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1. A general concern is that the studies that are cited in the NTP review for the confidence conclusions are of low quality and have high risk for bias.

We have conducted a meta-analysis that has been accepted for publication (J.V. Kumar, M.E. Moss, H. Liu et al., Association between low fluoride exposure and children's intelligence: a meta- analysis relevant to community water fluoridation, Public Health (2023, In press). The analysis clearly shows that fluoride exposure levels relevant to people living in communities with fluoridated water is not associated with a decrement in IQ or neurodevelopment in children.

We concluded that the uncritical acceptance of fluoride-IQ studies characterized by factors that raise the risk of bias, including non-probability sampling, inadequate attention to accurate measurement of exposure, covariates and outcomes, and inappropriate statistical procedures, has hindered methodological progress.

2. A specific concern relates to an issue that appears to be trivialized by the NTP authors: the use of urinary F measured from “spot” samples collected at a single point in time to characterize exposure. Epidemiologists show that such non-differential measurement error does not always lead to a “bias toward the null” (Yland et al, 2022).

While individual level exposure measures are generally preferred over group level measures, a key caveat is that the individual exposure measure is a valid representation of exposure. The NTP authors have relied heavily on studies that used individual measures of **spot urinary fluoride**, either maternal urine collected prenatally or children’s urine to support the association between higher total fluoride exposure and lower children’s IQ and other cognitive neurodevelopmental effects. The draft monograph (page 51, I-66) states *“Although there are concerns related to using urine samples (see the Risk-of-bias Considerations for Human Studies section for details), the evidence suggests that urinary fluoride is a reasonable measure of exposure.”* This statement is contradictory to the consensus in the scientific community that spot urinary fluoride measure is not a valid biomarker of long-term fluoride exposure. First, fluoride has a short half-life. Riddell at al. 2021, found that urinary fluoride levels varied substantially depending on participant behavior before sampling. Second, Rugg-Gunn et al. 2011, concluded that that daily urinary fluoride excretion (24 hours measurement) is suitable for predicting fluoride intake for groups of people, **but not for individuals**. Third, Thomas et al. 2016, found no association between maternal urinary F and maternal plasma F in the ELEMENT study. Fourth, Aylward et al. 2015, noted concerns related to substantial within- and between-individual variation in concentrations in individual spot samples due to the known pharmacokinetics of fluoride. They identified four key factors that lead to variation in spot samples: variation in urinary flow rate within and across individuals (which they note can vary by 2-3 fold in either direction); variation in creatinine excretion rates; variation in F excretion fraction; and temporal variation due to time of sampling relative to exposure. Finally, in 2014, the World Health Organization published a manual setting out the rationale, methods, and interpretation of the use of renal fluoride excretion. Urine collection over 24 hours is the recommended method, and multiple measurements are needed to calculate variability. The manual notes several areas of uncertainty associated with using urinary fluoride as a biomarker of fluoride exposure that must be considered in interpreting the findings of studies of urinary fluoride excretion. The WHO manual states that spot urinary samples are the least informative measure for studying fluoride exposure (WHO, 2014, p. 65).

Literature cited

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