Pregnancy exposure to organophosphate esters and the risk of attention-deficit hyperactivity disorder in the Norwegian mother, father and child cohort study.

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Environ Int. 2021 Apr 25;154:106549.
doi: 10.1016/j.envint.2021.106549.

BACKGROUND: Organophosphate esters (OPEs) are a class of flame retardants in common use. OPEs can easily leach from materials, resulting in human exposure. Increasing concentrations have been reported in human populations over the past decade. Recent studies have linked prenatal OPE exposure to hyperactivity and attention problems in children. Such behaviors are often found among children with attention-deficit hyperactivity disorder (ADHD), however, no study has investigated OPEs in relation to clinically assessed ADHD.
OBJECTIVE: To evaluate prenatal exposure to OPEs as risk factors for clinically assessed ADHD using a case-cohort study nested within the Norwegian Mother, Father, and Child Cohort Study (MoBa).
METHODS: We included in the case group 295 ADHD cases obtained via linkage with the Norwegian Patient Registry, and the sub-cohort group 555 children sampled at baseline, irrespective of their ADHD case status. Prenatal concentrations of OPE metabolites were measured in maternal urine collected at 17 weeks of gestation, and included diphenyl phosphate (DPHP), di-n-butyl phosphate (DNBP), bis(2-butoxyethyl) hydrogen phosphate (BBOEP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP). We estimated risk ratios and the corresponding 95% confidence intervals [95% CI] using logistic regression, adjusting for season of urine collection, child sex, birth year, and maternal depression, education, and sum of urinary di(2-ethylhexyl) phthalate metabolites (∑DEHP) concentration during pregnancy. To assess the overall impact of simultaneously decreasing exposure to all chemical constituents of an OPE-phthalate mixture, quantile based g-computation was implemented. The mixture constituents included OPE and phthalate metabolites commonly detected in our study. In all models, we considered effect measure modification by child sex and polymorphisms in genes encoding paraoxonase 1 (PON1) and cytochrome P450 (P450) enzymes. Mediation analysis was conducted using thyroid function biomarkers estimated from maternal blood collected at 17 weeks of gestation.
RESULTS: DPHP was detected in nearly all samples (97.2%), with a higher geometric mean among the case group (0.70 μg/L) as compared to the sub-cohort (0.52 μg/L). DNBP was commonly detected as well (93.8%), while BBOEP (52.9%) and BDCIPP (22.9%) were detected less frequently. A higher risk of ADHD was observed in children with greater than median exposure to DPHP during pregnancy (risk ratio: 1.38 [95% CI: 0.96, 1.99]), which was slightly higher among girls (2.04 [1.03, 4.02]) and children of mothers with PON1 Q192R genotype QR (1.69 [0.89, 3.19]) or PON1 Q192R genotype RR (4.59 [1.38, 15.29]). The relationship between DPHP and ADHD (total risk ratio: 1.34 [0.90, 2.02]) was partially mediated through total triiodothyronine to total thyroxine ratio (natural direct effect: 1.29 [0.87, 1.94]; natural

indirect effect: 1.04 [1.00, 1.10]; 12.48% mediated). We also observed an elevated risk of ADHD in relation to BDCIPP detection during pregnancy (1.50 [0.98, 2.28]). We did not observe notable differences in ADHD by DNBP (0.88 [0.62, 1.26]) or BBOEP (1.03 [0.73, 1.46]) during pregnancy. Simultaneously decreasing all constituents of common-detect OPE-phthalate mixture, specifically DPHP, DNBP, and 6 phthalate metabolites, by a quartile resulted in an ADHD risk ratio of 0.68 [0.64, 0.72].
CONCLUSION: Prenatal exposure to DPHP and BDCIPP may increase the risk of ADHD. For DPHP, we observed potential modification by child sex and maternal PON1 Q192R genotype and partial mediation through maternal thyroid hormone imbalance at 17 weeks gestation.