**Environmental exposures and their association with adverse pregnancy and developmental outcomes**

Jessica Trowbridge[[1]](#footnote-1), Rashmi Joglekar[[2]](#footnote-2), Tracey J Woodruff[[3]](#footnote-3)

**Pregnancy is a particularly vulnerable** **period of human development, rendering the mother and the developing fetus highly susceptible to the adverse effects of toxic chemical exposures.** For the mother, pregnancy is a time of rapid biological changes in the body to accommodate the developing fetus. These changes include increased blood production and volume, breast enlargement in preparation of breast feeding, and altered sugar processing and metabolomics, among many other physiological changes. Fetal development is also a period of rapid biological change, where the rate of cellular growth can’t keep up with cellular repair from environmental insults. (Barr, Bishop and Needham, 2007). Toxic chemicals can cross the placenta, and in some cases, concentrate in the fetus (e.g. mercury, PFAS) (Barr, Bishop and Needham, 2007; Trowbridge, Abrahamsson, *et al.*, 2023). As a result, the mother and developing fetus are highly susceptible to environmental chemical exposures, exacerbating the risk of pregnancy complications as well as irreversible developmental outcomes for the child (Barr, Bishop and Needham, 2007).

Exposures to environmental chemicals are widespread in the U.S. and globally, with studies of a nationally representative sample of the US population finding at least 43 different chemicals in everyone tested (Woodruff, Zota and Schwartz, 2011; Zota *et al.*, 2013; Trowbridge, Goin, *et al.*, 2023). Multiple adverse pregnancy outcomes, including gestational diabetes and other pregnancy related complications, are found to be associated with exposures to flame retardants (Zota *et al.*, 2013; Gao *et al.*, 2016), phthalates and other plasticizers (Welch *et al.*, 2022), perfluoroalkyl substances (PFAS) (Szilagyi, Avula and Fry, 2020; Abrahamsson *et al.*, 2022; Trowbridge, Abrahamsson, *et al.*, 2023), and other industrial chemicals (Woodruff, Zota and Schwartz, 2011; Trowbridge, Abrahamsson, *et al.*, 2023). These exposures have also been associated with adverse developmental outcomes, such as neurodevelopmental harm, including autism and ADHD, (Bennett *et al.*, 2016; Maenner, 2021; Payne-Sturges *et al.*, 2023), metabolic disorders (US EPA, 2015b), early pubertal onset (Biro, Greenspan and Galvez, 2012; Brix *et al.*, 2019; Leone and Brown, 2020) and certain childhood cancers (US EPA, 2015a).

Complications during pregnancy can also increase the risk for developing health complications later in life for both the mother and the child. For example, women with gestational diabetes are at increased risk for preeclampsia, and hypertensive disorders during pregnancy (ACOG, 2020), and women who had gestational diabetes are at increased risk for Type 2 diabetes (Noctor and Dunne, 2015) and as well as hypertension later in life (Sheiner, 2020). Similarly, children born to mothers who had gestational diabetes are at higher risk of obesity, diabetes, and cardiovascular disease themselves (Sheiner, 2020).

The link between exposure to environmental chemicals and adverse maternal and child health outcomes has been widely recognized by healthcare professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), and the International Federation of Gynecology and Obstetrics (FIGO). Statements by ACOG, FIGO, and the Project TENDR Consensus Statement, recognize that pregnancy is a particularly vulnerable period of development and emphasize the need to reduce prenatal exposure to toxic environmental agents (Bennett *et al.*, 2016, 2016; ACOG, 2021). These statements highlight the importance of considering the potential risks posed by environmental chemicals and advocate for policies that protect the health of pregnant women and their children from these harmful exposures.

**The rates of chronic health conditions in the mother and child have been increasing** **over the past several decades** **and are linked to health disparities**. Multiple studies have described these increasing trends occurring in parallel with increasing exposure to chemicals from petrochemical and plastics production (Woodruff, 2024). Because these trends have been observed over a relatively short period of time, they cannot be explained by genetic changes alone. Therefore, the adverse health impacts of toxic chemical exposures is a critical area of research (O’Rourke and Connolly, 2003; Di Renzo *et al.*, 2015; Giudice, 2021; Woodruff, 2024). Moreover, these adverse effects are further exacerbated by the disproportionate exposures and excess susceptibility. Environmental justice research sheds light on the disparities in exposure to toxic chemicals among susceptible populations. In the U.S., people living in communities where clusters of hazardous industrial and commercial facilities have been cited nearby are often people of color and low-income individuals, facing multiple threats from chemical releases and non-chemical stressors, like psychosocial stress due to limited access to healthy food and health care (Morello-Frosch and Shenassa, 2006; Solomon *et al.*, 2016; White, 2018; Giudice, 2021; Payne-Sturges, Gee and Cory, 2022; Woodruff, 2024).

Furthermore, race and ethnicity alone can contribute to disproportionate exposures to toxic chemicals from consumer products, adding to the toxic burden experienced particularly by women of color. Studies have found that products specifically marketed to women of color contain higher levels of toxic chemicals (Kobrosly *et al.*, 2012; Branch *et al.*, 2015). For example a study of a nationally representative sample of the U.S. population found that women with lower education and lower household incomes had higher phthalate metabolite concentrations compared to women with higher socioeconomic status (Kobrosly *et al.*, 2012). Since phthalate exposure is linked with various adverse pregnancy and reproductive health outcomes, this exposure disparity translates to health disparities (Zota and VanNoy, 2021). In addition to consumer products, exposure disparities by race and ethnicity or socioeconomic status are also seen for ambient exposures like air pollution and other environmental sources (Brody *et al.*, 2009; Alifa *et al.*, 2023).

Individuals are more susceptible to harm from chemical exposures in part due to extrinsic factors, such as socioeconomic status and experiencing psychosocial stress from racial injustice (Morello-Frosch and Shenassa, 2006; Eick *et al.*, 2022; Beard *et al.*, 2024). These factors play a crucial role in determining the health outcomes of pregnant women and their children. A 2023 scoping review identified 218 studies that evaluated the interactions between exposure to neurotoxicants and sociodemographic or socioeconomic factors, and found a disproportionate impact on low-income and racial and ethnic minority children (Payne-Sturges, Gee and Cory, 2022). These findings highlight the need for targeted interventions and regulations to eliminate exposures and address systemic inequities. In addition they highlight the need for comprehensive chemical risk assessments, ones that account for real-world chemical exposures and the social susceptibility factors that lead to disproportionate health impacts in vulnerable populations.

**International and federal agencies need to consider multiple chemical exposures and vulnerability factors in their evaluation and regulation of toxic chemicals to protect public health.** Unfortunately, in the United States, federal agencies that regulate toxic chemicals often fail to adequately consider exposure disparities or increased susceptibility to harm in their chemical risk assessment and risk management rules, further perpetuating exposure and health disparities (Koman *et al.*, 2018; Varshavsky *et al.*, 2019, 2023).

However, tools and methods exist to account for social and gender vulnerability factors that can be applied to ensure that the standards and regulations set by agencies protect even the most vulnerable populations from the harms of toxic chemical exposures (Varshavsky *et al.*, 2023) Scientists, clinicians, and public health officials have derived and advocated methods to account for health disparities in chemical risk assessment to ultimately improve decision making. Of particular note, the Science Action Network (SAN) of UCSF’s Program on Reproductive Health and the Environment has put forth five key recommendations for using the best available science in hazard and risk assessment, emphasizing the need to reflect real-world risks and offer stronger public health protections (Woodruff *et al.*, 2023). These recommendations aim to better protect public health by accounting for human variability and susceptibility (Varshavsky *et al.*, 2023), adopting probabilistic methods to address uncertainty (Nielsen *et al.*, 2023), improving exposure assessment methods (Vandenberg *et al.*, 2023), and considering chemical classes in exposure assessment (Maffini *et al.*, 2023).

In conclusion, the link between environmental chemicals and pregnancy outcomes is a critical issue that requires targeted interventions. Pregnant women, and accordingly the developing fetus, especially those experiencing multiple extrinsic susceptibility factors, are at a higher risk of adverse effects from exposure to toxic chemicals. It is essential to consider susceptibility factors and address environmental justice concerns to ensure the health and well-being of both mothers and their children. By implementing evidence-based recommendations and improving the integration of environmental justice research, we can work towards achieving health equity and protecting the most vulnerable populations. Below we highlight additional key papers and resources that demonstrate the link between exposures to toxic chemicals and susceptibility factors that can exacerbate the adverse health outcomes experienced by pregnant women and children.

**Other key papers:**

**Gaps in environmental justice relating to exposure and gender**

Casey, J. A., Daouda, M., Babadi, R. S., Do, V., Flores, N. M., Berzansky, I., González, D. J. X., Van Horne, Y. O., & James-Todd, T. (2023). Methods in Public Health Environmental Justice Research: A Scoping Review from 2018 to 2021. *Current environmental health reports*, *10*(3), 312–336. https://doi.org/10.1007/s40572-023-00406-7

This recent scoping review by Casey and colleagues’ sheds light on trends and gaps in environmental justice research methods and provides a range of recommendations for future research. Of the 402 identified articles published between January 2018 and December 2021, 50% described a theoretical EJ framework and 60% evaluated questions relating to socioeconomic status or race/ethnicity. None of the EJ studies that were identified considered gender or sexual minorities. Of the exposure studies, the most common exposure was air pollution (40%), while many personal exposure studies evaluated chemicals (35%). Main effect regression modeling was commonly used for exposure-only EJ analyses (50%) and the most common method in epidemiologic studies was effect modification (58%). Few studies used solution-oriented methods, including intervention-based studies and community-based participatory research. Recommendations proposed by the authors include:

1. Recognize that EJ, as an evolving field, confronts diverse and intersecting structural problems, which requires the careful contextualized application of the best available theory and methods.
2. Make EJ questions central in environmental health studies and use appropriate methods to answer them.
3. Limit the mischaracterization, misspecification, and/or omission of nuanced social constructs such as race, ethnicity, sex, and gender.
4. Obtain expertise from sociology and other fields in the design and implementation of EJ research.
5. Recognize the importance of community-engaged, community-based participatory, and community-relevant research.
6. Utilize more solution-oriented study design and statistical methods to address environmental justice, given the underlying goal of achieving health equity.
7. Rigorously design and evaluate interventions with a focus on health equity.
8. Expand the scope of EJ research to include Global South populations.

**Occupational toxic chemical exposures among women are rarely evaluated:**

Trowbridge, J., Gerona, R. R., Lin, T., Rudel, R. A., Bessonneau, V., Buren, H., & Morello-Frosch, R. (2020). Exposure to Perfluoroalkyl Substances in a Cohort of Women Firefighters and Office Workers in San Francisco. Environmental Science & Technology, 54(6), 3363–3374. <https://doi.org/10.1021/acs.est.9b05490>

Women of reproductive age are also women who work, and yet studies evaluating occupational exposures to toxic chemicals are often limited to studies in men. This remains true for high exposure and high-risk jobs like firefighting. This study of women firefighters in San Francisco, California, United States, measured multiple perfluoroalkyl substances (PFAS) in the participants samples. Levels were higher in women firefighters compared to office worker controls and were similar to levels found in male firefighters in a previous study. PFAS are chemicals linked to breast cancer as well as to adverse reproductive outcomes in both human epidemiology and animal studies.

Trowbridge, J., Gerona, R., McMaster, M., Ona, K., Clarity, C., Bessonneau, V., Rudel, R., Buren, H., & Morello-Frosch, R. (2021). Organophosphate and Organohalogen Flame-Retardant Exposure and Thyroid Hormone Disruption in a Cross-Sectional Study of Female Firefighters and Office Workers from San Francisco. Environmental Science & Technology. <https://doi.org/10.1021/acs.est.1c05140>

This paper in the same San Francisco cohort of women firefighters found higher levels of flame-retardant chemicals in women firefighters compared to non-firefighter controls. These flame retardants were found to have a negative impact on thyroid hormone in the women firefighters. Flame retardants exposure and thyroid hormone disruption are associated with increased breast cancer risk and adverse pregnancy and birth outcomes, including poorer child neurodevelopment in children exposed in-utero.

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1. Jessica Trowbridge, PhD MPH; Associate Research Scientist, Science, Policy and Engagement, PRHE [↑](#footnote-ref-1)
2. Rashmi Joglekar, PhD; Associate Director of Science, Policy and Engagement, PRHE [↑](#footnote-ref-2)
3. Tracey J Woodruff, PhD, MPH; Director of and Alison S. Carlson Endowed Professor for PRHE; Professor in the UCSF Department of Obstetrics, Gynecology and Reproductive Sciences and the Philip R. Lee Institute for Health Policy Studies; Director of the EaRTH Center

   Program on Reproductive Health and the Environment, University of California, San Francisco [↑](#footnote-ref-3)