Paracetamol use in pregnancy — neglecting context promotes misinterpretation

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We read with interest the recent Consensus Statement by Bauer et al. on paracetamol (*N*-acetyl-*p*-aminophenol (APAP), otherwise known as acetaminophen) use in pregnancy (Bauer, A. Z. et al. Paracetamol use during pregnancy — a call for precautionary action. *Nat. Rev. Endocrinol.* **17**, 757–766 (2021))[1]. This paper highlights potential developmental risks in children exposed to APAP in utero. We feel that further consideration of context might alter the societal recommendations proposed. This Correspondence is signed by 16 organizations and 63 individual researchers and clinicians (Supplementary Box 1), including the authors.

All drug use follows a risk–benefit calculation, which should consider both the mother and fetus during pregnancy. However, a tendency exists to prioritise direct fetal risks and to overlook other risks to either party[2]. Prescriber and patient anxiety about fetal risks has resulted in maternal deaths from pre-existing medical conditions due to undertreatment in pregnancy[3].

Doing nothing might at first appear to minimise the risk of harm. Inadequate treatment of pain and/or fever during pregnancy can be detrimental. Pain can itself have disruptive endocrine consequences[4], deleterious psychological effects might have a fetal effect[5], and immobility (which can result from untreated pain) can lead to venous thromboembolism. Pyrexia is associated with neonatal encephalopathy[6] and fetal teratogenicity, which might be reduced by APAP[7].

Alternative analgesics to APAP include non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Both have well-documented risks in pregnancy. NSAIDs are largely contraindicated in the third trimester due to risks of oligohydramnios and premature closure of the ductus arteriosus. First trimester opioid use might be associated with fetal anomalies, and in later pregnancy associated with neonatal abstinence syndrome.

Bauer et al.[1] state that some, but not all, human observational studies suggest associations with cryptorchidism, early female puberty and neurodevelopmental disorders, indicating APAP might be an endocrine-disrupting chemical (EDC). Notably, the only randomized controlled trial in humans found no difference in neurodevelopmental disorder prevalence[1]. We note that EDCs are ubiquitous and are emerging as leading environmental risks worldwide[8], being widely found in processed food, pharmaceuticals (including the NSAID ibuprofen), cosmetics and drinking water. Furthermore, APAP is highlighted as having potential negative effects throughout life (including on male fertility, with potential transgenerational effects), but restricted use is only recommended in pregnancy[1].

The authors emphasize that 65% of pregnant women report taking APAP[1], without discussing typical use. They acknowledge that timing and duration are probably critical factors, with evidence suggesting that exposure for >2 weeks during the late first or second trimester might be important. A 2020 survey reported that half of women taking APAP in pregnancy do so for <3 days[9].

This is the context in which we must consider the risks and benefits of APAP. The overarching societal message that has been drawn from this Consensus Statement[1] is that APAP use in pregnancy is unsafe and should be restricted in both use and access. We, and others[10], believe this interpretation is exaggerated and will further add to the burden of anxiety and guilt carried by pregnant mothers[2]. Casting doubts over established medications might be counterproductive for new therapies, including vaccines, potentially increasing hesitancy. We argue the available evidence supports neither a change in clinical practice (minimal use when necessary), restricting APAP availability to pharmacies, nor additional warning labels on packaging. Most importantly, research to establish the risks of EDCs in general is imperative.

There is a reply to this letter by Bauer, A.Z., Swan, S.H., Kriebel, D. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-022-00657-8 (2022).

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Competing interests
The authors declare no competing interests.

Supplementary information
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