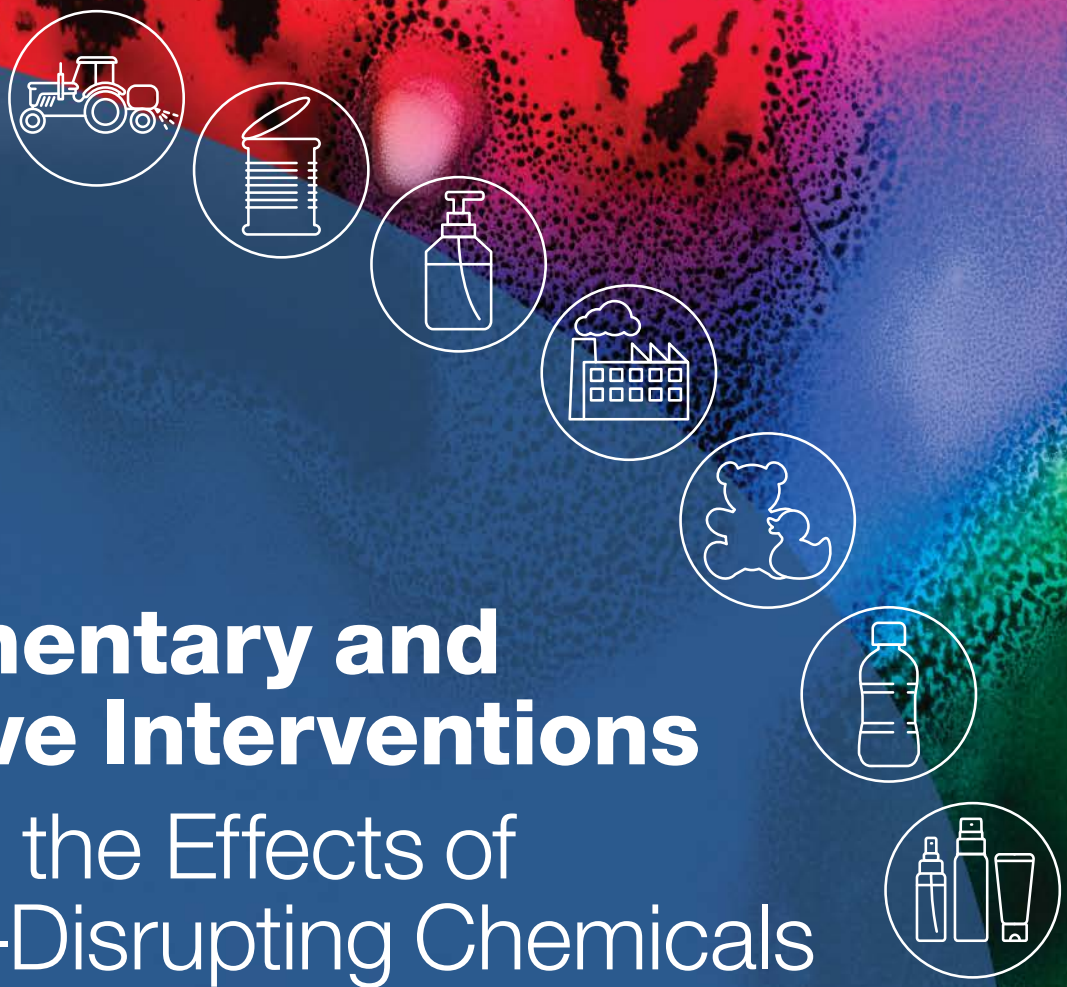

Complementary and Integrative Interventions

To Mitigate the Effects of Endocrine-Disrupting Chemicals

Full Meeting 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

Overview

Endocrine-disrupting chemicals (EDCs) are natural or human-made chemicals that mimic, block, or interfere with the endocrine system. These chemicals are associated with a wide array of health issues across the lifespan. They are found in everyday products, including cosmetics, food and beverage packaging, toys, carpets and furniture, pesticides, electronics and building materials, textiles and clothing, and flame retardants. They have also been detected in many municipal water supplies and in soil and air. Because of their ubiquitous presence, EDCs cannot easily be completely avoided or removed from the environment. Even those that have been banned for years 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 considered EDCs.

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 health effects of EDCs 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.

Introduction to the Workshop

Sekai Chideya, M.D., M.P.H., NCCIH; Helene M. Langevin, M.D., NCCIH; Richard Woychik, Ph.D., NIEHS; Stefan Pasiakos, Ph.D., Office of Dietary Supplements (ODS)

NCCIH has introduced a whole person approach to mitigating the effects of EDCs by considering the biological, behavioral, social, and environmental factors that interact to affect metabolic, endocrine, cardiovascular, immune, and respiratory dysfunction, as well as oxidative stress and genetic/epigenetic effects. Because of the overwhelming complexity of thousands of chemicals and their effects on all biological systems, measures are needed at both the policy level to reduce and eliminate exposures and the individual level (steps within an individual's control) to counter the effects of EDCs on health. NIEHS has a longstanding interest in identifying the conditions linked to EDCs, dating back to the prescribing of diethylstilbestrol (DES), which has estrogenic properties and was prescribed to women with a history of miscarriage and other pregnancy complications before being banned. Over time, NIEHS-funded research has found that some EDCs are harmful even at low exposure and are especially adverse during sensitive time periods of life.

Setting the Stage: An Introduction to the EDC Landscape

Heather Patisaul, Ph.D., NIEHS

Toxicology is arguably the oldest human discipline. Natural remedies date back centuries as do ways to poison enemies with natural products (e.g., hemlock, nightshade, arsenic). Classic toxicity testing was developed to detect poisons. Ancient Chinese, Egyptian, Hindu, and Greek documents include recipes

for poisons, medicines, and antidotes. It was not until the 1900s that the term "hormone" was coined with subsequent studies focused on how they affect all the cells, tissues, and organs of the body. In the mid 20th century, the role of hormones in sex determination as well as sex differentiation was first documented. The use of dichloro-diphenyl-trichloroethane (DDT) as a synthetic insecticide in the 1940s led to multifaceted adverse effects on birds, reptiles, and other wildlife, acting as a potent neurotoxin and having estrogenic and anti-androgenic effects even at low doses. Rachel Carson's *Silent Spring* raised public awareness about the detrimental roles of DDT and other pesticides, leading to the creation of NIEHS and the banning of DDT in 1971.

In 1991, Theo Coburn, Peter Myers, and Coralie Clement introduced the term "EDC" to differentiate these chemicals from overt poisons because they specifically disrupt the endocrine system. Since that time, studies have shown that exposure of the developing fetus or neonate to environmental concentrations of certain synthetic chemicals can cause biochemical, physiological, morphological, and behavioral anomalies in all species. In 2012, the Endocrine Society defined EDCs as "An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."[1]

Endocrine disorders associated with EDCs include reproductive problems, reduced fertility, reproductive tract abnormalities, early puberty in girls, obesity, type 2 diabetes mellitus, cardiovascular disease, neurological and behavioral problems, thyroid disease, impaired immune function, and hormone-sensitive cancers.[2] Four principles have emerged that enhance understanding of the critical mechanisms of EDCs and provide strategies for taking action:

1. **The timing makes the poison.** This recognizes that disruption of organ development or differentiation can set the stage for disease risk later in life. Disease manifestation may not occur for years or decades. Further, life stages that are particularly vulnerable to EDCs are fetal, infancy and young child, and puberty. As such, there are critical windows to intervene to control the timing of managing exposures.
2. **There are low-dose effects.** Unlike poisons, the risks and effects of EDCs do not increase with dose. However, effects may be different at lower or higher doses. Further, dosing matters even for EDCs that are naturally occuring (e.g., phytoestrogens) and not anthropogenic.
3. **We are all exposed to a mixture of chemicals all the time.** Studies on a single EDC may not predict the effects of a mixture. There are mixtures of mechanisms that lead to disease.
4. **Systems toxicology.** Effects on one organ can manifest in another.

Consumers can make a difference in their own exposures as well as the population's. For example, it was consumer demand, not regulation, that resulted in the removal of bisphenol A (BPA) from baby bottles and flame retardants from furniture. As more chemical exposure test kits appear on the market and in consumer's hands, toxicologic testing needs an overhaul. To be clinically meaningful, tests need to be reliable and valid, and a regulatory framework is required to assess them.

Lost in Translation No Longer: Building Clinical Action From Endocrine-Disruptor Science
Robert Sargis, M.D., Ph.D., University of Illinois Hospital & Health Sciences System

Ideally, regulatory systems that benefit all would be the most efficient and just approach for addressing the health threats of EDCs. However, current political, regulatory, and economic systems fail to protect public health. In addition, public denial about the effects of EDCs is similar to that which has surrounded denial about climate change, ranging from asserting they do not exist to believing that they do, but are not harmful.

As previously described, exposure to EDCs can exert adverse effects across the lifespan.[3] Later in life the effects of these chemicals are largely activational. Early in life, EDCs can install organizational effects that program increased long-term risk to metabolic diseases. Interventions to prevent adverse effects from such environmental toxicants include efforts aimed at disease prevention (address potential organizational effects) and disease treatment (address activational effects). However, there are key gaps in care, 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, despite a growing body of evidence to assist clinicians and patients in decision making[4]. Multifactorial intervention strategies are needed across the lifespan. It has been shown that many EDC exposures can be modified through safe and simple behavioral changes (e.g., diet, limiting exposures during pregnancy). These approaches need to be supported by social action to reduce, mitigate, or remove known exposures and screen new chemicals prior to their use.

Exposure reduction strategies through various interventions have been shown to be effective for phthalates, BPAs, benzophenone, and triclosan.[5,6] Antagonizing (adverse) developmental patterning can be achieved through dietary supplementation with methyl donors and elimination of BPA. Other effective interventions include improving maternal nutrition and using proven dietary supplements. And while reducing exposure to EDCs is the most effective strategy to reduce their toxic effects, a corresponding approach involves activating metabolizing systems to reduce the level of the active EDCs post-exposure, which can be achieved with specific dietary ingredients. In the real-world, people need to be empowered to reduce or attenuate their exposures but they do not always have choices or known options. Further, interventions do not always work, risks may have developed over a lifetime, and adherence is always a challenge. Regardless, individual action is not the primary solution to systemic problems. Education, engagement by professional organizations, and advocacy for science-based policy is equally if not more important.

While chemical mixtures are an increasing focus of research, mechanistic work is typically centered on one chemical, which poses risks to translation. There cannot be 80,000 distinct solutions for 80,000 chemicals. Rather, interventions are needed that target multiple EDCs or aim to 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.

Discussion

- Although focusing interventions on women of reproductive age is an effective strategy for preventing or mitigating exposures, clinicians should be mindful of not “blaming the woman” for exposures likely beyond her control. Clinicians should routinely ask preconceptual or pregnant women what type of work they do and in what environment, if relevant. Such information could identify potential exposures that can be mitigated. Clinical guidance should be based on evidence of effectiveness and efficiency, which is not always available or sufficient.
- An emerging body of evidence shows that certain nutrients have mitigating effects and that whole food is more healthful than processed foods. However, not all populations have access to affordable whole foods.
- Clinical data are needed to assess the reliability, validity, and clinical utility of environmental test kits as they come on the market. Clinicians need to be trained in collecting environmental

exposure information from patients and interpreting test results. Such skills are typically not a part of medical school curricula.

Community Member Perspective—Firefighting: EDC Exposures to Those That Serve
Neil McMillan, International Association of Fire Fighters

Firefighters encounter extreme environmental chemical exposures in their work, including polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs), metals, halogenated flame retardants, per- and polyfluoroalkyl substances (PFAS), and particulates. Acute exposures are as much a risk as chronic exposures, and legacy flame retardants remain a severe exposure risk.[7] These exposures are compounded by sleep deprivation and disruption, trauma, and a rising number of catastrophic climate events. Measuring exposures and assessing impact has been stymied by lack of access to research data collected by chemical companies.

Research has found flame retardant biomarkers in biological specimens of firefighters at concentrations well above general population levels. Comparisons of PFAS among female firefighters and office workers found the firefighters had higher serum concentrations of PFAS. High exposures were found to be associated with decreased thyroid hormone levels.[8]

Personal protective equipment (PPE) does not adequately protect against flame retardant exposure. Research has shown significant concentrations of polybrominated diphenyl ethers (PBDEs) in PPEs worn in contact with the skin, for which there is a high absorption rate. Firefighters may be exposed to brominated flame retardants embedded in their PPE.[9] Chemicals detectable on this gear have shown significant estrogenic activity resulting in potential perturbation in hormone-dependent tissues such as the prostate, testis, and cervix. Fire stations also harbor high levels of EDCs. PFAS dust has been found in highly concentrated levels in all areas of stations, although the turnout gear locker rooms show the highest levels.[10,11] High levels are attributed to the degradation of fluorinated polymers after exposure to elevated temperatures.[12] Numerous studies have documented the effects of PFAS on hormones that regulate cholesterol and glucose metabolism as well as inflammatory signaling molecules. These exposures have been linked to elevated risk of hypertension, and skin, prostate, brain, esophageal, and lung cancer.[13] Aqueous film-forming foam (AFFF) is a type of foam used to fight liquid-fueled fires. PFAS concentration levels of firefighters exposed to AFFFs are high and increase with years of exposure.

Despite this evidence, industry studies and interpretation of studies have been incomplete and misleading. In contrast, the Fire Fighter Cancer Cohort Study, initiated in 2016 by Jeffrey Burgess, has the long-term goal to follow 10,000 firefighters from multiple fire departments across the country over a 30-year period.[14] To date it has demonstrated elevated serum PFAS levels compared to national levels in at least two of four career fire departments. Preliminary evidence suggests PFAS exposure accelerates reproductiveaging, perhaps through epigenetic effects.[15] There should be a healthy effect in this cohort as firefighters tend to be young, healthy, and physically fit. Yet female members of this population experience high rates of preterm delivery, high rates of all adverse pregnancy and birth outcomes, and reduced ovarian reserve.[16,17] Children of firefighters are more likely than controls to have congenital cardiovascular anomalies, cleft lip and/or palate, and transverse limb deficiency.[18] These intergenerational effects are not only adverse for these workers and their families but also have implications for the future of the American fire service, which is a career often passed from generation to generation.

Discussion

Participants discussed the intergenerational and transgenerational effects of such exposures. Longitudinal studies of the World Trade Center cohort is the largest such study of this kind but has the unique advantage of being regional, whereas most other studies cross geographic areas and lack centralized recordkeeping. Participants discussed the need for occupational exposure monitoring before, during, and after an event or period of time to identify those at risk. Finally, safer options for PPE are available but regulatory and statutory restrictions have stymied adoption. Short-term protective approaches to acute exposures are sometimes sought at the policy level even when it is known that acute exposures over time can also be deleterious.

Lifestyle, Including Diet, Sleep, and Physical Activity
Moderator: Michele Marcus, Ph.D., M.P.H., Emory University

The Roles of High-Quality Diets in Mitigating the Deleterious Effects of EDCs in Pregnancy
Rita Strakovsky, R.D., Ph.D., Michigan State University

Nonpersistent EDCs such as parabens, phthalates, and bisphenols have been shown to drive adverse pregnancy outcomes. Maternal diet quality can be a mitigation strategy either through avoidance of dietary exposures or inclusion of diets with health benefits.[19] Rather than focusing on individual foods or nutrients within someone's diet, diet quality indices have been developed to consider dietary patterns in a wholistic manner. A research goal is to understand the molecular toxicological targets of EDCs and then evaluate dietary patterns that would essentially decrease susceptibility to their toxic effects. Two EDCs of interest are phthalates and parabens.

Maternal glucose levels are known to be predictors of fetal growth and pregnancy health outcomes. Both maternal diet and exposure to phthalates and other EDCs have been shown to dysregulate maternal glucose homeostasis.[20] Recent research aims to understand this entire pathway and determine whether poor quality maternal diets are associated with poor maternal metabolic health because of exposure to phthalates.

Phthalates are ubiquitous because they are used as plasticizers or as scent stabilizers. All persons in the National Health and Nutrition Examination Survey (NHANES) database show detectable levels of at least one phthalate metabolite, but typically many more.[21,22,23] Plasticizer phthalates and their recent replacements are primarily used in food processing and packaging applications to make plastics flexible and to protect food from the elements. Phthalates are known endocrine and metabolic disrupting chemicals, which has been confirmed in experimental and epidemiologic studies. 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.

Research has confirmed that individually, poor-quality diets are associated with exposure to some phthalates, and that phthalates are associated with poor maternal glucose homeostasis.[24] One possible reason that poorer diets are related to poor maternal health is because lower quality diets contain higher levels of phthalates, and these phthalates are associated with adverse maternal health outcomes, perhaps mediating as much as 11.7 percent of the outcome of poor maternal glucose homeostasis. In terms of public health messaging, these findings support the idea that by consuming higher quality diets in pregnancy, women are not only improving their nutrient profiles to support pregnancy health and fetal growth directly, but they are also decreasing exposure to potentially harmful endocrine disruptors.

Parabens were also 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.[25] There is solid evidence to suggest that parabens partly act by inducing inflammation and oxidative stress. Therefore, to mitigate the toxic effects of parabens, the goal should be to identify lifestyle or other factors that specifically target inflammation or oxidative stress. Diet is a feasible approach, as high-quality diets are both anti-inflammatory and have antioxidant properties. The relationships between maternal paraben exposure and newborn weight were assessed in women consuming high-quality versus low-quality diets. In girls of mothers with higher quality diet there were no associations of parabens with birth outcomes. Those born to mothers on low-quality diets had both lower birth weight and birth length.

Can Healthy Lifestyles Counteract Effects of EDCs on Women's Cardiometabolic Health?
Karen Peterson, R.D., D.Sc., University of Michigan

Exposures to phenols, phthalates, and parabens have been associated with chronic inflammation, which may play a role in the development of metabolic syndrome (MetS). There are plausible sequelae of EDC exposures during adulthood on cardiometabolic health. Current research frameworks prioritize the importance of early life exposures; less is known about consequences of EDC exposures on women's health. Women at midlife may be especially sensitive to EDC toxicant effects due to a changing hormonal milieu. Midlife encompasses menopausal transition, with fluctuating hormones and physiological symptoms. Body weight and abdominal obesity may increase, favoring insulin resistance and risk of hypertension and other chronic conditions. Cross-sectional studies suggest positive associations of EDCs with MetS and inflammation in women.

To characterize associations of phenol, phthalate, and paraben exposures with MetS and inflammation among Mexican women in midlife, a study explored modification by diet quality, physical activity, and sleep. Inflammatory cytokines were analyzed as were symptoms of potential MetS (e.g., waist circumference, body mass index [BMI], blood pressure, glucose, triglycerides, and high-density cholesterol). Usual dietary intake was queried and the percent of kcal derived from ultraprocessed food was assessed. Bivariate analysis showed a positive correlation between percent of energy from ultraprocessed foods and EDCs. However, no relationship was found between percent of diet from ultraprocessed foods and inflammatory cytokines. Further, EDC exposures in adulthood were related to higher odds of elevated triglycerides and hypertension 10 years later, but reduced odds ratios for high glucose and waist circumference. Ongoing research is focusing on the relationship of diet and sleep to MetS and the relationship of diet and sedentary activity to inflammation. It is possible that anti-inflammatory diets combined with healthy sleep and activity patterns could reduce EDC exposure and cardiometabolic risk. Context-specific information on EDC sources is needed to develop culturally competent interventions.

Preventing and Mitigating the Adverse Effects of PFAS Exposure
Joseph Braun, M.S.P.H., Ph.D., R.N., Brown University

PFAS have been detected in the blood of every tested American. Preventing exposure is the optimal method to prevent adverse health effects. This could include regulation or policy to ban PFAS use, area-level interventions to remove existing contamination to prevent future exposure, or individual-level actions to reduce exposure. Little can be done about prior exposure, but reductions in body burden through individual-level clinical interventions can be a last resort for those with high exposure. Examples of such strategies follow.

Indoor air filtration is one strategy for reducing chemical exposures. A DIY air filter designed by Richard Corsi and Jim Rosenthal (Corsi Rosenthal Box) was found to be effective at reducing particulates during the COVID-19 pandemic. Only one study examined its effectiveness for chemical pollutants, where it was found to reduce air levels of 6 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.[26] This box is an affordable, scalable, and sustainable intervention.

Gestational exposure to PFAS is associated with slightly higher childhood BMI scores and risk of overweight or obesity.[27] Ongoing studies are examining associations of gestational exposure to PFAS with adiposity and subsequent cardiometabolic consequences in older children. Exposure can be mitigated through physical activity.[28] In other research, PFAS-associated type 2 diabetes and microvascular disease were attenuated through exercise and diet.[29]

A novel approach to reducing PFAS levels in blood was tested in firefighters.[30] Participants with serum levels of perfluorooctane sulfonate (PFOS) of 5 ng/mL or more were randomly assigned to donate plasma every 6 weeks for 12 months, donate blood every 12 weeks for 12 months, or be observed only. Plasma and blood donations resulted in greater reductions in serum PFAS levels than observation alone over a 12-month period.

PFAS undergo substantial enterohepatic recirculation with accumulation in the liver. Cholestyramine is an anion exchange inhibiter that forms insoluble complexes with bile acid in the gut. It has been shown to inhibit reabsorption and increase fecal loss of cholesterol, suggesting that this inhibitor could also reduce the biliary reabsorption of PFAS. In a small, randomized study, oral intake of cholestyramine resulted in a reduction of PFOS from a baseline of 191 ng/ml to 111 ng/ml within 12 weeks of treatment.[31]

In the short-term, research to develop new interventions for individual use remains critical. Multimodal interventions are needed to prevent or reduce PFAS exposure and to prevent exposure-related health effects in communities with historical PFAS contamination. Evidence should be compiled to develop recommendations to prevent exposure, reduce ongoing exposure and body burden, and mitigate the health effects of exposure. At the policy level, change in industry practices and standards and regulation of PFAS as a class is needed.

Holistic Biobehavioral Interventions Decrease Circulating PFAS
Michael Petriello, Ph.D., Wayne State University

Biobehavioral research in humans at risk for cardiovascular disease (CVD) can lead to lifestyle modifications including mitigating the effects of EDC exposure. Serum concentrations of low-density lipoprotein cholesterol have been positively correlated with exposure to perfluorooctanoic acid (PFOA) and PFOS in humans.[32] A lifestyle intervention (HeartHealth), designed to address CVD risk factors through strategies to improve diet, decrease stress, and increase exercise, was delivered based on cultural sensitivity and self-care to promote behavior change.[33] Diet quality was measured by a healthy eating index calculated from food questionnaires. The intervention consisted of 12 biweekly group sessions focused on: (1) principles of self-care and CVD risk reduction; (2) depression control and stress reduction; (3) nutrition; (4) decreasing sedentary lifestyle and increasing daily physical activity levels; (5) managing multiple comorbid risk factors; and (6) smoking cessation and medication adherence. Food frequency questionnaires and geographic information system analyses were used to investigate PFAS hotspots and possible exposure routes.

Cholesterol levels were significantly decreased following the intervention. PFAS levels also decreased. In particular, PFOS was only positively correlated with total cholesterol post-intervention. These results provide evidence that that lipid-lowering via lifestyle modification can alter circulating levels and distribution of PFAS. However, associations between PFOS and total cholesterol may be dependent on the effectiveness of the intervention. More study is needed to determine if specific components of the intervention are key, or whether there are important "mixture effects" at play.

Clinical Detoxification: Elimination of EDCs From the Human Body: Blood, Urine, and SweatStudies
Detlef Birkholz, M.Sc., Ph.D., P.Chem., D.A. Birkholz, Analytical Consultant, Inc.

Although life expectancy has improved over the last century in developed nations, the expanding prevalence of chronic and degenerative illness of late is debilitating many health care systems. Exposure to toxic chemicals may well be a cause. At minute levels, toxic compounds can cause hormone disruption, immune dysregulation, cell damage, altered genetic influence, allergy induction, liver compromise, and cancer promotion.

Numerus studies have focused on the excretion of EDCs by measuring blood, urine, and sweat levels of these compounds. Perfluorinated compounds (PFCs) accumulate in human blood and tissues, have long elimination half-lives, and are increasingly linked to assorted health concerns.[34,35] As noted previously, there is compelling evidence that oral cholestyramine is effective at hastening elimination of various PFCs from the human body. Conversely, oral *Chlorella pyrenoidosa* was not found to be effective at removing PFCs.[36] In addition, sauna depuration and treatment with saponin compounds and zeolites does not appear effective in facilitating the excretion of PFCs.

Polychlorinated biphenyls (PCBs) are additives in oils, electrical equipment, and hydraulic machinery. They are also used for applications in which chemical stability is required for safety, operation, or durability (e.g., waxes, inks, paints, adhesives, plasticizers, joint glues). They have been found at high levels in urine and sweat. Relatively higher levels in sweat suggest that perspiration may be a more efficient method of excreting these congeners compared to urinary elimination. Induced perspiration does appear to hasten the elimination of some, but not all, PCB congeners from the human body.[37]

Sweat BPA concentrations are also consistently much higher than urine. Data suggest that BPA likely bioaccumulates to some degree in humans, is retained in tissues (likely adipose), and excretes in sweat.[38] The finding that little or no BPA is excreted in urine while considerable levels are found in sweat suggests that current biomonitoring via serum or urine may not provide a reliable indication of the BPA toxicant burden.

None of the tested PBDE congeners have been found in urine and are most effectively excreted into perspiration.[39] Research participants who induced perspiration through exercise excreted the greatest proportion of type PBDE-28; those who used an infrared sauna excreted the most type PBDE-100; and those who used a steam sauna excreted the most type PBDE-153. Variations in excretion rates may be related to the concentration of sebaceous glands in different body areas or individual physiological variations. Regular sessions of induced perspiration should be considered cumulatively as a potential clinical modality to diminish body burdens of many xenobiotics, including PBDEs.

From a therapeutic standpoint, induced sweating may be one clinical intervention for eliminating some toxic elements. From a public health perspective, clusters of people, such as firefighters or welders may

be advised to regularly undertake induced sweating. From a biomonitoring perspective, perspiration may serve as a more sensitive body fluid for measurement compared with blood because some toxic elements are frequently not detected in serum but may be found in sweat samples from the same individual.[40] In sum, determining body burden of toxic environmental chemicals is essential in determining possible causes of chronic disease and in determining whether mitigation is appropriate and effective. Analyzing blood and urine alone may be inappropriate for some chemicals.

Discussion

Participants discussed other factors to be considered when testing individual-level interventions, such as access and feasibility, the need for more concerted outreach in highly exposed populations or geographic areas, the role of other variables in burden and response such as immunosuppression and genetic factors, and the need to expand testing for those PFAS that are most prevalent in the environment.

The Microbiome and Metabolome
Moderator: Hye-Sook Kim, Ph.D., NCCIH

Endocrine-Disrupting Chemicals and Affects on the Gut Microbiome: The Perils and the Promise
Cheryl Rosenfeld, D.V.M., Ph.D., University of Missouri

There is growing evidence that developmental exposure to BPA, genistein (a phytoestrogen), and ethinyl estradiol (estrogen routinely used in birth control products) leads to long-term effects on the gut microbiome. These effects occur in alignment with other factors affecting the gut biome such as diet, prescription drugs, stress, geography, and the life stage. With a combined 100 trillion cells and more than 22 million gene products, including those that replicate host neurotransmitters, gut grape can dramatically shape brain development. The gut-microbiome brain axis has been shown to be a multidirectional communication pathway that enables the gut microbiota to communicate with the brain directly or indirectly through signaling pathways to influence brain physiology, function, and even behavior.[41] Microbiota can produce neurotransmitters that travel to the brain to induce central nervous system effects, where they might stimulate inflammatory cell production of cytokines or production of metabolites. Environmental chemical-induced gut microbiome changes may subsequently induce pathophysiological responses in the host, where host genetic, epigenetic, and phenotypic status also play a role.

Research has shown the neurobehavioral effects of developmental exposures to genistein and BPA in a mouse model.[42] Results suggest that developmental exposure to genistein disrupts normal sociocommunicative behaviors in mice. This is likely due to disruptions in neural programming but might also be caused by exposure-induced microbiota shifts and changes in gut metabolites. These preclinical models provide the basis for exploring ways to exploit the gut microbiome in disease treatment including those conditions attributed to EDC exposure. 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 postbiotic supplementation.

Sex Steroid Modulation of the Gut Microbiome and Implications for EDC Mitigation
Varykina Thackray, Ph.D., University of California, San Diego

The gut microbiome has been linked to many diseases that differentially affect males and females, for example, autoimmune, neurological, metabolic, and reproductive disorders. Numerous studies have discovered differences in the types of bacteria between males and females. This differentiation occurs during puberty when sex hormones are produced.

To understand how sex influences the gut microbiome, DNA-based molecular methods were used to compare the intestinal-specific microbiomes of a mouse model with a genetically inactivated reproductive axis with wild-type mice.[43] Both sex and the reproductive axis affected gut microbial diversity in an intestinal section-specific manner (i.e., small or large intestine). Significant differences in intestinal microbial diversity were found between the male and female mutant mice, likely because sex chromosome factors affect the gut microbiome. Studies in the rodent reflect these observations. Removal of ovaries or testes in rodents results in changes in the gut microbiome.[44] In the mouse, gonadectomy with steroid replacement results in a gut microbiome that is more similar to intact mice than gonadectomized mice.[45]

Studies in humans have demonstrated that changes in gut microbiome are associated with hypo- or hypergonadism. For example, the gut microbiome of post-menopausal women differs from pre-menopausal women and is more similar to male gut microbiome.[46] Further, hyperandrogenism is associated with changes in the gut microbiome in women with polycystic ovary syndrome including decreased biodiversity and changes in specific bacteria.[47]

EDCs mimic or block steroid action and have the potential to affect the microbiome in the same way as sex steroids. This has implications for EDC mitigation. The gut microbiome is highly modifiable by diet and microbial-based therapeutics including prebiotics and probiotics. Changes in sex steroid levels associated with pathology may be mitigated by modulation of the gut microbiome including fecal microbiota transplant, prebiotics, and probiotics. Research is needed to understand: how EDCs modulate gut microbial composition and function and how this influences the host; how EDC effects on the gut microbiome affect development and pathology of disorders associated with sex bias/sex steroids; and which prebiotics, probiotics, and postbiotics mitigate EDC effects.

Gut Microbes Are a Barrier to Dietary EDCs
Jordan Bisanz, Ph.D., Penn State University

The sum of all the microbial genes is orders of magnitude higher than the human genome. Gut microbes outnumber the host 10:1 and the genetic potential of gut microbiota outnumbers the host greater than 100:1.[48] Yet we only understand a small fraction of what most of these genes actually do. This reservoir of function makes gut microbes capable of diverse metabolic capacity to affect xenobiotics. Gut microbes play a role in acting as a first barrier against the absorption of xenobiotics, and particularly EDCs, and are an underappreciated component of pharmacokinetics and pharmacodynamics.[49] Orally consumed xenobiotics must pass through microbes before absorption into blood stream. As such, they may be subject to metabolism and sequestration preventing (or encouraging) activity. This raises the potential of manipulating gut microbes to prevent absorption into the bloodstream. Recent studies have shown that microbes manipulate host xenobiotic transport. One study demonstrated that P-glycoprotein is a "hydrophobic vacuum cleaner," blocking absorption of a broad spectrum of xenobiotics.[50] This occurs through small molecules produced by gut microbes inhibiting P-glycoprotein and thereby increasing xenobiotic absorption to blood.

EDCs are common in drinking water, seafood, and grains. Arsenic, mercury, lead, and others have been broadly linked with endocrine-disrupting activity including increased reproductive aging.[51,52] Some metals are termed metalloestrogens because of their ability to bind to estrogen receptors or displace estradiol. Microbes have been found to sequester and metabolize metals. They do not destroy metals but rather modify them through redox reactions and (de)methylation. In addition, many metals are passively absorbed on the cell wall due to charge interactions. Metals sequestered by gut microbes may be accumulated and shed in feces. A human proof-of-concept study performed in Tanzanians exposed to significant metal pollution in Lake Victoria showed that daily probiotic yogurt supplementation significantly reduced blood mercury and arsenic in pregnant women who were eating it with other foods.[53] Minimal effects were seen in children who were eating it without other foods at school, suggesting that the probiotics need to be ingested with the foods that are contaminated so they can bind with the metals and sequester them.

A logical next step is to engineer probiotics to detoxify metals to decrease absorption into the blood stream. One approach is to generate recombinant strains to have high basal metal sequestration activity and to not colonize the human gut well (i.e., they will transit out of the body carrying metals). A recent study found that PFAS exhibit off-target effects on human fecal microbiotas. These effects exhibit interindividual variation and concomitant effects on the transcriptome and metabolome. The level of toxicity was correlated with the number of fluorines in the PFAS. Electron microscopy depicted the intracellular accumulation of adsorbable organic fluorines. Microbiota-targeted interventions could manipulate gut microbes that act at the critical moment of absorption of xenobiotics into the blood stream. Presently, probiotics and fermented foods can be incorporated into the diet with few negative effects. These low-cost interventions can be sustained long term to counter continuous EDC exposure.

Modulating the Microbiome and Metabolome With Prebiotics, Probiotics, and Postbiotics to Mitigate EDC-Induced Metabolic Deregulation
Diana Roopchand, Ph.D., Rutgers University

The organophosphate flame retardants (OPFRs) consist of many compounds, the most common of which are tricresyl phosphate (TCP), triphenyl phosphate (TPP), and tris (1,3-dichloro-2-propyl) phosphate (TDCPP). These are most commony ingested in dust and interact with either estrogen receptor α (ERα) alone or ERα and peroxisome proliferator-activated receptor γ (PPARγ). These receptors are critical regulators of energy homeostasis. Energy homeostasis is balanced through coordinated regulation of food intake and energy expenditure. Peripheral markers of energy status include blood glucose and free fatty acids, insulin and leptin, and ghrelin. These regulators communicate with the brain to control feeding behaviors and activity levels.

The arcuate nucleus (ARC) of the hypothalamus is a critical platform for integrating circulating signals of hunger and satiety, reflecting energy stores and nutrient availability. Since OPFRs interact with ERα and PPARγ receptors, which are largely present in the ARC, they may be disrupting energy homeostasis. Maternal exposure to mixtures of OPFRs in mice have been shown to result in increased systolic and diastolic blood pressure in adult male offspring but not females.[54] In many studies, maternal exposure to OPFRs results in other sex-specific physiological, behavioral, developmental, and reproductive effects in offspring.[55,56,57] In adult mice, OPFRs stimulate weight gain and fat mass in high-fat diet-fed males only.[58] The effects of a high-fat diet and OPFRs on body mass, fat mass, and altered feeding behavior in the mice were lost in whole body ERα and PPARγ knockout mice, suggesting OPFR requires ERα or PPARγ to potentiate the effects of a high-fat diet. These studies suggest that over time, consistent, minor disruptions of energy homeostasis may culminate in the development of obesity, MetS, and diabetes.

EDC exposure can promote gut dysbiosis, impaired gut barrier, and intestinal inflammation, a common triad in many metabolic disorders.

Numerous other molecular targets of EDCs include those related to energy metabolism, cholesterol, and bile acid metabolism, epigenetic modification, and mitochondrial effects. Most studies have focused on specific compounds or classes of EDCs, but real-world exposures consist of mixtures of EDCs.

Prebiotics, probiotics, and postbiotics can mitigate or repair the EDC-induced triad of gut dysbiosis, impaired gut barrier, and inflammation. In addition, dietary polyphenols alter the gut microbiome to promote metabolic health.[59] Polyphenolic compounds are abundant in plants and are readily found in fruit and vegetables. In particular, grape polyphenols (GPs) may improve metabolic homeostasis by altering gut microbiota and by changing microbial- or host-derived metabolites, largely due to their poor absorption. Mechanisms for GP-induced improvement of glucose tolerance have been observed in mice.[60] These findings have been repeated in a proof-of-concept study in overweight and obese human volunteers.[61] Participants experienced increased insulin sensitivity and decreased plasma insulin, total cholesterol, blood markers for liver dysfunction, and blood markers for inflammation. In a separate study, changes to gut microbiome and metaproteome were found to be transient and profiles returned to baseline by day 10, suggesting microbial community adaptation.[62] In another study, GP supplementation reduced fasting glucose in healthy participants in association with increased serum hyocholic acid and increased relative abundance of *Akkermansia muciniphila,* which is up to 4 percent of gut microbiota in healthy subjects, with attenuated metabolic syndrome symptoms.[63] This was the first study showing a relationship between dietary prebiotic GPs and fasting blood glucose. Larger studies in subjects with normal and impaired glucose tolerance are needed to confirm associations

Food is a major source of EDCs as chemicals are used on crops, and in food packaging and additives. A diet of ultraprocessed, packaged foods contributes to the burden. Whole foods that feed the gut microbiota by delivering prebiotics and probiotics, to favor production of postbiotics, mitigate the effects of EDCs. Organically grown crops show higher polyphenol levels than conventionally grown foods.

Discussion

Discussants speculated about the role of the microbiome and which components of EDC exposure might be related to the collection of all microbes, such as bacteria, fungi, viruses, and their genes, that naturally live on and in our bodies. Sex differences, geography, ethnicity, diet, and other factors can affect the microbiome and explain interindividual and interspecies differences in response to exposures. Germ-free mice are useful tools to understand the influential components of the microbiome. Research is needed to determine which prebiotics and probiotics work best in variable contexts and settings.

Supplements and Natural Products
Moderator: Sekai Chideya, M.D., M.P.H., NCCIH

Natural Products and EDC Mitigation: Identifying Promising, Plausible, and Practical Options
Sekai Chideya, M.D., M.P.H., NCCIH

Natural products, which include botanicals, vitamins and minerals, probiotics and prebiotics, and supplements, might assist in the mitigation of EDC exposure. Many natural products have chemical structures that interact with human biochemistry and physiology and are required for hormone structure and function and to mediate biochemical reactions. Examples of vitamins and minerals essential for

hormone production and function include iodine and vitamins B5, B6, and D. Importantly, vitamins and EDCs often compete for access to receptors. As such, high EDC levels can prevent vitamin uptake, leading to a variety of deficiencies. Further, higher vitamin levels may block EDC binding and uptake. Observational studies confirm that the effects of some EDCs worsen if vitamin levels are low.

Nonvitamin natural products can also block EDC cellular access. For example, carbamate pesticides have a similar structure to and bind the same receptor as melatonin. Overactivation of the receptor may increase the of risk of cancer or diabetes. Melatonin supplementation may blunt the effects of carbamate and some other pesticides. Some products physically bind or block EDC absorption (e.g., chlorella, probiotics), leading to increased excretion and decreased accumulation. Even if they do not directly interact with EDCs, natural products may counter their downstream effects. Promising clinical trials are assessing the role of natural products in enhanced excretion and decreased bioaccumulation of EDCs, decreased EDC-associated oxidative stress, and reduced hormone dysfunction. Despite some promising results, the effects seen in animals are not always confirmed in humans and human trials are generally small and observational.

The Need for EDC Mitigation Strategies and Promising Findings on Fish Oil Supplementation
Melissa Melough, Ph.D., R.D., University of Delaware

Diet is a key source of many EDCs, but there are few evidence-based dietary recommendations to help consumers reduce their exposure. One recent review summarized 13 existing intervention studies that used various dietary approaches to reduce EDC exposure.[64] Key characteristics of these interventions included eating more fresh and minimally processed foods and avoiding foods that were packaged and processed. Importantly, there are limitations to recommendations resulting from these studies. Each of the diets promotes consumption of plentiful fruits and vegetables, prioritize whole grains, and leave little room for snack foods that are likely to be processed, so they are not likely to be accessible, sustainable, or feasible for many people.

NHANES data provide a large nationally representative sample to study diet and assess how people are truly eating in America, including how they may be trying to implement dietary recommendations in their diets. Using data from NHANES 2013–2016, associations of dietary patterns with exposure to non-persistent EDCs potentially consumed through diet were measured in spot urine samples using three healthy diet scores: Healthy Eating Index (HEI), relative Mediterranean Diet, and Dietary Approaches to Stop Hypertension.[65] Estimated associations were sometimes in the negative direction, indicating a protective effect of these healthy diets against EDC exposure. However, the associations were just as often in a positive direction, showing increased exposure with a healthier diet. Nearly all of the estimates were nonsignificant. Thus, following these healthy diets does not guarantee reduced exposure to many EDCs likely due to widespread contamination across the food supply and diverse exposure sources. Further, some healthy diets are not sustaimable in the real-world environment. Changes in food production practices is likely the most effective way to reduce contamination.

Phthalates are one class of EDCs that may promote obesity through alterations in PPAR signaling with resulting effects on lipid metabolism and adipocyte differentiation. The obesogen hypothesis posits that EDCs and other chemicals can alter metabolism and susceptibility to obesity.[66,67] Prenatal and early childhood exposure are believed to be the most sensitive periods for obesogen action. Prenatal exposure to several phthalate metabolites is linked with lower birthweight but increased childhood adiposity at age 3 or 4 years, likely related to oxidative stress levels in pregnancy.[68] Obesity in this early stage of childhood has been linked with persistent obesity into adulthood. Both low and high molecular weight

phthalates have been implicated. Some studies have noticed sex differences, and heterogeneity exists among studies.

Eicosapentaenoic acid, and docosahexaenoic acid (DHA) are key omega-3 polyunsaturated fatty acids (PUFAs) found primarily in marine sources. They have extensive biological benefits and promote antioxidant enzyme activity, mitochondrial fatty acid oxidation, PPAR-gamma activation, and anti-inflammatory cytokine production.[69,70] Omega-3 PUFAs are under consumed in pregnancy. The ability of fish oil to reduce oxidative stress associated with phthalate exposure during pregnancy is a promising approach to mitigating the effects of this EDC. Current studies of anti-oxidative dietary patterns or fish consumption report improved pregnancy and postnatal outcomes.

Folate as Mitigation Measure for Endocrine-Disrupting Chemicals
Yu Zhang, Ph.D., Harvard University

Dietary consumption of some food groups has been shown to be inversely associated with serum PFAS concentrations. In particular, folate has been found to reduce the body burden of environmental pollutants and offset their detrimental health effects. Evidence suggests that folate and PFAS could share similar transport carriers, potentially leading to an inverse association between them in humans. Epidemiological evidence suggests that phenol and phthalate exposure is associated with lower probability of 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. Experimental evidence shows that a diet with folic acid or other methyl donors mitigates BPA-induced oxidative stress and genetic and epigenetic changes in experimental animals.[71]

A large sample of 2,802 adolescents and 9,159 adults in NHANES revealed consistent inverse associations for most examined serum PFAS compounds in relation to folate concentrations as measured in either red blood cells or serum.[72] Similar negative associations were found between serum folate concentrations and PFAS concentrations. A separate cohort study of 1,400 mother-singleton pairs in the United States found that higher early pregnancy plasma PFAS concentrations were associated with lower birth weight and gestational age.[73] These findings were observed only among mothers in the lowest quartile of prenatal folate status as measured by dietary intake or a plasma biomarker. PFAS exposure has also been associated with reduced antibody levels. Higher red blood cell folate has been associated with lower serum PFAS concentrations in adolescents. A study of 819 adolescents in NHANES found inverse associations between serum PFAS and rubella antibodies in those with higher red blood cell folate concentrations.[74] In sum, folate shows promise as a potential mitigation measure for EDCs including phenols, phthalates, and PFAS. Future studies are needed to validate findings in diverse populations and more research is needed to determine the optimal range of folate intake in mitigating the health impact of EDCs.

Discussion

Questions were raised about plant-based substitutes to fish oil, such as algae oil. Although both supplements provide omega-3 fatty acids, algae oils do not contain eicosapentaenoic acid, so they are not a true substitute. Further, fish oil is likely purer than whole fish, which might harbor their own EDCs and heavy metals. Although flax seeds contain fatty acids, they cannot convert into other fatty acids, so their benefits are more limited than fish oil.

Mindfulness in the Face of Toxicity: A Framework for Endocrine-Disrupting Chemical Prevention and Mitigation
Moderator: Jennifer Baumgartner, Ph.D., NCCIH
Eric Loucks, Ph.D., Brown University

A framework exists for understanding why, when, and how to adapt mindfulness-based programs (MBPs) to specific populations and contexts, such as reducing or mitigating stress in individuals exposed to environmental toxins. To develop an effective and feasible adapted MBP, fundamental knowledge domains are required: delivery setting (e.g., workplace, digital); culture, values, and communication patterns of the target demographic group; existing effective interventions for the target outcome; and the etiology of the target health outcome.[75] Adapting mindfulness programs happens not only by researchers, but also by mindfulness teachers and developers, who endeavor to best serve the populations and contexts they work with.

An example of an adaptation is mindfulness-based blood pressure reduction through emotion regulation, attention control, and self-awareness about, for example, lifestyle, diet, and exercise. A randomized clinical trial of 201 participants assessed whether an adapted mindfulness training program improves interoception and adherence to the Dietary Approaches to Stop Hypertension (DASH) diet.[76,77] At 6 months follow-up, the program improved the Multidimensional Assessment of Interoceptive Awareness score by 0.54 points, and the DASH score by 0.62 points, compared with control.[78] Given the high burden of hypertension on cardiovascular disease, this program offers an approach to improve self-awareness and adherence to evidence-based determinants of hypertension, such as the DASH dietary pattern.

Mindfulness training in the context of EDC exposures might also focus on self-regulation (emotion regulation, attention control, self-awareness). Context includes the sources of the exposure. Attention control can inform decisions about, for example, diet, drinking water, use of food containers, or purchase of products with plastics. Attention control at the individual and family level is one of many strategies to prevent and treat EDC exposure.

Five factors to consider when deciding whether to adapt a mindfulness program focus on the need, the population and context, needed adaptations, benefit-cost assessment and sustainability, and whether an effective approach already exists.[79] Eight steps to adaptation progress from determining need and feasibility to pilot and randomized controlled trials to replication, scalability, dissemination, and implementation. Finally, program development must be culturally relevant.

Discussion

Questions were raised about whether mindfulness interventions can alleviate the allostatic load or burden in susceptible populations. Stress has been shown to 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.

Community Member Perspective: Historia De Una Campesnia (History of a Farmworker)
Hormis Bedolla, Alianza Nacional de Campesinas

Ms. Bedolla is the regional organizer for the State of New York at Alianza Nacional de Campesinas (Alianza), where she coordinates the Proyecto Madre Tierra (Mother Earth Project) within Alianza's

Environmental Justice and Pesticides Initiative. Originally from Mexico, she immigrated to the United States in 2003, and has since worked as a campesnia (farmworker). Ms. Bedolla described her experience over 20 years working on apple farms, where she was never trained in the safe application of applying pesticides. Over the years she has been exposed to insecticides, fungicides, rodenticides, and other chemicals. Her exposure to pesticides occurred by breathing them in, ingesting them, and absorbing them through the skin and eyes. These exposure are not restricted to the field but are carried into the home. Exposures are in high concentrations and involve multiple chemicals. Even workers not applying pesticides are exposed because of a high rate of drift and their long hours in the fields.

Acute pesticide exposure occurs over a short period of time, and symptoms include (but are not limited to) headaches, dizziness, weakness, nausea, skin rashes or burning, and vision problems and blindness. Chronic exposure occurs over longer periods of time and depending on the type of pesticide can affect health in a variety of ways: cancers; 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. Ms. Bedolla and members of her community experience high rates of miscarriages, premature births, and low birth weights. Pregnant mothers are also at risk of exposure to pesticides from their working spouses or living in camps near the fields. Ms. Bedolla described her experiences with her three children who were born prematurely with very low birth weights and cardiovascular anomalies.

In addition to experiencing high rates of exposures and the subsequent health effects, farmworkers lack labor protections and adequate regulations and enforcement. Their immigration status and lack of insurance can prevent or deter them from seeking appropriate medical care. Availability of medical insurance and knowledge and training on the health effects of exposure for both workers and health care providers would alleviate some of the consequences of exposures as workers can self-protect by wearing appropriate clothing and following recommendations about removing residues from their environment. However, the burden cannot be solely on the worker. The farming industry and pesticide producers have the power and resources to adhere to health and safety requirements and improve practices.

Discussion

There is a double-edged sword to developing effective exposure reduction and mitigation interventions in that it gives the food production and chemical industries and employers an “out” for reducing exposures in the first place. Messaging about these interventions has to be carefully crafted to convey that self-care is only one approach to reducing harm. Consumers have the power to influence the production industry by being more selective in the produce they buy, based not just on the label but also the producer. In addition, high levels of food waste results in more production of food, which places even greater strain on the workforce.

From Evidence to Action—Reducing Exposure and Mitigating Risks
Carmen Messerlian, M.Sc., Ph.D., Harvard University

Generational health is the planning of passing health to future generations. Child health begins before conception and early life environments are generational. Our social, natural, and built environments affect reproductive health across the lifespan and health span, affecting mental and reproductive health, reproductive success, and stress and adaptation. What a couple is doing today in the preconception window of vulnerability will affect their grandchild’s health span and lifespan. An integrated framework

for generational health focuses on prevention and early intervention. Science has spent decades studying and engineering the genome and has not expended similar energy on engineering or tailoring the chemical environment.

Mitigating EDCs for generational health can reduce their reproductive, developmental and neurological, and metabolic and immune effects. Top-down strategies include international guidelines, policy regulations, and advancements in EDC research. Bottom-up strategies include consumer behavior, strengthening community resilience, and investment in private sector and new technology. A SWOT analysis of EDC mitigation approaches informs actions. A strength is increased public awareness and scientific understanding of EDCs while a weakness is the difficulty the public faces in completely avoiding exposure due to the prevalence of chemicals in modern life. An opportunity is the development of safer alternatives and stricter regulatory policies. A significant threat is ongoing introduction of new chemicals with potential EDC properties into the market. These factors exist against a challenging landscape of global prevalence of EDCs, multiple routes of exposure, and the existence of large vulnerable populations (e.g., pregnant women, firefighter, farmworkers).

Consumers have some agency of control in the products they purchase, such as those in plastic containers, cosmetics and personal care products, cleaning products, and furniture and electronics. But that control is somewhat minimized by the lack of chemical-free alternatives and lack of access. With contaminated water, an individual can install water filtration systems or avoid water bottled in plastics, or advocate for safe drinking water. Dietary exposures and supplements can help counteract the effects of exposures. Choosing locally sourced foods, understanding labels, and practicing good food preparation and storage habits are additional measures generally within individual control. Choosing safer personal care products provides another strategy to reduce exposures. Green-cleaning and maintenance (e.g., eco-friendly cleaning products, proper ventilation, and replacement of air filters) provide another set of options. Finally, technological devices used by everyone emit EDCs, so proper handling and use is important. Top-down approaches are needed to reduce population risks and protect vulnerable populations through advocacy, community engagement, and global cooperation.

One example of a bottom-up strategy is being tested in the Preconception Intervention Program for Healthy Reproduction (PIPER), a randomized controlled trial to examine the impact of an intervention involving food and drinks, personal care products and cosmetics, and home and cleaning practices, on male, female, and couple-based fertility outcomes. Participants complete questionnaires and provide biospecimens to measure phthalate exposures. A correlative Scientific Early Life Environmental, Health & Development Program (SEED Program) provides educational resources about EDCs and health. Another example is the Collaborative for Women's Environmental Health program, which focuses on educating physicians about toxic chemicals and pregnancy.

In the private sector, Sorette is a company that provides a marketplace and a seal of approval for products that have been evaluated by a scientific board for evidence of safety. Another private sector initiative is developing health technology that individuals can use to access information on their social, natural, and built environments. The goal is optimal reproductive health with a focus on sleep, wellness, nutrition, and environmental exposures. The company is capturing the exposome among couples through a multimodal data platform and creating opportunities to personalize interventions by looking at biomarkers and other factors to reduce exposure burden. Media outlets (e.g., website, podcasts) also provide an opportunity to translate scientific information for public consumption.

Discussion

Discussion focused on three major issues. The first centered on whether a seal of approval generated by a for-profit entity is susceptible to corruption or fraud. This outcome can be mitigated by appointing a scientific advisory board with no conflicts that reviews the evidence and comes to a conclusion that can be replicated by another body. A second issue was concern that the regulatory agenda is highly conflicted, sometimes leading to outcomes that protect producers and industry over consumers. One way to counter that effect is to use science in necessary litigation. Scientists should not avoid serving as experts in cases that require their view of the evidence. A third topic centered on low-hanging fruit for individual mitigation. The most pragmatic approach is to help people select actions that they feel they can control (e.g., consume fewer processed foods or personal care products) and not overwhelm them with information and difficult choices. "A little action is better than none."

Welcome to Day 2
Emmeline Edwards, Ph.D., NCCIH

The topic of this workshop requires a whole person approach to health, which is a growing focus across NIH. Multiple funding opportunities exist in which an EDC component could be added to leverage existing, ongoing, and planned population-based studies. These include the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Initiative, the Environmental influences on Child Health Outcomes (ECHO) Program, the Adolescent Brain Cognitive Development Study (ABCD Study®), and a planned precision probiotics initiative at NCCIH.

Community Member Perspective
Laurene Allen, L.I.C.S.W., Merrimack Citizens for Clean Water

Mrs. Allen is a community-based clinical social worker, co-founder of the Merrimack Citizens for Clean Water community advocacy group, and a founding member of the National PFAS Contamination Coalition. She started advocating in 2016 for the needs of residents in Merrimack, New Hampshire, after learning that her family and community were exposed to industry-attributed PFAS contamination of drinking water. Although PFOA and PFOS were the only chemicals in this class to be initially identified as problematic to the community, it was subsequently found that air emissions and industry discharges from two local plastics manufacturers resulted in the presence of 21 additional PFAS chemicals in the community water supply.

With little support from industry or local government, Merrimack Citizens for Clean Water organized locally in community engagement, education, and advocacy efforts at the local, state, and Federal levels. Mrs. Allen and her team have focused on raising awareness of community health effects believed to be associated with both past and ongoing PFAS exposure and conducted a health survey to assess disease morbidity in the community. Exerting pressure on state agencies and the U.S. Environmental Protection Agency (EPA) to conduct widespread testing of water and air stack emissions, the organization discovered hundreds of PFAS compounds in an ongoing contamination pathway. Over time, more areas were tested, revealing more PFAS contamination of private wells and waterways. Remediation efforts are underway but too slow. Further, taxpayers dollars are funding much of the remediation requirements for public water providers, waste water facilities, and in an innumerable number of homes. Absent effective regulatory guidance from the EPA, states such as New Hampshire have been left on their own to struggle with a pathway forward and residents have had no choice but to become their own self-educated advocates. As a self-taught expert, Mrs. Allen has expanded the Merrimack efforts to involve citizen advocates from across the nation and is leading efforts to reach a holistic and integrated Federal

response to PFAS exposure that ensures that health science drives environmental policy and community support measures.

EDCs as Drivers of Health Disparities
Moderator: JoyAnn Courtney, Ph.D., NIH/Office of the Director

Endocrine-Disrupting Chemicals and Cancer Disparities
Lindsey Treviño, Ph.D. , City of Hope, Los Angeles

EPA defines environmental justice as "The fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income, with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies." This concept has been recognized for decades, particularly first by Dr. Robert D. Bullard who found that Black people made up 25 percent of the population in Houston from the 1930s to 1978, but 82 percent of the waste dumped in Houston was in Black neighborhoods. Numerous studies in the past 20 years have documented high levels of BPA, methylparaben, and propylparaben in human urine in the general population, but at significantly higher levels among non-Hispanic Black and Mexican American populations compared to non-Hispanic White populations.[80,81]

According to the National Cancer Institute, cancer disparities are adverse differences in cancer-related measures such as the number of new cases and deaths, cancer-related health complications, quality of life after cancer treatment, financial burden screening rates, and stage at diagnosis that are shouldered by certain groups belonging to certain ancestry, racial, or ethnic minority populations. It is well documented that exposure to EDCs may be playing a role in cancers of the breast, ovary, skin, and uterus. Research evaluating associations among 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.[82] Various efforts are underway to elucidate the mechanisms of EDC action and identify their key characteristics (i.e., common features of hormone regulation and action). Future research is needed to determine if reducing exposures decreases risk of cancers with known disparities. Further, do EDCs interfere with therapies, particularly for hormone-responsive cancers, resulting in potential disease progression and recurrence? Finally, do EDCs play an indirect role in the development of cancer disparities in the context of diabetes/obesity?

EDCs as Drivers of Disparities in Disease Burden and Societal Costs
Leonardo Trasande, M.D., M.P.P., New York University

Disproportionate exposures to EDCs are widely documented in racial and ethnic minorities and low-income subpopulations. Because EDC-related diseases are costly, there is an additional economic burden associated with these exposures. Current estimates of EDC disease burden and costs focus on fewer than 5 percent of EDCs and often subsets of diseases and costs are examined, leading to a severe underestimate of total costs. Even so, the health effects from EDCs are estimated to cost the United States $340 billion annually, primarily due to neurological conditions and the use of flame retardants.[83]

In an effort to quantify disease burdens and related economic costs due to legacy PFAS exposures in the United States, in 2018 a meta-analysis identified previously published exposure-response relationships, and calculated PFOA- and PFOS-attributable increases in 13 conditions.[84] These increases were then applied to census data to determine annual PFOA- and PFOS-attributable cases of disease, from which economic costs due to medical care and lost productivity were calculated. PFAS-attributable disease

costs were estimated at $5.52 billion across five primary disease endpoints. This estimate represented the lower bound, with sensitivity analyses revealing as much as $62.6 billion in overall costs. This study demonstrated the large potential economic implications of regulatory inaction.

Higher exposure to diabetogenic EDCs, such as BPA and phthalates has been observed in Latinos and African Americans in the United States.[85] Non-White populations seem to have higher exposure to EDCs, such as phthalates, which may disproportionately increase the incidence of endometriosis, among other female reproductive health outcomes. Factors driving the disproportionate exposure to several EDCs includes differences in food consumption, usage of consumer products, as well as built environmental conditions driven at least in part by socioeconomic status. Disparities in disease burden translate to disparities in costs. Costs are higher for non-Hispanic Blacks and Mexican Americans. In the short-term, there are safe and simple steps families can take at home to limit these exposures and thereby reduce disease burden and cost (e.g., through diet, personal care products, air filtration) and some of these can and should be made available to low-resource communities.

Environmental Injustice of Beauty
Ami Zota, Sc.D., Columbia University

Ethyl, methyl, and propylparabens 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 suggesting they are linked to health effects. Breast Cancer Prevention Partners has a new campaign about safer products made for and by Black people. Ingredient cards highlight some of the top toxic chemicals and where they are found, for example, fragrances (phthalates) and skin lighteners (hydroquinone, corticosteroids, and mercury). The life course impacts of personal care products on women's health include pregnancy complications, uterine fibroids, and breast, ovarian, and uterine cancers.

The term "environmental injustice of beauty" reframes disparities in beauty product-related exposures as an environmental justice concern.[86] The Black and Latinx populations use more products across multiple categories, for example, hair products, skin lightener, cosmetics, and fragrances.[87] Vaginal douching has been shown to contribute to racial differences in phthalate exposure.[88] Although personal product use is cast as a behavior that an individual controls, the reality is that many factors influence how women think about beauty and the consequent products they use. Social, economic, and historical factors influence what society finds to be beautiful. And these factors and pressures are not the same for all women but vary according to one's social position. Women of color are inherently outside of culturally preferred beauty norms. Consequently, they experience racism and sexism, which may lead them to use certain products as an adaptive response. For example, Black women are most likely to report use of chemical hair straightener.[89]

An intervention, the Taking Stock Study, is being tested to determine if it can advance beauty justice among Black and Latina women through achieving and maintaining natural hair styles and avoiding the chemicals linked to breast cancer. Participants use an app to record use of products. For example, formaldehyde releasers are common in body lotions, face creams, soaps, and hair products. Sixty-six percent of Taking Stock participants were found to be using such products. Additional research is testing the use of targeted and nontargeted approaches to analyze the effects of hair relaxer use on urine concentrations of formaldehydes before, during, and after treatment.

EDC Workplace Exposures as a Contributor to Health Disparities: An Opportunity for Public Health Action To Mitigate Health Inequities
Lesliam Quirós-Alcalá, Ph.D., M.Sc., Johns Hopkins University

As mentioned above, Black and Latina women have higher body burden of chemicals found in personal care products and cosmetics compared to non-Hispanic White women. This is likely due to sociocultural differences in product use (e.g., product type and frequency of use). There are more than 700,000 hairdressers in the United States. They are primarily female, earn low wages, are an average age of 38 years, and 30 percent are Black or Latina. They face multiple environmental and social risk factors and barriers in accessing safety resources and are unaware of workplace hazards. Chemical exposures among hairdressers remain understudied and research to date is very limited. There are a few studies on indoor contaminants in salons, particularly in the United States. Epidemiologic studies are limited or inconclusive and primarily conducted in Europe.

Studies of indoor air found VOC median concentrations 2 to175 times higher in salons versus office spaces.[90] 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. There are similar findings for phthalate biomarker concentrations.[91] Monoethyl phthalate (MEP), found in many personal care products, are 2 to 41 times higher in the urine of hairdressers than women in the general population.[92] Prenatal exposure to MEP is linked to preterm birth, decreased anogenital distance in male infants, and pregnancy complications. Even services perceived as less toxic and referred to as "natural hair" services are linked to high chemical exposures. Finally, respiratory disease development and control is of concern among hairdressers, who have a higher rate of asthma than the general population.

Resiliency Against EDC-Associated Diseases
Moderator: LaVerne Brown, Ph.D., OD/ODS

The Trans-NIH Resilience Working Group defines resilience as "the capacity to resist, adapt to, recover, or grow from a challenge." EDCs represent a stressor that can challenge resilience outcomes across multiple domains. Efforts to mitigate these stressors can enhance resilience.

Military Exposures to Emerging Chemical Toxicants of Concern*
Mark Williams, Ph.D., COR, Defense Centers for Public Health-Aberdeen

Military service members are 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 from exposure to pesticides, combustion products and fumes, and solvents. A significant barrier to improving health care for service members and veterans is the inability to determine whether a diagnosed medical condition is related to a previous exposure. Individuals are often unaware of the toxic substances to which they were exposed, and it is difficult to retrospectively reconstruct an individual's exposure history. This results in frequent denial of claims for health care and disability compensation.

There have been extensive legislative and Federal agency efforts to efforts to address not only exposures of active duty service members and veterans but also possible generational health effects. For example, Section 302 of the Promise to Address Comprehensive Toxics Act of 2022 (PACT Act) requires the Departments of Veterans Affairs and Defense to establish and maintain a list of identified substances,

chemicals, and airborne hazards known to have occurred on or after August 2, 1990, in 16 countries where troops were stationed. This list presumes potential exposure of service members to airborne hazards at levels that might reasonably contribute to adverse health effects. New emerging activities and concerns focus on the health effects of electronic cigarettes and vaping and exposures to micro- and nano-plastics with regard to resilience and force readiness. Observational "field data" on service members and veterans reveal the health effects of exposures. Laboratory-based studies that use "pristine" plastics to model health effects and mechanisms are not real-world, environmentally representative materials. Detailed studies are needed that better model environmental exposures in the military setting to advance understanding of their physical and chemical toxicity and countermeasures to enhance resilience and therefore force readiness.

Resilient Sisterhood Project
Lilly Marcelin, M.S., Resilient Sisterhood Project

The Resilient Sisterhood Project's mission is to "educate and empower women of African descent regarding common, yet rarely discussed, diseases of the reproductive system that disproportionately affect them." As mentioned above, exposure to EDCs results in numerous hormone-related and other reproductive health conditions (e.g., fibroids, endometriosis, early puberty), which are especially damaging in vulnerable populations such as Black women who are socioeconomically disadvantaged and lacking access to reliable services and resources. The Product Options in Women-Engaged Research (POWER) Project is using social media to empower women to reduce Black women's exposures to toxic chemicals in consumer products. Participants engage in learning workshops to learn about products and then log their product use using a smartphone app. The goal is to build resilience through providing objective, widely available, and digestible scientific information to those who are most affected.

Resilience to EDCs
Jyoti Mishra, Ph.D., M.B.A., University of California, San Diego

Weather-related disasters, such as wildfires worsened by a rise in global temperatures, are resulting in environmental stress and the mental health sequelae of PTSD, depression, and anxiety. A resilience research study assessed chronic mental health symptoms observed after wildfire, such as the deadly Camp Fire in California of 2018. Chronic effects are long-lasting, still prevalent 6 months to 1 year after the disaster and appear even among those indirectly exposed. The chronic effects include a three-times greater prevalence of PTSD and a 1.5 to 2 times greater prevalence of depression and anxiety.[93] Observational research shows that age, greater personal resilient belief, mindfulness, sleep, and exercise protect mental health in community members in the context of climate trauma. Individuals with stronger ties within their community are also protected from the mental health outcomes of climate trauma. An intervention integrating community-led eco-mindfulness is being tested based on mental health, cognitive, and brain assessments to determine if individuals can reconnect with nature in a positive away after a traumatic event, thereby boosting their resilience.

Can Sulforaphane Protect Developing Brains From Chemical Disruption?
Karen Litwa, Ph.D., East Carolina University

Sulforaphane is a natural plant compound (phytochemical) derived from cruciferous vegetables (e.g., broccoli, Brussels sprouts). It has been shown to have antioxidant, antimicrobial, and anti-inflammatory properties and thus might protect the developing neural circuits of the brain and prevent altered neural circuitry resulting from chemical exposures that leads to neurodevelopmental disorders. Fetal exposure

to valproic acid (VPA) is known to cause autism spectrum disorder (ASD) in humans and autism-like behavior in mice. The mechanisms by which VPA mediates alterations in neural circuit development were found using human brain spheroids that mimic the developing cortex of the brain. The impact of sulforaphane on VPA-induced outcomes in the mouse was assessed, including oxidative stress, synapse formation and function, and gene expression.[94] Sulforaphane was able to reduce oxidative stress caused by VPA, promoting normal development of synapses by upregulating the expression of antioxidant gene products, engaging the body's endogenous defense mechanisms, and leading to normal synaptic development and function in the developing brain as represented by these cells in vitro. This effect was seen at a low dose but can be toxic at higher doses, so dose will be important.

Discussion

Molecular, systems, and social aspects can promote resilience. Biomarkers such as as oxidative stress and metabolic signatures can be used to assess highly functioning systems and to identify interventions that build resilience. For interventions aiming to reduce use of products containing EDCs, patterns of use of social media and purchasing of products can be measures of success with the assumption that success results in reslience. Changes in cognitive and neurological functions following an intervention can indicate bolstered resilience.

Health Care Provider Perspective
Military Occupational & Environmental Exposures to Endocrine-Disrupting Chemicals (EDCs): Addressing Veterans' Concerns
Omowunmi Osinubi, M.D., M.Sc., M.B.A., U.S. Department of Veterans Affairs (VA)

The War-Related Illness and Injury Study Center (WRIISC) is a National VA Post-Deployment Health Resource program with three centers focused on clinical care, research, and education. The VA is uniquely qualified to care for veterans with health concerns related to potentially toxic exposures. There are 16.2 million veterans in the United States, with 9 million seeking care through the Veterans Health Administration (VHA). Approximately 42 percent of those seeking care are concerned about military exposures. All veterans referred to the Center have an initial consultation with a thorough medical record review. A comprehensive multidisciplinary evaluation is the next step, followed by an environmental exposure assessment, which includes both military occupational and nonmilitary exposures. VA providers are trained on how to collect and describe environmental exposures.

There are more than 800 military bases in the United States and more than 150 of these are listed as EPA Superfund Priority Sites. Environmental contaminants at these sites include: petroleum fuels/solvents; petroleum-related constituents such as PCBs, dioxins, PFAS, and furans; pesticides and insecticides; and heavy metals. More than 700 bases are being evaluated for PFAS use and release. Exposure dates exist from the Korean War to the present, with Agent Orange during the Vietnam war highlighting the health concerns. Many potential exposures are associated with the Gulf War. Military exposures can be physical and psychological (e.g., incoming fire, explosions, loud noises, mental stressors); chemical (e.g., solvents, cleaning agents, depleted uranium, nerve agents); from protective measures (e.g., vaccines, antimalarial agents); biological (e.g., animal/insect bites, infectious agents, biological weapons); or airborne (e.g., smoke, burn pits, sand and dust storms). How the substance enters the veteran's body (inhalation, ingestion, dermal, injection) can be just as important as the particular agent of concern.

For each case, an exposure assessment focuses on who, when, where, what, and why the exposures occurred and then how it might affect health. Predisposing factors (antecedents such as family history),

precipitating factors (e.g., childhood trauma, military occupational exposures and trauma), and perpetuating factors (e.g., sleep, diet, family, and social support) are assessed. A veteran's exposure timeline is then developed based on premilitary, military (deployments and duty stations), and post-military civilian time periods. The veteran's top health concerns are considered in light of military exposures and whether they are contributing to current health status. These determinations are needed to decide whether VA benefits should be provided. Veterans have beliefs about their exposures that need to be acknowledged, and 30 percent report that their health worsened after joining the military.

Because veterans get their medical information from many sources, they need a trusted source of information based on evidence. However, communication about exposures is challenged by lack of data, perceived delays in release of information, uncertainty about health effects, and conflicting interpretation of data. Further, lay perceptions of risk often differ from experts. Risk perception is not misperception; patients' differing perceptions are valid and rational. Communicators and providers need to acknowledge and account for differing perceptions.

Discussion

Participants asked about VA's training programs in exposure assessment and whether they are available to non-VA medical schools. WRIISC provides post-deployment health education to veterans, families, and loved ones of deployed veterans, health care providers, and the general public. WRIISC does not see pregnant women so there is little focus on reproductive health issues; however, the program is cognizant of the intergenerational effects of exposures.

Community Member and Clinician Panel To Inform Research
Moderator: Wendy Weber, N.D., Ph.D., M.P.H., NCCIH

Viola Waghiyi, Alaska Community Action on Toxics; Amy Tamayo, J.D., Alianza Nacional de Campesinas; Laurene Allen, L.I.C.S.W., Merrimack Citizens for Clean Water; Marya Zlatnik, M.D., University of California, San Francisco; Sheela Sathyanarayana, M.D., M.P.H., University of Washington; Omowunmi Osinubi, M.D., M.Sc., M.B.A., U.S. Department of Veterans Affairs

Dr. Weber asked the panel their top priorities for research. Responses included the following topics:

- How do we effectively educate health care providers about the health effects of environmental exposures so patients and members of communities do not feel dismissed, given that most medical school curricula insufficiently address environmental exposures? Community members have knowledge that should be tapped and health care providers need the tools to know which questions to ask. The burden of proof should not be placed on the exposed population.
- There may be difficult cultural factors (e.g., immigration, discrimination, sense of privacy about one's body) at play in exposed populations, which makes it important to work with community-based organizations and trusted voices. Funding is needed to support such outreach.
- Community-centered and -based research efforts can be critically informative. Community organizers need technical assistance in collecting and analyzing data and applying for grants. External investigators need to shadow community members to determine what research questions are most important to them.
- There are some defined communities of people who have experienced similar exposures, such as beauty salon workers and firefighters. These and other cohorts can be assessed to determine other factors contributing to health and disease in addition to similar exposures.

- Most people experience multiple chemical exposures and experience multiple health effects. Some communities might be exposed to entire classes of compounds. Yet research traditionally has been centered on one exposure or one outcome, an approach that is too slow. Multidisciplinary studies of multiple exposures and outcomes with a whole person perspective are likely to yield better answers faster. These are also likely to yield potential solutions by focus, that is, individual treatment versus population-based approaches versus regulatory and legal actions.
- Healing and remediation can begin before all the evidence is available. Using baseline data, the effects of obvious interventions can be tracked over time. We have enough information on many chemicals (e.g., phthalates); there are positive intervention studies as well as null studies. These results need to be translated and disseminated. "Don't let your research die in a journal."
- Most research has focused on legacy PFAS using blended rates. Existing test panels are incomplete and misleading. New EDCs need to be added to existing panels and more research is needed on the reliability, comprehensive, and clinical validity and utility of existing and newly developed panels.

Putting It All Together and Next Steps
Moderators: Thad Schug, Ph.D., NIEHS, and Sekai Chideya, M.D., M.P.H., NCCIH

This workshop highlighted the ways in which EDCs affect our bodies and health. Speakers described the mechanisms by which EDCs act, the pathways they affect, and the consequences of exposures. Data were presented that underscore the higher risk to some communities and workers and the disparate presence and effects of these contaminants on specific populations.

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. The Veterans Administration provides a model of how lifestyle changes and appropriate clinical care can improve the lives and health of those exposed to EDCs. Education campaigns are needed to inform consumers and patients about products that contain EDCs so they can act individually to avoid these chemicals. Research has found that avoidance of such products 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.

Despite progress in recent years, several challenges remain. Although there are vast numbers of EDCs in the environment, few are sufficiently characterized to be the targets of 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 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. Despite these challenges, much has been learned about reducing exposures and mitigating effects. Clinicians, patients, and consumers need evidence-based guidance about EDC testing and mitigation strategies to choose what is useful and feasible.

Participants discussed the need to also focus on delivering educational efforts to reduce exposures through, for example, consumer choices, appropriate and safe use of PPE when needed, and use of water and air filtration systems. Testing these interventions involves little to no harm to research participants. 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? Further, at what critical stage 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.

Ideally, interventions that address multiple EDCs at once will have the greatest impact. This requires studies that include different populations and life stages, including vulnerable groups and populations with multiple conditions. NCCIH Director Dr. Helene M. Langevin closed the meeting by noting that the research community is starting to understand how to deal with problems with complex inputs and outputs. The exposome is a good example as a strategy to measure all exposures of an individual in a lifetime and how those exposures relate to health. Smart trial designs recognize that an individual's exposure begins before birth and involves environmental and occupational sources. The exposome is applying novel methods to understand how exposures interact with someone's unique characteristics such as genetics, physiology, and health history. Advanced computational models can be used to see how the complex network of influencing factors changes over time. This workshop provided hope that interventions focused on the whole person, from the psychological to the molecular level, can diminish the negative effects of EDCs.

* The videocast/recording of this presentation is not available.

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