2.5 µg BPA/kg bw/day makes it unlikely that this is a plausible BPA treatment-related lesion."*

In May 2016, the European Food Safety Authority (EFSA) published a comprehensive report (Beausoleil et al., published as Varret et al., 2018) investigating potential evidence for NMDR in the area of food

[1] Only when modifying the dataset of Delclos et al. (2014) by removing the results of females in a certain phase of estrus from their analysis, did the authors claim to find one NMDR effect for samples in the "traditional part" of investigating the Delclos study data.

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safety, defining, among other, six criteria for the identification of evidence for NMDR. The research work was carried out by a group of four public health and safety authorities from Austria (AGES), France (ANSES), the Netherlands (RIVM) and Sweden (Karolinska). In 2019 Badding et al. applied these systematic criteria for the identification of evidence for NMDR to analyze the statistically significant findings on mammary gland (and all other significant endpoints) from the CLARITY-BPA core chronic study. Badding et al., 2019 concluded that *"increased mammary gland adenocarcinomas observed at the lowest dose in the stop-dose arm female rats at 2 years met only two of the six Varret et al. (2018) checkpoints, indicating little evidence for a NMDR." "Overall, our analysis found little evidence for NMDR in the endpoints evaluated in the CLARITY-BPA Core Study. The results of this analysis are consistent with and support the conclusions reached in the CLARITY-BPA Core Study report."*

Insufficient description of novel method prevents meaningful assessment of results

In Montevil et al., 2020, the description of the novel exploratory measuring technique is extremely limited. No historical data are available that would allow to put the findings into a broader context. The method to fit data points apparently applies curve fitting mathematics without explaining respective biological plausibility. The insufficient documentation of the novel methodology does not provide any information that would allow the assessment of the relevance and suitability of this new method for the detection of biologically plausible and reasonable effects. For example, a meaningful cause-response-related connection between the 91 parameters and the mathematical analysis is not described. It is therefore not possible to assess the meaning of the described findings. The authors´ conclusion on evidence for non-monotonic dose response, often referred to as low dose effects, from BPA therefore appears highly questionable.

*A Combined Morphometric and Statistical Approach to Assess Nonmonotonicity in the Developing Mammary Gland of Rats in the CLARITY-BPA Study;
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