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EDITORIAL COMMENTARY

An ounce of prevention is worth a pound of cure: time to focus on preconception workplace reproductive health

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Few opportunities exist in environmental reproductive medicine where we can have a direct impact on offspring health. Prevention of adverse child health outcomes has received less attention than understanding their etiology. Yet, the preconception and early pregnancy periods afford a unique opportunity to intervene and limit early life exposures that may result in harm with potentially lifelong consequences. Workplace exposures—whose largest burden involves reproductive-aged women and men—have been hard to investigate largely because of the complexity of measurement and challenges with follow-up. Case–control designs lend themselves to studying rare and often devastating outcomes, including birth defects. In the study by Spinder *et al.* (2021), published in this issue of *Human Reproduction*, the authors tackle a complex area of birth defects research using a nested case–control design by leveraging two large independent cohorts—the European Concerted Action on Congenital Anomalies and Twins in Northern Netherlands (Eurocat NNL) and the Lifelines Cohort—both with overlapping catchments from The Netherlands—to determine the extent to which endocrine disrupting chemicals (EDCs) are associated with urogenital birth defects. Here, Spinder *et al.* use occupational data from these cohorts to address a significant gap in our knowledge. In so doing, the authors draw our attention to an often-forgotten area of occupational epidemiology—that fertility, pregnancy and offspring health of reproductive-aged women (and men) matter in the workplace.

Congenital anomalies of the kidney and urinary tract systems (CAKUT) and hypospadias occur in approximately 43 and 17 births for every 10 000 in Europe, respectively (EUROCAT, 2021). The origins of urogenital anomalies involve abnormal embryonal renal development and abnormalities in renal migration or of the urinary collecting systems (Jain and Chen, 2018). As with all congenital anomalies, defects can range in severity; the more devastating and complex cases are diagnosed at birth and milder cases are typically recognized during childhood. The lifelong implications to children born with such disorders cannot be underestimated and early life exposures through a mother's (or father's) workplace may be a putative cause. In the absence of strong data on pathogenesis, it is hypothesized that environmental and genetic causes interact. Fetal development is driven by a delicate hormonal balance and any distortions result in either adaptations or aberrations. EDCs can alter critical pathways needed to achieve conception, maintain pregnancy and deliver healthy offspring. Such chemicals have been shown to influence androgenic and estrogenic hormonal processes (among others) and certain occupations are linked to substantially higher body burdens of pesticides, phthalates, phenols, organic solvents and other byproducts (Brouwers *et al.*, 2009; Bergman *et al.*, 2012).

One of the major limitations of investigating urogenital and other birth defects is the challenge of identifying and classifying all types of cases. However, since 1981, Eurocat NNL has been collecting data on children born with congenital anomalies up to the age of 10 years at diagnosis, carefully registering all livebirths, stillbirths, pregnancy losses and elective terminations. The registry includes data collected via parent questionnaires on demographics, medical history, pregnancy information, anthropometry, and substance, tobacco and medication use in the preconception and early pregnancy periods, as well as occupational history. The present study (Spinder *et al.*, 2021)—one of the

largest and most comprehensive investigations on environmental–occupational exposure and urogenital birth defects to date leveraged this high-quality data to identify cases of birth defects. As such, the authors were able to categorize subtypes of CAKUT as: (i) malformations of the renal parenchyma; (ii) anomalies of the urinary collecting system; (iii) abnormal embryonic migration of kidneys and other urinary tract anomalies; and (iv) combinations of urinary anomalies (Bakker *et al.*, 2018). They also identified and examined hypospadias diagnosed in male livebirths. The authors excluded cases with genetic or chromosomal defects as well as siblings with the same defects. Controls—defined as children without congenital anomalies born between 1997 and 2013—were selected from the Lifelines cohort, a prospective, population-based study of health across three generations. Participants were recruited from general medical practices from the study catchment areas. Parents of healthy control children (aged between 6 months and 18 years) were asked to participate and complete a questionnaire that overlapped with the Eurcat NNL data collection methods, thus limiting differential information bias and ensuring comparable accuracy across cases and controls.

Among the innovative aspects of this study was the application of the Job Exposure Matrix (JEM) developed by Van Tongeren *et al.* (2002) to translate employment history into meaningful exposure categories. Two study authors independently classified maternal job descriptions using the International Standard of Classification of Occupations 1988 (ISCO88). Using the occupational categories, the authors then identified exposure profiles per occupation through the JEM. Initially, nine separate chemical groups were identified based on participants' employment history: polycyclic aromatic hydrocarbons (PAHs), polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants and a composite group (benzophenones, parabens and siloxanes). Participants were classified as having a history of either unlikely, possible or probable exposure to each of these nine chemical groups using job title information. Technical analysis and coding were done by three external occupational experts and helped minimize differential misclassification. Due to substantial correlation across chemical exposure subgroups, however, the authors chose to combine organic solvents with alkylphenolic compounds as one exposure group, and another separate group containing phthalates, benzophenones, parabens, and siloxanes. Few participants ($n = <5$) were exposed to polychloride organic compounds, bisphenol A and flame retardants and thus precluded further examination of these compounds.

Overall, this study examined four broad EDC exposure categories—pesticides; PAHs; alkylphenolic compounds with organic solvents; and phthalates, benzophenones, parabens and/or siloxanes—across 537 cases with CAKUT, 371 cases with hypospadias and 5602 control children born between 1997 and 2013 in a comparable geographic area. The authors estimated adjusted odds ratios and 95% CIs using multivariable logistic regression comparing any occupational exposure to EDCs (possible or probable) with no (unlikely) exposure in cases and controls. As with most birth defects, the authors found sex-specific differences, with boys (70% of cases) more likely to be affected with urogenital anomalies compared with girls (30% of cases). Also, consistent with prior literature on congenital malformations, mothers tended to be younger and have a lower BMI, were less likely to take folic acid supplementation, more likely to report smoking and alcohol use during pregnancy, and were more likely to present fertility issues compared with controls. A major strength of this study—and unlike much of the prior occupational exposure research in this area—is that the authors had reliable covariate data through self-reported questionnaires that were relatively consistent across case–control status. Adjusting for many relevant confounding factors, including child sex, birth year, maternal age, BMI, education, alcohol, smoking and folic acid use, as well as fertility problems, reduced the potential for residual confounding. Of course, as with all case–control studies, concern over recall bias may have led cases of anomalies more likely to report exposures to other covariate risk factors than controls. Importantly, however, both types of chemical compounds and levels of exposure were ascertained comparably between cases and controls using the JEM rather than relying on self-reporting, limiting differential misclassification by case status. Besides recall bias, it should also be noted that this study did not consider the variability of exposure over time, the dose-response relationships related to levels of exposure, and the potential influence of co-exposure to other exposures not included in the JEM.

Equipped with this large, nested case–control design, the authors reported robust and consistent associations between 'any' exposure to organic solvents and/or alkylphenolic compounds (1.41, 95% CI: 1.01, 1.97) and phthalates, benzophenones, parabens and/or siloxanes (1.56, 95% CI: 1.06, 2.29) and all congenital anomalies of the kidney and urinary tract. Pesticides and PAHs—the other two exposure groups examined in this study—were not associated with CAKUT. Perhaps most saliently, this study was able to more deeply examine subgroups of CAKUT associated with occupational exposure to EDCs. Here, they found that exposure to any phthalates, benzophenones, parabens and/or siloxanes was primarily associated with anomalies specific to the urinary collecting system (1.62, 95% CI: 1.03, 2.54) or combinations of CAKUT (2.90, 95% CI: 1.09, 7.71), but not to other types of urinary defects nor defects of the kidney. Further analysis revealed fairly pronounced sex-specific effects with boys prenatally exposed to any phthalates, benzophenones, parabens or siloxanes being at risk of defects of the urinary collecting system (1.85, 95% CI: 1.06, 3.23) but not girls (1.34, 95% CI: 0.60, 2.99). However, imprecision due to smaller sample size (girls, $n = 160$ cases, boys, $n = 370$) may have precluded a firmer determination based on significance and the authors did not conduct any tests for effect measure modification or interaction. In contrast, girls were at higher risk of CAKUT in relation to prenatal exposure to organic solvents and/or alkylphenolic compounds (1.87, 95% CI: 1.11, 3.14) compared with boys (1.20, 95% CI: 0.77, 1.85). These findings, while imprecise, suggest chemical-specific effects that may be driven by different pathways and mechanisms across sexes that involve early fetal programming at the time of sexual differentiation, which occurs very close to the timing of urinary tract development.

Hypospadias is a complex genital anomaly affecting male births characterized by abnormal positioning of the urethral opening. Severity can range from mild distortions of location close to the tip of the penis to more marked abnormalities with the urethral anatomical opening at the base of the penis, scrotum or perineum. Almost all types require surgical intervention and the long-term clinical sequelae can include urinary and sexual dysfunction and infertility. While the authors reported an absence of an association between any EDC group examined and hypospadias (1.26, 95% CI: 0.95, 1.65), a more critical interpretation of the study findings suggests that PAHs (1.37, 95% CI: 0.91, 2.07) and phthalates, benzophenones, parabens and/or siloxanes (1.21, 95%

Figure 1. Prioritized occupations and their exposure to endocrine disrupting chemicals for preconception and prenatal primary, secondary and tertiary workplace prevention strategies.

CI: 0.73, 2.01) may be associated with a higher risk of hypospadias compared to all controls (i.e. all unexposed boys and girls). When restricting the control group to males only—and one can argue this is the more appropriate comparison group given that only boys are at risk of the outcome—the adjusted odds ratios increase slightly to 1.42 (95% CI: 0.93, 2.16) and 1.26 (95% CI: 0.75, 2.11) for PAHs and phthalates, benzophenones, parabens and/or siloxanes, respectively.

In utero sexual differentiation and urogenital track formation begin—almost simultaneously—very early in pregnancy, around the 4th gestational week, and continue until the 15th week (Rehman and Ahmed, 2021). For the vast majority of working women, pregnancy is detected only after the 5th or 6th gestational week. We also know that socioeconomically disadvantaged women tend to have important delays in pregnancy detection and first access to prenatal care. In this study, women exposed to organic solvents and/or aklylphenolic compounds worked in occupations related to the agricultural sector and as laboratory technicians. Women exposed to phthalates, benzophenones, parabens and/or siloxanes were mostly employed as cleaners, hairdressers and cosmetologists or beauticians. Indeed, these occupations are consistent with most previous studies that have identified a common core of maternal occupations with significant implications for EDC exposures on reproduction (Vrijheid *et al.*, 2003; Ormond *et al.*, 2009; Morales-Suárez-Varela *et al.*, 2011; Kalfa *et al.*, 2015; Spinder *et al.*, 2021). Consequently, these job areas should be prioritized and targeted for workplace policy action and prevention strategies that begin in the preconception period for both members of the couple and continue throughout gestation and the postnatal period (see Fig. 1).

Mechanistic data are often based on toxicological studies testing high exposure doses of isolated chemicals/metabolites. Nevertheless, phthalates, phenols and parabens are known reproductive and developmental toxicants that may trigger biological responses at environmentally relevant concentrations (You and Song, 2021). Moreover, these EDCs often co-occur and behave as mixtures leading to additive, and in some cases synergistic, effects (Martin *et al.*, 2021). Although exact mechanisms for male urogenital malformations are not fully understood, a recent adverse outcome pathway network supports the biological plausibility of convergence between mixtures of phthalates, pesticides, phenols and pharmaceuticals that include sequential key events such as altered steroidogenesis, decreased androgen levels, altered gene expression and protein synthesis in androgen-dependent tissues, and disturbed balance between apoptosis and cell proliferation, which may finally lead to urogenital malformations (Kortenkamp, 2020). Notably, occupational exposure often leads to much higher and sustained exposure concentrations compared to general population settings, also resulting in a mixture of similar or diverse chemical families (cosmetics, plasticizers, organic solvents, pesticides, heavy metals, disinfectants, etc.).

Jobs where personal care products and cleaning solutions are in high use, such as beauty salon workers and cleaners, present a risky environment for preconception and pregnancy. Women (and men) in these occupations constitute a vulnerable population all too often forgotten in workplace health. Considering the burden of disease associated with urogenital malformations and other birth defects, improved workplace safety policies are needed to prevent exposure to women and couples trying to conceive or those already pregnant. One of the major challenges, however, remains the difficulty in motivating employers and corporations to take workplace reproductive health and safety seriously.

Sincere workplace prevention efforts, however, would go much further and include primary, secondary, and tertiary approaches that minimize risk beyond birth defects (Rose, 1985; Roman, 1990; Rose *et al.*, 2008). The socioeconomic burden of population exposure to EDCs is considerable and probably much higher than initially estimated at hundreds of billions of US dollars annually in both Europe and the USA (Attina *et al.*, 2016). Prevention is—and will always be—the most cost-effective environmental health strategy. Prevention always pays off and gains will be maximized if protection starts as early in the reproductive life cycle as possible. Preconception—the origin of new human life—must be consciously protected. Even in the face of scientific uncertainty, invoking the precautionary principle is simply common sense. In the presence of such evidence, the moral imperative should be the protection of children's health and the preservation of future generations.

Authors' roles

C.M. conceptualized and drafted the commentary. Y.Z. researched and cited evidence. Y.Z., Y.S. and Y.W. reviewed, edited and provided critical interpretation. V.M. edited and provided deep insights and interpretation and additional context and text. All authors approved the final copy.

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Conflict of interest

The authors have no conflicts of interest.

References

Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon J-P, Myers JP, DiGangi J, Zoeller RT, Trasande L. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes Endocrinol* 2016;**4**: 996–1003.

Bakker MK, Bergman JEH, Fleurke-Rozema H, Streefland E, Gracchi V, Bilardo CM, De Walle HEK. Prenatal diagnosis of urinary tract anomalies, a cohort study in the Northern Netherlands. *Prenat Diagn* 2018;**38**:130–134.

Bergman Å, Heindel JJ, Jobling S, Kidd K, Zoeller TR; World Health Organisation and United Nations Environment Program. *State of the Science of Endocrine Disrupting Chemicals*. 2012.

Brouwers MM, van der Zanden LFM, de Gier RPE, Barten EJ, Zielhuis GA, Feitz WFJ, Roeleveld N. Hypospadias: risk factor patterns and different phenotypes. *BJU Int* 2009;**105**:254–262.

EUROCAT. *European Platform on Rare Disease Registration*. 2021. https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en (11 October 2021, date last accessed).

Jain S, Chen F. Developmental pathology of congenital kidney and urinary tract anomalies. *Clin Kidney J* 2018;**12**:382–399.

Kalfa N, Paris F, Philibert P, Orsini M, Broussous S, Fauconnet-Servant N, Audran F, Gaspari L, Lehors H, Haddad M *et al.* Is hypospadias associated with prenatal exposure to endocrine disruptors? A French Collaborative Controlled Study of a cohort of 300 consecutive children without genetic defect. *Eur Urol* 2015;**68**: 1023–1030.

Kortenkamp A. Which chemicals should be grouped together for mixture risk assessments of male reproductive disorders? *Mol Cell Endocrinol* 2020;**499**:110581.

Martin O, Scholze M, Ermler S, McPhie J, Bopp SK, Kienzler A, Parissis N, Kortenkamp A. Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. *Environ Int* 2021;**146**: 106206.

Morales-Suárez-Varela MM, Toft GV, Jensen MS, Ramlau-Hansen C, Kaerlev L, Thulstrup A-M, Llopis-González A, Olsen J, Bonde JP. Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: a study in the Danish National Birth Cohort Study. *Environ Health* 2011;**10**:3.

Ormond G, Nieuwenhuijsen MJ, Nelson P, Toledano MB, Iszatt N, Geneletti S, Elliott P. Endocrine disruptors in the workplace, hair spray, folate supplementation, and risk of hypospadias: case-control study. *Environ Health Perspect* 2009;**117**:303–307.

Rehman S, Ahmed D. *Embryology, Kidney, Bladder, and Ureter*. 2021. https://www.ncbi.nlm.nih.gov/books/NBK547747/ (10 October 2021, date last accessed).

Roman PM. *Alcohol Problem Intervention in the Workplace: Employee Assistance Programs and Strategic Alternatives*. United States: Greenwood Publishing Group; 1990.

Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985;**14**: 32–38.

Rose G, Khaw K-T, Marmot M. *Rose's Strategy of Preventive Medicine*. Oxford: Oxford University Press; 2008. Retrieved 19 January 2011.

Spinder N, Bergman JEH, van Tongeren M, Boezen HM, Kromhout H, de Walle HEK. Maternal occupational exposure to endocrine disrupting chemicals and urogenital anomalies in the offspring. *Hum Reprod* 2022;**1**:142–151.

Van Tongeren M, Nieuwenhuijsen MJ, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B. A job-exposure matrix for potential endocrine-disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias. *Ann Occup Hyg* 2002;**46**:465–477.

Vrijheid M, Armstrong B, Dolk H, van Tongeren M, Botting B. Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. *Occup Environ Med* 2003; **60**:543–550.

You HH, Song G. Review of endocrine disruptors on male and female reproductive systems. *Comp Biochem Physiol C Toxicol Pharmacol* 2021;**244**:109002.