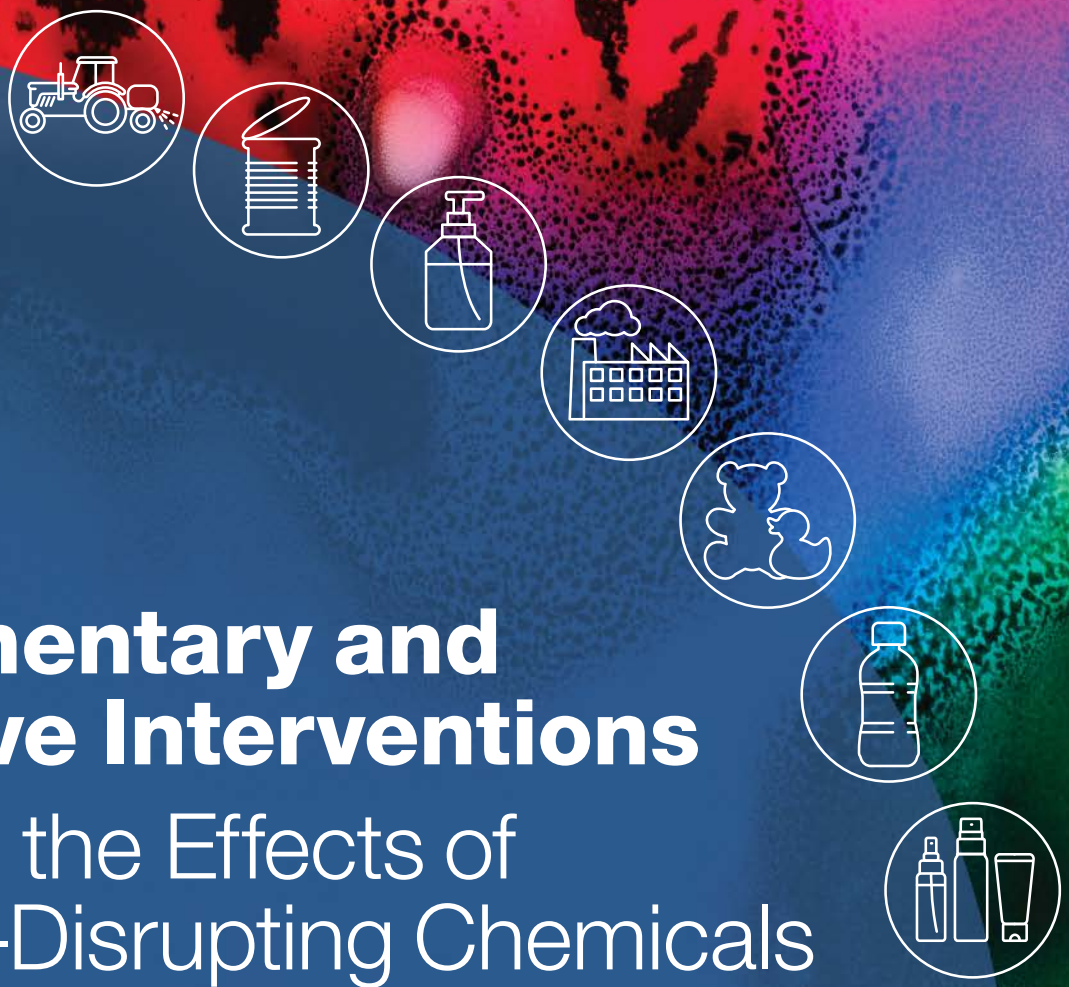

Complementary and Integrative Interventions

To Mitigate the Effects of Endocrine-Disrupting Chemicals

Executive Summary

National Center for Complementary and Integrative Health

Complementary and Integrative Interventions To Prevent and Mitigate the Effects of Endocrine-Disrupting Chemicals

June 10–11, 2024

Executive Summary

Endocrine-disrupting chemicals (EDCs) are natural or human-made chemicals that mimic, block, or interfere with the endocrine system. They are associated with a wide array of health issues across the lifespan. EDCs are found in everyday products and because of their ubiquitous presence it is virtually impossible to completely avoid them or remove them from the environment. For example, polyfluoroalkyl substances (PFAS) have been consistently detected in blood samples in the National Health and Nutrition Examination Survey (NHANES) database.[1,2,3] Even those chemicals that have been banned for years, such as dichloro-diphenyl-trichloroethane (DDT), live on in our bodies and the environment. According to the Endocrine Society, there are nearly 85,000 human-made chemicals in the world, and 1,000 or more of those could be EDCs. Current estimates of EDC disease burden and costs focus on fewer than 5 percent of EDCs, leading to a severe underestimate of total costs. Even so, the health effects from PFAS and perfluorooctane sulfonate (PFOS) in the United States were estimated to be $62.6 billion in 2018.[4]

The National Center for Complementary and Integrative Health (NCCIH) partnered with the National Institute of Environmental Health Sciences (NIEHS) and the National Institutes of Health (NIH) Office of Dietary Supplements and Office of Disease Prevention to hold a 2-day workshop to stimulate discussion about and interest in investigating ways to reduce and mitigate the effects of EDCs in those already exposed, and to prevent future exposures. Speakers from scientific, clinical, advocacy, and community-based organizations presented their research findings, practices, and perspectives on this complex issue, which requires a whole-person mindset and a multidisciplinary research strategy to improve health. This was the first meeting to explore emerging and preliminary data and to highlight a growing field of science. Attendees recommended future research directions.

Health Effects of Exposures

Endocrine disorders associated with EDCs include obesity, type 2 diabetes mellitus, cardiovascular disease, reproductive problems (e.g., reduced fertility, reproductive tract abnormalities), early puberty in girls, neurological and behavioral problems, thyroid disease, impaired immune function, and hormone-sensitive cancers.

- Numerous studies have documented the effects of PFAS on hormones that regulate cholesterol and glucose metabolism and inflammatory signaling molecules. These exposures have been linked to elevated risk of hypertension, and skin, prostate, brain, esophageal, and lung cancer.[5,6] Preliminary evidence suggests PFAS exposure accelerates reproductive aging, perhaps through epigenetic effects.[7,8]
- Phthalates are pervasive because they are used as plasticizers or as scent stabilizers. All persons in the NHANES database show detectable levels of at least one phthalate metabolite, but typically many more.[9] Phthalate exposure in pregnancy has been associated with adverse pregnancy and birth outcomes, neurodevelopmental problems and obesity in children, and impaired maternal health in pregnancy and postpartum.[10]

- Parabens were measurable in 100 percent of reproductive-aged women in NHANES. They too have been associated with adverse pregnancy and birth outcomes, especially in female newborns.[11] There is evidence to suggest that parabens act by inducing inflammation and oxidative stress.
- Perfluorinated compounds (PFCs) accumulate in human blood and tissues, have long elimination half-lives, and are increasingly linked to assorted health concerns.[12]
- Exposures to phenols, phthalates, and parabens have been associated with chronic inflammation, which may play a role in the development of metabolic syndrome.
- Serum concentrations of low-density lipoprotein (LDL) cholesterol have been positively correlated with exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) in humans.[13] Higher LDL levels are associated with increased risk of cardiovascular disease and mortality.
- Polychlorinated biphenyls (PCBs) are additives in oils, electrical equipment, and hydraulic machinery. They have been found at high levels in urine and sweat and have adverse effects on the immune, reproductive, nervous, and endocrine systems.[14,15,16]
- There is growing evidence that developmental exposure to bisphenol A (BPA) and ethinyl estradiol leads to long-term adverse effects on the gut microbiome.[17] The gut microbiome has been linked to diseases that differentially affect males and female, for example, autoimmune, neurological, metabolic, and reproductive disorders. The organophosphate flame retardants (OPFRs) consist of many compounds that are most commonly ingested in dust and interact with either an estrogen receptor alone or with a peroxisome proliferator-activated receptor. These receptors are critical regulators of energy homeostasis and communicate with the brain to regulate feeding behaviors and activity levels.
- Ethyl, methyl, and propylparaben and PFAS are found in personal care and beauty products, which are weakly regulated. Companies can often add them to products with little oversight. This means some of these chemicals are used in products despite years of research that suggest they are linked to numerous health effects.
- Research evaluating associations between PFAS, phenols, and parabens and self-reported previous cancer diagnoses in an NHANES cohort found that people who developed those cancers have significantly higher levels of these chemicals in their bodies.[18] However, causal associations have not yet been established.
- EDCs are common in drinking water, seafood, and grains. Arsenic, mercury, lead, and other heavy metals may be linked with endocrine-disrupting activity including increased reproductive aging.[19,20]

High-Risk Populations

While all living organisms are at risk of exposure to EDCs, certain populations face greater risks.

- Numerous studies in the past 20 years have documented high levels of BPA, methylparaben, and propylparaben in human urine, but at significantly higher levels among non-Hispanic Black and Mexican American populations compared to non-Hispanic white populations.[21,22,23] Disproportionate exposures to EDCs are widely documented in racial and ethnic minorities and low-income subpopulations. Factors driving the disproportionate exposure to several EDCs include differences in food consumption, usage of consumer products, as well as built environmental conditions driven at least in part by socioeconomic status.

- Firefighters encounter extreme environmental chemical exposures, some of which are EDCs, in their work, including polycyclic aromatic hydrocarbons, volatile organic compounds (VOCs) and semi-volatile organic compounds, metals, halogenated flame retardants, PFAS, and particulates. Acute exposures to all chemicals, including EDCs, may present as much a risk as chronic exposures.[24] These exposures have been linked to elevated risk of hypertension, and skin, prostate, brain, esophageal, and lung cancer.[25] Children of firefighters are more likely than children of non-firefighters to have congenital cardiovascular anomalies, cleft lip and/or palate, and transverse limb deficiency.[26] Female firefighters experience high rates of preterm delivery, high rates of all adverse pregnancy and birth outcomes, and reduced ovarian reserve.[27,28]
- Farmworkers are exposed to insecticides, fungicides, rodenticides, and other chemicals by breathing them in, ingesting them, and absorbing them through the skin and eyes. Exposures are in high concentrations and involve multiple chemicals, including EDCs. Chronic exposure occurs over longer periods of time and depending on the type of pesticide can affect health in a variety of ways: different types of cancer, birth defects and premature births, reproductive, respiratory, immune, neurological and learning problems, organ damage, and disruption of the endocrine system. Contact with pesticides can be especially harmful during pregnancy.
- There are more than 700,000 hairdressers in the United States. Studies of indoor air found VOC median concentrations significantly higher in hair salons versus office spaces.[29] Further, particulate matter concentrations are higher in salons serving Latina/Black clientele versus all Black clientele. Higher VOC biomarker concentrations in urine were also found in hairdressers versus office workers and were higher among hairdressers serving Black and Latina clientele. Monoethyl phthalate (MEP), found in many personal care products, is found at levels 2 to 41 times higher in the urine of hairdressers than in women in the general population.[30] Prenatal exposure to MEP is linked to preterm birth, decreased anogenital distance in male infants, and pregnancy complications.
- The Black and Latino populations use more personal care and beauty products across multiple categories, for example, hair products, skin lightener, cosmetics, and fragrances. Women of color have a higher body burden of chemicals found in personal care products and cosmetics compared to non-Hispanic White women.[31]
- Military service members are or have been exposed to numerous toxins, and toxic environments, such as Agent Orange, radiation, contaminated water, burn pits, oil fires, and PFAS. Toxicant exposure may be related to deployment itself (e.g., chemical warfare agents, depleted uranium, hexavalent chromium) or results from exposure to pesticides, combustion products and fumes, and solvents. Ascertaining how exposures affect health is challenging.
- Pregnancy is a high-risk time for exposures. Epidemiological evidence reveals that phenol and phthalate exposure is associated with lower probability of in vitro fertilization (IVF) success, longer time to pregnancy, and higher risk of autism in children for women with low or no folate consumption preconception or during pregnancy.

Preliminary Findings on Interventions To Prevent, Mitigate, and Reduce the Effects of Exposures

Preventing exposure is the optimal method to prevent adverse health effects. Such measures include regulation and enforcement to ban, for example, PFAS use, area-level interventions to remove existing contamination to prevent future exposure, or individual-level actions to reduce exposure. Reductions in body burden through individual-level clinical interventions can be a strategy for those with high exposures and a preventive measure for all. Several studies have demonstrated what can be done by individuals to reduce or mitigate the effects of EDCs on current and future generations. These include:

making lifestyle choices that include more dietary plants and fiber, physical activity, and sufficient sleep; supporting a healthy and diverse gut microbiome; correcting vitamin deficiencies; boosting the use of antioxidants; managing stress; and building physical and emotional resiliency. These steps might be especially effective in populations experiencing health disparities. Research has found that avoidance of products containing certain chemicals may reduce EDC levels in the body. At the population level, social and policy approaches are needed to eliminate or reduce the release of more EDCs into the environment. Preliminary studies indicate the potential of the following interventions:

- Early data suggest that anti-inflammatory diets combined with healthy sleep and activity patterns may reduce EDC uptake by the body and cardiometabolic risk.
- Lipid-lowering via lifestyle modification may alter circulating levels and accumulation of PFAS in the body.[32]
- Plasma and blood donations by firefighters result in greater reductions in serum PFAS levels than observation alone over a 12-month period.[33]
- Folate shows promise as a potential mitigation measure for EDCs including phenols, phthalates, and PFAS.[34]
- Data suggest that BPA likely bioaccumulates to some degree in humans, is retained in tissues (likely adipose), and is excreted in sweat. Induced sweating may be one clinical intervention for eliminating some toxic elements.[35]
- New insights into the inner workings of the gut microbiota–brain axis provide mechanistic insight. This in turn expands the potential for new early diagnostic and treatment approaches for neurobehavioral disorders originating from EDC-induced gut dysbiosis, such as prebiotic, probiotic, and/or post-biotic supplementation. The gut microbiome is highly modifiable by diet and microbial-based therapeutics. Probiotics, whole foods, and fermented foods can be incorporated into the diet with few negative effects.[36] These low-cost interventions can be sustained long-term and may counter the effects of continuous EDC exposure.
- Indoor air filtration is a promising strategy for reducing chemical exposures. One study found it can reduce air levels of six PFAS as well as 71 other chemicals, effectively decreasing exposure to toxic components of the exposome such as respiratory pathogens, particulates (e.g., wildfire smoke), and chemical pollutants.[37]
- Polyphenolic compounds are abundant in plants and are readily found in fruit and vegetables. In particular, grape polyphenols may improve metabolic homeostasis by altering gut microbiota and by changing microbial- or host-derived metabolites, largely due to their poor absorption.[38]
- The Taking Stock Study is being tested to determine if it can advance beauty justice among Black and Latina women by achieving and maintaining natural hair styles and avoiding chemicals linked to cancer.
- Vitamins and EDCs often compete for access to receptors. As such, high EDC levels may prevent vitamin uptake and worsen vitamin deficiencies. Observational studies confirm that the effects of some EDCs worsen if certain vitamin levels are low. Conversely, supplementing vitamins may reduce uptake of some EDCs by competing for access to cellular receptors.
- The ability of fish oil to reduce oxidative stress associated with phthalate exposure during pregnancy may be a promising approach to mitigating the effects of this EDC
- Mindfulness training in the context of EDC exposures might also focus on self-regulation (emotion regulation, attention control, self-awareness). Attention control at the individual and family level is one of many strategies to prevent and treat EDC exposure. Attention control can inform decisions about, for example, diet, drinking water, use of food containers, or purchase of products with plastics.

- Stress may increase the effects of PFAS exposure. If mindfulness can be shown to engage in the stress pathways it has the potential to reduce the effects of stress on the health effects of exposures.

Despite progress in mitigation strategies, key gaps remain in care and there is insufficient attention in clinical practice guidelines to the links between exposure and disease, and no mention of individual-level interventions to address adverse impacts of EDCs.[39] The Veterans Administration currently uses a model that includes lifestyle changes and appropriate clinical care to improve the health and well-being of those exposed to EDCs. Clinicians, patients, and consumers need evidence-based guidance about EDC testing and mitigation strategies to choose what is useful and feasible. Education campaigns are needed to inform consumers and patients about products that contain EDCs so they can act individually to avoid these chemicals. Top-down strategies are needed, including international guidelines, policy and regulation, and advancements in EDC research. For example, following a healthy diet does not guarantee reduced exposure to many EDCs due to widespread contamination across the food supply and diverse exposure sources. Further, some healthy diets are not sustainable in the real-world environment. Changes in agricultural and food production practices and removal of EDCs in household products are the most effective ways to reduce contamination and improve health. Community-based advocacy has been a potent approach to seeking change, albeit slow.

Research Needs

Despite progress in recent years, several challenges remain.

- Although there are thousands of EDCs in the environment, few have been sufficiently characterized, which complicates targeting them for interventions.
- Strategies are needed to prioritize populations, diseases, or communities on which to focus research efforts; for example, those with occupational exposures, childbearing women, or peripubertal children.
- Studies with more vulnerable populations such as children, pregnant women, or the medically frail must be conducted ethically and safely but are often harder to get approved.
- Importantly, how will clinically meaningful improvement following an intervention be measured and defined?
- Another challenge is translating animal models to human trials. The right animal model or multiple animal models can provide critical information about the mechanisms and pathways used by EDCs.
- Randomized controlled studies of interventions to mitigate the effects of EDCs are rare and RCTs on the most pervasive chemicals should be prioritized, moving forward.
- Mechanistic work has typically focused on one chemical, which poses risks to rapid translation. There cannot be 80,000 distinct solutions for 80,000 chemicals. Rather, interventions are needed that target multiple EDCs and mixed exposures to more expediently improve multiple health outcomes.
- Environmental justice and exposure disparities require efforts to more holistically integrate environmental exposures into the social and structural determinants of health and more broadly into assessments of the drivers of health disparities and their remedies.

Research should focus not only on prevention and harms but also resilience; that is, how can we strengthen the whole system by finding the protective pathways and intervening to prevent the progression of disease? Furthermore, at what critical lifestage will a given intervention be most

impactful? Research findings need to be translated into interventions and lifestyle choices that are both accessible and practical, especially in resource-limited areas.

Finally, healing and remediation can and should begin before all the evidence is available. Using baseline data, the effects of obvious interventions can be implemented and tracked over time. We have enough information on some approaches to prevent or mitigate the effects of many chemicals (e.g., phthalates) to act. It will be important to disseminate both positive and null research results.

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