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Reply to 'Paracetamol use in pregnancy — caution over causal inference from available data'; 'Handle with care — interpretation, synthesis and dissemination of data on paracetamol in pregnancy'

Ann Z. Bauer, Shanna H. Swan, David Kriebel, Zeyan Liew, Hugh S. Taylor, Carl-Gustaf Bornehag, Anderson M. Andrade, Jørn Olsen, Rigmor H. Jensen, Rod T. Mitchell, Niels E. Skakkebaek and David M. Kristensen

We are pleased that Alwan et al. and Damkier et al. have responded to our call for a review of our Consensus Statement (Bauer, A. Z. et al. Paracetamol use during pregnancy — a call for precautionary action. *Nat. Rev. Endocrinol.* **17**, 757–766 (2021)[1]). We welcome the support of Alwan et al. (Alwan, S. et al. Paracetamol use in pregnancy — caution over causal inference from available data. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-021-00606-x (2021)[2]) and Damkier et al. (Damkier, P. et al. Handle with care — interpretation, synthesis and dissemination of data on paracetamol in pregnancy. *Nat Rev. Endocrinol.* https://doi.org/10.1038/s41574-021-00605-y (2021)[3]) for a focused research effort to further investigate prenatal exposure to paracetamol (otherwise known as acetaminophen or *N*-acetyl-*p*-aminophenol (APAP)) as a risk factor for adverse reproductive and neurodevelopmental outcomes.[3]

We agree that limitations and uncertainties remain despite the large body of available data, therefore, we avoided any inference of causality in our Consensus Statement[1]. We believe, however, that available data provide sufficient evidence for concern and a recommendation of precautionary action. The availability of a large body of experimental data, largely consistent with observational data, is an important consideration in our evaluation. Ethical considerations rule out clinical intervention trials for APAP in pregnancy, so animal studies, which are not subject to confounding or bias, are an essential source of evidence and support for causality.

As stated in our paper[1] and in the TENDR statement[4], we recognize our responsibility to take action even in the face of uncertainty, given the serious consequences of inaction. We believe precautionary action should be taken when scientific evidence indicates that a chemical or medication is of substantial concern. Evidence of toxicity, particularly when epidemiological, toxicological and mechanistic data align, should constitute a sufficient signal to trigger prioritization and action. The studies we detailed provide consistent signals from all three types of research. However, we recognize the limitations of the existing literature and the need for epidemiological studies with more precise exposure and confounder assessment, and mechanistic studies that provide a more complete understanding of the mechanisms by which APAP might adversely affect development.

Whether or not to make indication-specific recommendations is a judgement call that should be made after weighing the potential risks and benefits of APAP use in pregnancy. We agree that for fever and severe pain during pregnancy, APAP is a necessary and appropriate[5] treatment. While people are generally apprehensive about the use of medications during pregnancy, APAP is perceived by pregnant women to be the safest[6] and is the most frequently used of all medications[7]. In our study, many pregnant women did not recall APAP use when asked a generic question about medication use, but recalled use when asked specifically about APAP[8]. Furthermore, a 2016 position paper of the EBCOG stated that many pregnant people use over-the-counter medications routinely and do not tell their physician[9]. These findings suggest that many people view APAP as conveying negligible risk, instead of being a 'true medication' with potential adverse effects.

For these reasons, the signatories confirm their belief that women should be cautioned from early pregnancy to use APAP only when indicated, at the lowest dose and for as short a time as possible, and to contact their physician or pharmacist when uncertain about its use. Our recommendations should not increase maternal anxiety, as they only suggest adherence to current guidelines[9,10].

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Competing interests
The authors declare no competing interests.