REVIEW ARTICLE

FOSSIL-FUEL POLLUTION AND CLIMATE CHANGE
Caren G. Solomon, M.D., M.P.H., *Editor*, and Renee N. Salas, M.D., M.P.H., *Guest Editor*

Health Effects of Fossil Fuel–Derived Endocrine Disruptors

Tracey J. Woodruff, Ph.D., M.P.H.

From the Program on Reproductive Health and the Environment, Environmental Research and Translation for Health Center, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, San Francisco. Dr. Woodruff can be contacted at tracey.woodruff@ucsf.edu.

N Engl J Med 2024;390:922-33.
DOI: 10.1056/NEJMra2300476

Pollution, including air pollution, water pollution, pollution from lead and other chemicals, and toxic occupational exposures, is the leading cause of premature death globally, with more than 90% of pollution-related deaths occurring in low- and middle-income countries.[1] Chemical pollution is estimated to be responsible for at least 1.8 million deaths each year.[1] This number is probably an underestimate, since less than 5% of approximately 350,000 chemicals registered for use globally have been adequately studied; most countries do not require testing for chemical health harms or disclosure of use.[2-4]

Chemical pollution is driven by the extraction, production, and use of fossil fuels (coal, oil, and gas), and fossil fuels are also the primary driver of climate change.[5] Many fossil fuel–derived chemicals (petrochemicals) interfere with the function of the endocrine system.[5-7] These endocrine-disrupting chemicals (EDCs) are present in many industrial and everyday products (e.g., plastics, building materials, children's toys, fabrics and dyes, detergents, cosmetics, and pesticides).[2,5,8] Exposures have been linked to multiple adverse human health conditions, including cancer, neurodevelopmental harm, and infertility.[3,4,6,7,9,10]

Fossil-fuel consumption and petrochemical production are more than 15 times higher than they were in the 1950s.[3] Over the past 7 decades, the prevalence of multiple chronic health conditions and attributable deaths has been increasing in the United States and globally.[4,11] In the United States, for example, between 1990 and 2019, increases in the rates of neurodevelopmental disorders, diabetes, chronic respiratory disease, and cancer ranged from 28% to 150%.[12] Numerous medical societies, government agencies, and systematic reviews have concluded that exposure to chemicals and pollution, including EDCs, is an important risk factor for multiple diseases and health inequities and probably contributes to these increases, though temporal associations alone cannot be interpreted as causal.[4,8,13-16]

More recently, multinational fossil-fuel corporations have increased production of plastics and other petrochemicals, as demands increase for making the transition from oil and gas to renewable energy sources in order to address climate change[6,17] (Fig. 1). Since the U.S. "shale revolution" (the marked increase in U.S. oil and gas production through fracking and horizontal drilling, beginning in the early 2000s), the United States now accounts for 40% of the global capacity for ethane-based petrochemicals, with a boom in production of single-use plastics as a new revenue source.[6,21] Producing plastic and plastic-related chemicals can be more lucrative than selling methane and ethane for fuel, heat, or electricity.[5]

Currently, petrochemicals account for 12% of global oil demand but are on course to account for more than a third of the growth in worldwide oil demand by 2030 and nearly half the growth by 2050.[22] As part of petrochemical growth, plastic production is predicted to grow by a factor of almost 3, from more than

KEY POINTS

Health Effects of Fossil Fuel–Derived Endocrine Disruptors

- Pollution is the leading cause of premature death globally.
- Fossil fuels contribute to chemical pollution through production of petrochemicals, many of which interfere with hormonal function (endocrine-disrupting chemicals [EDCs]). Examples include perfluoroalkyl and polyfluoroalkyl substances in food packaging and fabrics and phthalates in plastics and consumer products.
- Petrochemical production is increasing, and people are exposed through contaminated air, water, food, and manufactured products (e.g., plastics, pesticides, building materials, and cosmetics).
- EDCs can increase several health risks, including cancer, neurodevelopmental harm, and infertility.
- Risks are higher with exposures during fetal and child development and with exposure to multiple EDCs and occur at low exposure levels. Exposures are higher in communities of color and low-income communities and contribute to health inequities.
- Clinicians can provide advice to patients toward reducing some exposures, but policy change is needed to establish legal requirements for comprehensive safety testing and to reduce health threats from petrochemicals. Clinicians are important advocates for these changes.

400 million metric tons to 1100 million metric tons by 2050.[18] Plastic production involves the use of numerous EDCs, both in the polymer derived from the raw material (e.g., styrene and polyvinyl chloride) and in the additives (e.g., flame retardants, perfluoroalkyl and polyfluoroalkyl substances [PFASs], and phthalates).[6]

Recognition of environmental contributors to disease has increased among some clinicians, particularly specialists in obstetrics and gynecology,[4,23] pediatrics,[24] and endocrinology.[7] However, the increase in fossil fuel–driven EDC exposures and associated health harms requires a broader understanding among health professionals of the risks associated with EDCs and strategies to mitigate and prevent exposures.

OVERVIEW OF EDCS

HEALTH EFFECTS

An EDC is "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action."[7] EDCs can disrupt hormonal activity through multiple mechanisms, including interfering with hormone receptors; altering hormone synthesis, distribution, circulation, and metabolism; inducing epigenetic changes; and altering hormone receptor expression or transport across cell membranes.[25] Disrupting hormonal activity can increase the risk of multiple downstream health conditions, including female and male reproductive harms (e.g., impaired ovarian development and decreased sperm quality), metabolic disorders (e.g., obesity and diabetes), hormone-sensitive cancers (e.g., breast, prostate, and testicular cancers), and neurodevelopmental harms (e.g., intelligence quotient [IQ] decrements and attention deficit–hyperactivity disorder).[3,4,7,8,23] EDCs can increase the risk of disease even at very low levels of exposure because of population-level factors that can increase disease susceptibility, including intrinsic factors (e.g., underlying medical conditions, life stage, and genetics) and extrinsic factors (e.g., food insecurity, poverty, racism, and discrimination), as well as simultaneous exposure to multiple EDCs. Consequently, experts believe that there is no risk-free level of exposure to these chemicals across the population.[26,27]

Since it would be unethical to conduct randomized clinical trials of EDC exposure, the evidence base linking EDCs to health harms is derived largely from experimental studies in animals and human observational studies.[4,7,28] There are several types of observational human studies, with higher quality studies generally being those that have followed participants over time with adequate exposure assessment and with analyses that have been adjusted for relevant confounders that can bias results if not adequately addressed. Animal models have reasonable concordance with human studies, though the results in animals can

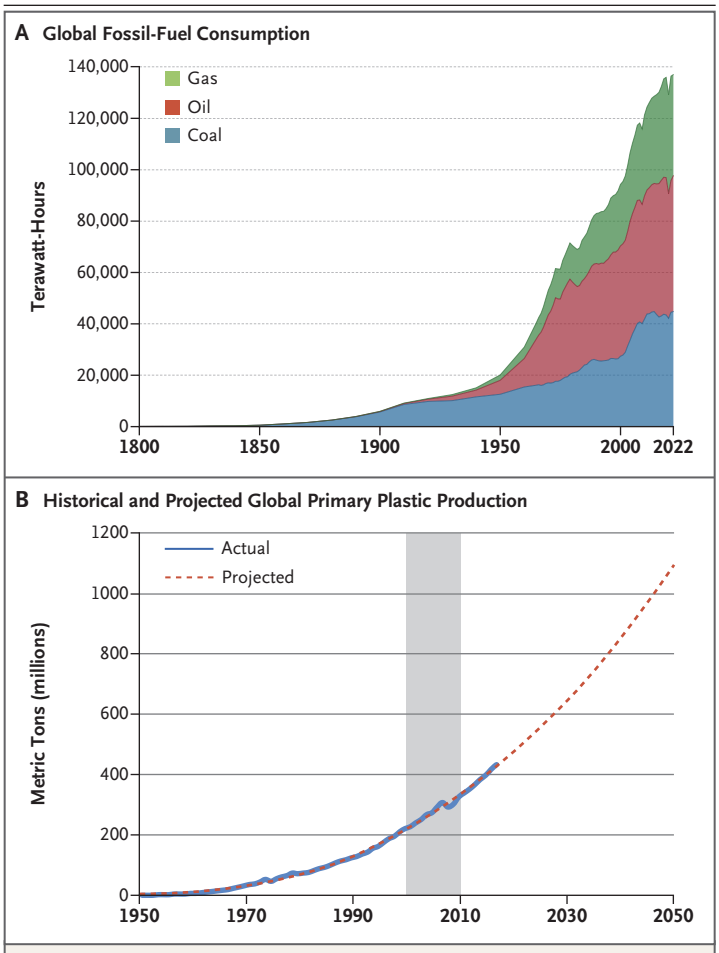

Figure 1. Trends in Global Fossil-Fuel Consumption and Primary Plastic Production.

Panel A shows global fossil-fuel consumption from 1800 to 2022. Panel B shows historical and projected global primary plastic production. The shaded area indicates the period known as the "shale revolution" in the United States (2000 through 2010). Data are from Geyer,[18] the Energy Institute,[19] and Smil.[20]

underestimate human effects, since they do not represent the full range of human variability or vulnerability to chemical exposures.[29] In vitro assays and computer modeling or simulations are increasingly used to identify EDCs, primarily through interactions with hormone receptors or alterations in hormone synthesis, though further validation is ongoing.[7,25]

Systematic reviews, sometimes including meta-analyses, adhering to recommended methodologic practices, are considered the highest quality method for evaluating and synthesizing environmental health evidence.[9,27,29,30] Methods for evaluating and synthesizing the results of observational human studies and animal studies in environmental health have been adapted from Cochrane systematic review methods to evaluate the quality of the evidence, GRADE (grading of recommendations, assessment, development, and evaluations) to assess the certainty of the evidence, including considering potential biases, and environmental health frameworks.[31,32] These methods, including the Navigation Guide and the U.S. National Toxicology Program's Office of Health Assessment and Translation methods, provide a bottom-line summary of evidence linking environmental exposures to health effects and classifying the hazard to health (ranging from "not classifiable" to "probably" to "known," though the nomenclature can vary) and are recommended by the National Academies of Sciences, Engineering, and Medicine (NASEM).[29-32] Other robust reviews include those conducted by authoritative bodies including state, national, and international agencies.

DEVELOPMENTAL EXPOSURES

Embryonic and fetal development can be uniquely sensitive to EDC-induced perturbations,[4,7,8] and the health effects of even low-level in utero exposure can be manifested at birth (e.g., low birth weight or preterm birth and birth defects), in childhood (e.g., neurodevelopmental effects), or in adulthood (e.g., cancer and cardiovascular disease).[3,4,7,8] A systematic review of observational studies of polybrominated diphenyl ethers (PBDEs), a toxic class of flame retardants, showed that there was sufficient evidence to conclude that prenatal PBDE exposures increase the risk of IQ decrements in children.[30] PBDEs can alter thyroid hormone levels during pregnancy. Thyroid hormones are critical for brain development,[33] and even small decrements in maternal thyroid hormone levels, including subclinical decrements,[34] are associated with adverse neurodevelopmental outcomes in offspring,[35] including lower IQ levels.[34]

The European Food Safety Authority concluded, on the basis of a systematic review, that developmental exposure to bisphenol A (BPA), a plasticizer known to mimic estrogen, is likely to increase the risks of immunotoxic effects (e.g., asthma or allergy), developmental neurotoxic effects, and toxic effects on the female reproductive system (e.g., abnormal ovarian development) later in life, even at extremely low levels of exposure.[10] BPA is listed as a developmental and re-

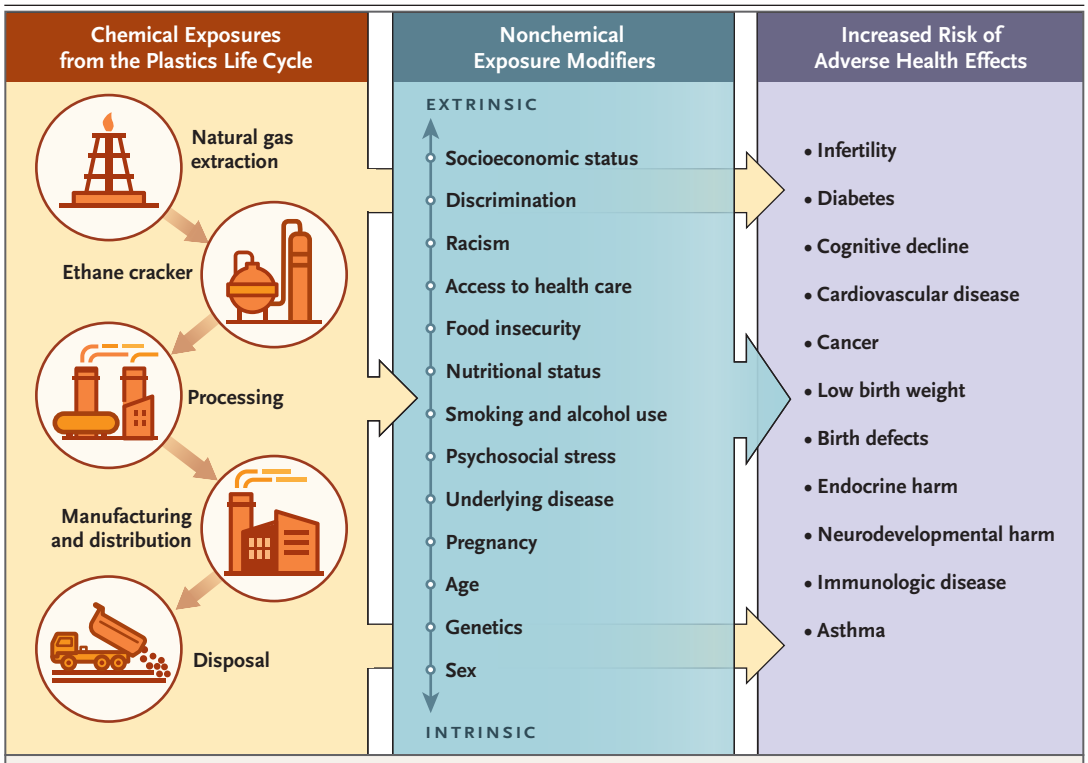

Figure 2. Adverse Effects of Chemical Exposures on Health Outcomes.

Chemical exposures from the plastics life cycle (from fossil-fuel extraction and processing to product manufacturing, distribution, and disposal) interact with social vulnerabilities and biologic susceptibilities, resulting in adverse health outcomes. These lists are not exhaustive.

productive toxicant by the state of California under Proposition 65 (which requires the state to regularly maintain a list of chemicals that cause cancer, reproductive harms, or developmental harms).[36] In addition, in utero exposure to dichlorodiphenyltrichloroethane (DDT), which can influence the estrogen system, is associated with increased risks of hypertension and breast cancer in adulthood.[37,38] Finally, there is evidence that the effects of EDCs can be transmitted to subsequent generations through alterations to the epigenome.[3,7,8]

SOURCES

Production, distribution, and disposal of plastics and other materials made from petrochemicals, with subsequent degradation in the environment, lead to a perpetual cycle of human exposure to EDCs from contaminated air, food, drinking water, and soil (Fig. 2).[6,21] Exposures also occur in home, school, and workplace indoor environments from multiple consumer and building products.[2,7,8]

EDCs contaminate the food supply from various sources, including production practices (e.g., agricultural pesticide use), processing (e.g., leaching of chemicals such as BPA, phthalates, and PFAS from plastic in food-processing equipment), and packaging (e.g., plastics and petrochemical-derived inks and cardboard and canned-food linings), with indirect contamination from fossil-fuel pollutants in the environment.[6,21,23] Personal care products and cleaning products typically include EDCs, such as PFAS, phthalates, parabens, nonylphenols, and triclosan, which may be individually identified on the label or, for some products, hidden under the category of "fragrance."[7,23] Flame retardants, PFAS, and phthalates are commonly found in building materials and consumer products, including artificial turf, carpets, stain-resistant fabrics, flooring, cabinets, insulation, furniture foam, computers, and other electronics.[7,21,23,39] EDCs can migrate from myriad sources and aggregate in dust; people are then exposed through inhalation, inges-

tion, or dermal absorption.[40] A systematic review identified more than 40 chemicals in household dust, many of them EDCs, including flame retardants, phthalates, and PFAS.[40] Similarly, oil spills, leaching from landfills, and the use and contamination of water in shale extraction have led to extensive pollution of drinking and ground water in the United States from petrochemical-derived EDCs.[6]

CUMULATIVE EXPOSURES

Given the known widespread exposure in the population to multiple petrochemical-derived EDCs in products and the environment, national biomonitoring data and individual epidemiologic studies have measured approximately 150 chemicals in urine and blood, including samples obtained during pregnancy.[41,42] These include heavy metals (e.g., lead), agrochemicals (e.g., DDT and chlorpyrifos), flame retardants (e.g., PBDEs), petrochemicals found in plastics and rubber (e.g., BPA, phthalates, and PFAS), personal care products and food additives (e.g., phthalates and parabens), and chemicals emitted during industrial processes (e.g., polycyclic aromatic hydrocarbons).[2,42] This represents a fraction of potential EDC exposures, since standard detection technology measures less than 1% of total chemicals in use.[2] The National Research Council concluded that cumulative exposures to multiple EDCs that adversely affect the androgen system in utero (including phthalates and certain pesticides) increase the risk of adverse male reproductive development, as compared with exposure to these chemicals individually,[43] and recommended extending cumulative risk assessments to other chemicals more generally.

EXAMPLES OF FOSSIL FUEL–DERIVED EDCS

Selected key examples of EDCs derived from fossil fuels used in plastic production are reviewed below. (Table 1 includes more information on their effects and on other fossil fuel–derived EDCs.[3,4,7,8,23,30])

PFAS is a class of approximately 15,000 chemicals widely used in nonstick applications, including cookware and food packaging, water- and stain-resistant clothing and carpets, and plastics production to coat items such as bottles and processed-food containers.[2,6,56] Systematic reviews and authoritative bodies have found sufficient evidence linking multiple chemicals of this class with an increased risk of adverse health outcomes, including reduced fetal growth, dyslipidemia, a decreased antibody response to vaccines, and an increased risk of kidney cancer.[9] In addition, there is limited suggestive evidence of increased risks of gestational hypertension and preeclampsia, breast and testicular cancer, and thyroid disease and dysfunction.[9]

Phthalates include dozens of structurally similar chemicals that are used to make plastics more durable and pliable, to help dissolve other materials, and to serve as fragrance stabilizers in consumer products.[6,43] A number of these chemicals have been shown to be antiandrogenic (e.g., inhibiting testosterone production in the developing male fetus), and systematic reviews have shown moderate evidence that a subset of these chemicals have adverse effects on male and female reproduction (e.g., infertility, decreased sperm count, and decreased ovarian reserve) and increase the risks of metabolic disorders (e.g., insulin resistance and diabetes).[43,44]

Bisphenols are a group of aromatic compounds used in polycarbonate plastic products (e.g., water bottles, food storage containers and packaging, and eyeglasses), epoxy resin liners of aluminum cans, and other consumer goods such as thermal paper receipts.[7] As noted above, exposure to BPA, the most well-known compound in this class, has multiple adverse effects on health.[7,10] Although BPA has been removed from several products globally, including certain children's toys, plastic bottles, and some thermal receipt paper (for store receipts), owing to its toxicity, the use of similarly toxic substitutes such as bisphenol S and bisphenol F has increased.[57]

ENVIRONMENTAL INJUSTICE

EDC exposures and health outcomes are distributed unequally. An analysis of nationally representative data showed that serum and urine levels of multiple EDCs, in particular pesticides, heavy metals, and chemicals found in consumer and personal care products, among non-Hispanic Black women, Hispanic women, women of other racial or ethnic groups, and multiracial women were persistently higher, sometimes more than 4 times higher, than the levels among non-Hispanic White women, a finding that is independent of other demographic factors.[41] Similar racial and ethnic

disparities have been found among pregnant women.[42]

Black, Latinx, or low-income communities account for the majority of people who reside near the thousands of U.S. facilities producing, storing, or using highly toxic chemicals, many of which are petrochemical-derived EDCs.[58] The residents of these communities have increased exposure to chemical (and air) pollution.[59-62] These disproportionate exposure burdens are in part due to historically racist policies, such as government-sanctioned housing discrimination ("redlining"), which led to colocation of communities of color with polluting industries.[63] Workers, particularly low-wage workers, in plastic production, construction, agriculture, cleaning services, beauty and nail salons, and health care are also exposed, on average, to higher concentrations of EDCs, including phthalates, pesticides, and heavy metals, than the general public.[8,23] In addition, there is greater use of certain personal care products containing EDCs by communities of color, such as certain types of hair products and vaginal products used by Black women, attributed in part to racist marketing practices promoting Eurocentric or "White" beauty standards for appearance and exploiting concerns about "odors."[64]

Higher EDC exposures in low-income populations and communities of color occur with other factors contributing to disease, including economic and social stressors (e.g., poverty and discrimination) and biologic susceptibility (e.g., preexisting health conditions, developmental life stage, and genetic factors) to further exacerbate health inequities[27] (Fig. 2).

CLINICAL DECISION MAKING WITH LIMITED DATA

The greatest challenge to reducing harmful EDC exposures is the lack of legal requirements for comprehensive safety testing before the chemicals are used in production and in the marketplace, unlike the requirement that pharmaceuticals undergo safety testing before they are used in production, are sold, or receive regulatory approval. The United States and most other countries have limited and sometimes no requirements to test chemicals and pesticides for endocrine or other health effects before use.[14,27] Additional challenges arise from frequent delays in regulatory action to reduce toxic exposures, owing in part to a lack of laws requiring data on potential health harms and disclosure of where chemicals are used, released, and discarded. Such delays, and the substantial health harms that result, have occurred even when there is robust evidence of harms (e.g., with exposures to lead, asbestos, and polychlorinated biphenyls).[65] More recently, the FDA denied requests to promptly reassess the safety of using phthalates in food-contact materials. Nine phthalates remain in the food supply, despite the FDA's acknowledgment that its approvals for these uses are based on exposure and toxicologic information from the 1960s to the 1980s[66] and despite the availability of more recent evidence of harm (Table 1).

Contributing to regulatory delays are strategies used by polluting industries, including "weaponizing" scientific uncertainty to foster distrust in scientific findings and lobbying for weaker regulations.[71] For example, previously secret industry documents show that the industries knew about the health harms of PFAS decades before the scientific and public health community did.[72] In addition, there is evidence that studies sponsored by the chemical industry are more likely to report findings that are favorable to the industry's products than are studies without industry sponsorship.[27] Chemical industry tactics perpetuate the life cycle of harmful chemicals and are similar to tactics used by the fossil-fuel industry to delay action on climate change.[73]

The result is a growing burden of toxic chemical exposures, mostly beyond individual and clinical control. Additional challenges for clinicians include a lack of required training in environmental health in medical schools and residency programs, unfamiliarity with the multitude of chemicals to which patients are exposed, and the complexity of addressing ways to mitigate chemical exposures and associated hazards. The Institute of Medicine (now the National Academy of Medicine) recommended in the 1990s that "principles and concepts of environmental health must be taught and continually reinforced throughout undergraduate and postgraduate medical education and training," but implementation is still needed.[74]

Protecting health and advancing health equity require that clinicians take a precautionary approach and act on uncertain evidence.[9,14] A 2022 NASEM review of clinical decision-making for PFAS exposures recommends that clinicians base

Table 1. Examples of Fossil Fuel–Derived Chemicals with Known, Likely, or Suspected Endocrine Effects.*

Chemical Class and Examples	Major Exposure Sources	Health Effects		Specific Effects
		Known or Likely	Suspected	
PFASs: PFOA, PFOS, PFHxS, PFBS, PFBA†	Consumer products (e.g., nonstick cookware, stain-resistant clothing), building materials (e.g., stain-resistant carpeting), personal care products (e.g., cosmetics, menstrual products), food packaging materials, drinking water, industrial facility releases, legacy environmental exposures	Decreased infant and fetal growth, dyslipidemia, decreased antibody response to vaccines in children and adults[9]	Kidney cancer, testicular and breast cancer, gestational hypertension and preeclampsia, thyroid disease and dysfunction[9]	A meta-analysis of 24 studies showed a 10.5-g decrement in birth weight per 1-ng increase in PFOA/ml, and an analysis of 29 studies showed a 3-g decrement in birth weight per 1 ng PFOS/ml increase.[45] EPA's proposed new standard to reduce drinking water levels of PFOA and PFOS to 4.0 ppt is projected to result in savings of $175 million annually because of increased birth weight and reduced deaths attributed to low birth weight.
Ortho-phthalates: DEHP, DBP, BBP, DEP, DINP	Food, personal care products (e.g., fragrances), food packaging materials, building materials (e.g., PVC flooring), industrial facility releases	Male reproductive toxicity (e.g., sperm effects), decreased anogenital distance,[30,44] preterm birth,[44] metabolic disorders (e.g., insulin resistance, diabetes)[44]	Spontaneous abortion,[44] neurodevelopmental harms (e.g., ADHD)[46]	A meta-analysis of 5 studies showed that a log increase in gestational DEHP levels was associated with a 4% reduction in anogenital distance in human male offspring, reflecting reduced fetal testosterone production.[30]
Flame retardants: PBDEs, organophosphate ester flame retardants (OPFRs)	Consumer products (e.g., electronics, furniture, mattresses, children's products), personal care products (e.g., nail polish), plastics, industrial facility releases, legacy environmental exposures	Impaired neurodevelopment[47]	Altered thyroid function in newborns,[33] reproductive toxicity[4,23]	A meta-analysis of 4 U.S. and European studies showed that an increase by a factor of 10 in PBDE exposure during pregnancy was associated with a decrement of 3.7 IQ points in the offspring.[47]
Bisphenols: BPA, BPS	Polycarbonate plastic products (e.g., water bottles, food-storage containers and packaging, eyeglasses), epoxy resin liners of aluminum cans, and other consumer goods such as thermal paper receipts[36]	Adverse effects on ovarian development and function,[48] female reproductive toxicity, impaired neurodevelopment, metabolic abnormalities, immune system abnormalities[10]		A study of 700 couples from China showed that an increase of 1 ln unit in urinary concentrations of BPA in women was associated with a longer time to pregnancy (OR, 0.87; 95% CI, 0.78–0.98) and an increased risk of infertility (OR, 1.23; 95% CI, 1.00–1.50).[49]‡
Heavy metals: lead, cadmium, mercury, arsenic[2]	Consumer products (e.g., dishware, ceramics, jewelry, children's products), spices, personal care products (e.g., skin lighteners), tobacco smoke, industrial facility releases, legacy environmental exposures	Impaired neurodevelopment, male reproductive toxicity (e.g., impaired semen quality, fertility effects), female reproductive toxic effects, cancer, immunosuppression[36,50]		A pooled analysis with a total of 1333 children from 7 longitudinal cohort studies showed a 6.9-point reduction in IQ with an increase in blood lead levels by a factor of approximately 10.[51]
Pesticides: organophosphate pesticides, neonicotinoids, pyrethroids, DDT[2]	Food and drinking water, insecticides, rodenticides, herbicides, spray drift from use in agricultural fields	Impaired neurodevelopment (e.g., lowered IQ),[36] reduced sperm quality[52]	Increased susceptibility to childhood cancers (e.g., leukemia and brain tumors), increased susceptibility to testicular cancer, impaired fetal growth[3,4,23]	A birth cohort study of 329 children showed an average 7-point IQ deficit for children in the highest quintile of exposure to organophosphate pesticides during pregnancy, as compared with those in the lowest quintile of exposure.[53]

Volatile organic compounds: benzene, formaldehyde, toluene	Consumer products (furniture, textiles, glues, paints, detergents, disinfectants), personal care products (cosmetics, fragrances, nail polish), tobacco smoke, gas-stove emissions, fireplace emissions, industrial facility releases	Respiratory toxicity, lung cancer, nasopharyngeal cancer, leukemia, acute neurologic harm (e.g., dizziness, vomiting), female reproductive toxicity (e.g., increased time to pregnancy, spontaneous abortion risk), altered male reproductive system, reduced fetal growth[3,4,23,54]	A meta-analysis of 15 studies showed an elevated risk of leukemia (RR, 1.54; 95% CI, 1.18–2.00) among workers exposed to high levels of formaldehyde.[55]

* The health effects are based on authoritative reviews from the United States and globally.[3,8,23] Known or likely health effects are those for which associations with a given class of endocrine-disrupting chemicals (EDCs) or EDCs in that class have been classified in a robust or systematic review as known, causal, sufficient, presumed, likely, robust, or moderate. Suspected health effects are those supported by a lower level of evidence. The list of reported health effects is not comprehensive. ADHD denotes attention deficit–hyperactivity disorder, BBP benzyl butyl phthalate, BPA bisphenol A, BPS bisphenol S, DBP dibutyl phthalate, DDT dichlorodiphenyltrichloroethane, DEHP di(2-ethylhexyl)phthalate, DEP diethyl phthalate, DINP diisononyl phthalate, EPA Environmental Protection Agency, IQ intelligence quotient, ln natural logarithm, OPFR organophosphate ester flame retardant, OR odds ratio, PBDE polybrominated diphenyl ether, PFAS perfluoroalkyl and polyfluoroalkyl substances, PFBA perfluorobutanoic acid, PFBS perfluorobutanesulfonic acid, PFHxS perfluorohexane sulfonate, PFOA perfluorooctanoic acid, PFOS perfluorooctane sulfonate, RR relative risk, and PVC polyvinyl chloride.

† Some chemicals in this class are also persistent pollutants that, owing to their physical structure, persist and bioaccumulate in the environment, thus leading to biomagnification up the food chain and ongoing and widespread exposures through multiple sources, including dust and food.[3]

‡ Data supporting the reproductive toxicity of BPA, which has been classified as "known" or "likely," are based primarily on robust animal models.[10,36]

their decisions on the following considerations: proportionality (balancing plausible harms and benefits proportionally), justice (advancing health equity and respecting human rights; considering the sociohistorical context, existing structural inequalities, and issues of agency [the power a community has to advocate for itself in conflicts]), autonomy (providing for informed decision making by patients and respecting their values), feasibility (considering resource availability), and adaptability (responding to new information about harms, benefits, and other relevant considerations).[9]

CLINICAL PRACTICE RECOMMENDATIONS

Clinicians may be reluctant to address environmental exposures because of competing demands on clinical time and lack of preparation for assessing environmental exposures and answering patients' questions.[3] However, even without special expertise, clinicians can provide a basic assessment and general guidance for minimizing toxic exposures.

Patients — particularly those at high risk for disproportionate exposures (e.g., people who work in or live near manufacturing or waste-processing facilities[75] — should be asked about exposures in the workplace, home, and recreational activities. (An example of an environmental exposure history is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Referral to a specialist is appropriate if toxic exposure is suspected but there is uncertainty about how to assess or manage it. A Pediatric Environmental Health Specialty Unit, located in every region of the United States, offers clinical guidance for reproductive and child health and environmental exposures.[67] Occupational and environmental health specialists can provide expertise and advice regarding workplace exposures and workers' rights, particularly for pregnant workers, who should be advised of their right to minimize potentially harmful workplace exposures.[68,76]

Table 2 provides guidance for reducing toxic exposures that can be shared with patients; many of the recommendations can be implemented easily and at low cost.[4,23,24,67-69] (Additional materials are provided in the Supplementary Appendix.[77]) The feasibility of some recommendations, however, varies according to economic status and other factors (e.g., buying pesticide-free organic

Table 2. Examples of Recommendations for Reducing Exposure to Toxic Chemicals.*

Recommendation Category	Examples
Diet and food preparation and storage	Consume less meat and more fruits, vegetables, and whole grains, because certain chemicals can concentrate in animal fat. Eat fresh (and if accessible and feasible, organic) produce whenever possible; always wash raw produce to decrease exposure to pesticides. Avoid or minimize intake of foods with a high risk of contamination (e.g., fish containing high levels of mercury, such as swordfish and bluefin tuna). Avoid fatty foods, because persistent chemicals concentrate in fats. Avoid packaged and highly processed foods (e.g., fast food) when possible, to decrease exposures to chemicals such as phthalates and PFAS. Store food in nonplastic containers, such as glass, ceramic, or stainless steel containers (if accessible and feasible), instead of plastic containers, and avoid microwaving food or drinks in plastic containers. Substitute cookware made from nontoxic materials (e.g., cast iron, stainless steel, and ceramic cookware) for nonstick cookware.
Cleaning and other products	Use nontoxic cleaning products (e.g., baking soda, vinegar, and lemon). Use a wet mop or wet cloth to clean floors and surfaces in order to avoid distributing dust containing chemicals in the air. Remove shoes before entering the house to avoid tracking in contaminants. Minimize use of toxic insect control methods; prioritize alternative control methods (e.g., eliminate standing water, which provides an insect breeding ground; use screens on doors and windows; protect skin with clothing as much as possible). Substitute professional wet cleaning for chemical dry cleaning. Use volatile organic compound–free or water-based home improvement materials. Select flame retardant–free foam products. Use less-toxic personal care products (e.g., those that are paraben-free and unscented). Avoid synthetic turf fields. (If synthetic turf must be used for sports, do not eat or place water bottles on field; on returning home, keep sneakers or cleats outside, shower, and wash clothes separately.)
Work	Pregnant people or those planning a pregnancy who are exposed to toxic chemicals at work should request a change in duties to avoid these exposures. (Guidance can be obtained from an occupational health specialist or union representative.) Request information and training about hazardous substances in the workplace. Employers are required by law to provide such information and training, including access to handouts about toxic substances, called Safety Data Sheets. Request information about substitutes for toxic substances and other ways to prevent harmful exposures, such as use of personal protective gear (which should be provided by employers). People who work with toxic chemicals should shower and change clothing immediately after returning home from work and should keep work tools and clothing away from other people and living areas in the home.
Advocacy	Engage in partnerships and advocacy to support policies that reduce exposure to toxic chemicals and promote decarbonization and detoxification through reductions in fossil-fuel dependence and production of harmful EDCs.

* These recommendations are based on clinical guidelines from professional societies and health organizations.[4,23,24,67-70] Recommendations at the individual level can help lower exposures to toxic chemicals, but because of deficiencies in the law, most exposures are beyond individual control.

produce), underscoring the need for systemic changes that provide equitable access to nontoxic foods and products.

Currently, there are standard clinical measurements for only a handful of pollutants (e.g., lead and mercury), and testing is usually limited to patients identified as having a high risk of exposure. For most chemicals, access to testing is limited to participants in research studies. Recently, NASEM recommended that clinicians offer PFAS testing to patients likely to have a history of elevated exposure, on the basis of testing of local water systems and certain jobs such as firefighting and food or hospitality work.[9]

PUBLIC HEALTH AND SOCIETAL INTERVENTIONS

People can reduce exposures to some chemicals through individual actions,[4,78] but most exposures are beyond individual control. For example, although washing fresh produce is recommended

to avoid pesticide exposure, chemicals such as the carcinogen 1,4-dioxane are pervasive in drinking water and water used to grow crops. Lack of disclosure of chemicals in most products and lack of health hazard information for most petrochemicals pose further challenges.[4,7,27] Although purchasing choices can send signals to the marketplace and foster changes in chemical use, this approach unfairly places the burden on the consumer and has limited success without widespread consumer demand. In addition, removing an individual chemical from products often results in the substitution of a similar toxic chemical.[79]

Policy changes at the state and federal levels, through legislation and regulation, are essential to increase transparency, systematically reduce harmful chemical exposures, improve human and environmental health, and protect the most affected communities. Many medical societies have recommended government policies to reduce exposure to harmful environmental agents.[4,7,14,23] Reducing health harms from petrochemicals requires policies that promptly and substantively reduce fossil-fuel extraction, production, and use — an approach known as decarbonization and detoxification.[5,70] Examples of relevant legislation include requirements for stricter safety testing of chemicals before approval and for disclosure and tracking of where chemicals are used throughout their life cycle, full or partial bans of harmful chemicals, bans on single-use plastics, and bans or reductions of pesticides and other contaminants in food.[4,7,14,23] Health professionals — individually or through professional societies — have an important role in advocating for legislation to reduce chemical exposures, particularly among subgroups of the population that are most exposed and most susceptible.

CONCLUSIONS

There is an urgent need for the clinical community to address the growing burden of exposure to EDCs, largely derived from petrochemicals, in order to prevent a broad range of associated health harms. With projected increases in fossil-fuel production in the United States and globally, despite the recommendations of the United Nations Intergovernmental Panel on Climate Change and other groups to rapidly reduce production, the problem will continue to grow.[80] In addition to counseling their patients, clinicians can be critical advocates for policy changes to both decarbonize and detoxify the economy in order to address the combined health threats of petrochemical-derived EDCs and climate change.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Swati Rayasam for assistance with research and earlier versions of the figures, and Nicholas Chartres, Daniel Axelrad, Allison Rozema, Ariel Eastburn, Susan Lamontagne, and Rashmi Joglekar for assistance with the preparation of the manuscript.

REFERENCES

1. Fuller R, Landrigan PJ, Balakrishnan K, et al. Pollution and health: a progress update. Lancet Planet Health 2022;6(6):e535-e547.
2. Pellizzari ED, Woodruff TJ, Boyles RR, et al. Identifying and prioritizing chemicals with uncertain burden of exposure: opportunities for biomonitoring and health-related research. Environ Health Perspect 2019;127:126001.
3. Strauss FJ III, Barbieri R, Dokras A, Williams CJ, Williams Z, eds. Yen & Jaffe's reproductive endocrinology: physiology, pathophysiology, and clinical management. 9th ed. Philadelphia: Elsevier, 2024.
4. Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynaecol Obstet 2015;131:219-25.
5. Trowbridge J, Goin DE, Abrahamsson D, Sklar R, Woodruff TJ. Fossil fuel is the common denominator between climate change and petrochemical exposures, and effects on women and children's health. Int J Gynaecol Obstet 2023;160:368-71.
6. Landrigan PJ, Raps H, Cropper M, et al. The Minderoo-Monaco Commission on Plastics and Human Health. Ann Glob Health 2023;89:23.
7. Gore AC, Chappell VA, Fenton SE, et al. EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev 2015;36(6):E1-E150.
8. European Parliament's Committee on Petitions. Endocrine disruptors: from scientific evidence to human health protection. Brussels: Policy Department for Citizen's Rights and Constitutional Affairs, March 2019.
9. National Academies of Sciences Engineering and Medicine. Guidance on PFAS exposure, testing, and clinical follow-up. Washington, DC: National Academies Press, 2022.
10. EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), Lambré C, Barat Baviera JM, et al. Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA J 2023;21(4):e06857.
11. Global Burden of Disease Collaborative Network. Global Burden of Disease study 2019 (GBD 2019) results. Seattle: Institute for Health Metrics and Evaluation. 2020 (https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/506e0780ef3ccc7350532717f33eec09).
12. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.
13. Council on Environmental Health. Chemical-management policy: prioritizing children's health. Pediatrics 2011;127:983-90.
14. American Public Health Association. A precautionary approach to reducing American exposure to endocrine disrupt-

ing chemicals. November 9, 2010. (Policy no. 20104) (https://www.apha.org/policies-and-advocacy/public-health-policy-statements/policy-database/2014/07/09/09/03/a-precautionary-approach-to-reducing-american-exposure-to-endocrine-disrupting-chemicals).
15. Bergman A, Heindel JJ, Kasten T, et al. The impact of endocrine disruption: a consensus statement on the state of the science. Environ Health Perspect 2013;121(4):A104-A106.
16. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Reducing prenatal exposure to toxic environmental agents: ACOG Committee opinion, number 832. Obstet Gynecol 2021;138(1):e40-e54.
17. Net zero by 2050. Paris: International Energy Agency, May 2021 (https://www.iea.org/reports/net-zero-by-2050).
18. Geyer R. Production, use, and fate of synthetic polymers. In: Letcher TM, ed. Plastic waste and recycling: environmental impact, societal issues, prevention, and solutions. London: Academic Press, 2020:13-32.
19. Energy Institute. Statistical review of world energy. 2023 (https://www.energyinst.org/statistical-review).
20. Smil V. Energy and civilization: a history. Cambridge, MA: MIT Press, 2017.
21. Chemicals in plastics: a technical report. Geneva: United Nations Environment Programme, 2023.
22. The future of petrochemicals. Paris: International Energy Agency, 2018 (https://www.iea.org/reports/the-future-of-petrochemicals).
23. ACOG Committee. Exposure to toxic environmental agents. Fertil Steril 2013;100:931-4.
24. Council on Environmental Health. Pediatric environmental health. 4th ed. Itasca, IL: American Academy of Pediatrics, 2019.
25. La Merrill MA, Vandenberg LN, Smith MT, et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 2020;16:45-57.
26. National Research Council. Science and Decisions: Advancing Risk Assessment. 2009.
27. Woodruff TJ, Rayasam SDG, Axelrad DA, et al. A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health 2023;21:Suppl 1:132.
28. Resnik DB. Randomized controlled trials in environmental health research: ethical issues. J Environ Health 2008;70:28-30.
29. National Academies of Sciences Engineering and Medicine. Building confidence in new evidence streams for human health risk assessment: lessons learned from laboratory mammalian toxicity tests. Washington, DC: National Academies Press, 2023 (https://doi.org/10.17226/26906).
30. National Academies of Sciences Engineering and Medicine. Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals. Washington, DC: National Academies Press, 2017.
31. Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 2014;122:711-8.
32. Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect 2014;122:1007-14.
33. Zhao X, Wang H, Li J, Shan Z, Teng W, Teng X. The correlation between polybrominated diphenyl ethers (PBDEs) and thyroid hormones in the general population: a meta-analysis. PLoS One 2015;10(5):e0126989.
34. Korevaar TIM, Muetzel R, Medici M, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 2016;4:35-43.
35. Thompson W, Russell G, Baragwanath G, Matthews J, Vaidya B, Thompson-Coon J. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2018;88:575-84.
36. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. The Proposition 65 list. (2015-01-28T14:44-08:00) (https://oehha.ca.gov/proposition-65/proposition-65-list/).
37. Cohn BA, La Merrill M, Krigbaum NY, et al. DDT exposure in utero and breast cancer. J Clin Endocrinol Metab 2015;100:2865-72.
38. La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD, Cohn BA. Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. Environ Health Perspect 2013;121:594-9.
39. Lauria MZ, Naim A, Plassmann M, Fäldt J, Sühring R, Benskin JP. Widespread occurrence of non-extractable fluorine in artificial turfs from Stockholm, Sweden. Environ Sci Technol Lett 2022;9:666-72.
40. Mitro SD, Dodson RE, Singla V, et al. Consumer product chemicals in indoor dust: a quantitative meta-analysis of U.S. studies. Environ Sci Technol 2016;50:10661-72.
41. Nguyen VK, Kahana A, Heidt J, et al. A comprehensive analysis of racial disparities in chemical biomarker concentrations in United States women, 1999–2014. Environ Int 2020;137:105496.
42. Buckley JP, Kuiper JR, Bennett DH, et al. Exposure to contemporary and emerging chemicals in commerce among pregnant women in the United States: the Environmental influences on Child Health Outcome (ECHO) Program. Environ Sci Technol 2022;56:6560-73.
43. National Research Council. Phthalates and cumulative risk assessment: the tasks ahead. 2008 (https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=202508).
44. Radke EG, Yost EE, Roth N, Sathyanarayana S, Whaley P. Application of US EPA IRIS systematic review methods to the health effects of phthalates: lessons learned and path forward. Environ Int 2020;145:105820.
45. Economic analysis for the proposed per- and polyfluoroalkyl substances national primary drinking water regulation. Washington, DC: Environmental Protection Agency, 2023.
46. Engel SM, Patisaul HB, Brody C, et al. Neurotoxicity of ortho-phthalates: recommendations for critical policy reforms to protect brain development in children. Am J Public Health 2021;111:687-95.
47. Lam J, Lanphear BP, Bellinger D, et al. Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. Environ Health Perspect 2017;125:086001.
48. Office of Environmental Health Hazard Assessment. Chemicals considered or listed under proposition 65. Bisphenol A (BPA) (https://oehha.ca.gov/proposition-65/chemicals/bisphenol-bpa).
49. Wang B, Zhou W, Zhu W, et al. Associations of female exposure to bisphenol A with fecundability: evidence from a preconception cohort study. Environ Int 2018;117:139-45.
50. Environmental Protection Agency. Integrated Science Assessment (ISA) for lead (third external review draft, November 2012) (https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=242655#Download).
51. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 2005;113:894-9.
52. Knapke ET, Magalhaes DP, Dalvie MA, Mandrioli D, Perry MJ. Environmental and occupational pesticide exposure and human sperm parameters: a navigation guide review. Toxicology 2022;465:153017.
53. Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect 2011;119:1189-95.
54. Environmental Protection Agency. IRIS toxicological review of formaldehyde

— inhalation. 2022 (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=248150).
55. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutat Res 2009;681:150-68.
56. Environmental Protection Agency. Navigation panel to PFAS structure lists. 2022 (https://comptox.epa.gov/dashboard/chemical-lists/PFASSTRUCT).
57. Pelch K, Wignall JA, Goldstone AE, et al. A scoping review of the health and toxicological activity of bisphenol A (BPA) structural analogues and functional alternatives. Toxicology 2019;424:152235.
58. Orum P, Moore R, Roberts M, Sánchez J. Who's in danger? Race, poverty, and chemical disasters: a demographic analysis of chemical disaster vulnerability zones. Brattleboro, VT: Environmental Justice and Health Alliance for Chemical Policy Reform, May 2014.
59. Tessum CW, Paolella DA, Chambliss SE, Apte JS, Hill JD, Marshall JD. $PM_{2.5}$ polluters disproportionately and systemically affect people of color in the United States. Sci Adv 2021;7(18):eabf4491.
60. Pullen Fedinick K, Taylor S, Roberts M. Watered down justice. March 27, 2020 (https://www.nrdc.org/resources/watered-down-justice).
61. Samuels G, Freemark Y. The polluted life near the highway: a review of national scholarship and a Louisville case study. Washington, DC: Urban Institute, 2022 (https://www.urban.org/research/publication/polluted-life-near-highway).
62. Bolden AL, Schultz K, Pelch KE, Kwiatkowski CF. Exploring the endocrine activity of air pollutants associated with unconventional oil and gas extraction. Environ Health 2018;17:26.
63. Cross RI, Huynh J, Bradford NJ, Francis B. Racialized housing discrimination and population health: a scoping review and research agenda. J Urban Health 2023;100:355-88.
64. Michelle F. An odor of racism: vaginal deodorants in African-American beauty culture and advertising. Advert Soc Rev 2011;11(4) (https://muse.jhu.edu/article/407304).
65. European Environment Agency. Late lessons from early warnings: the precautionary principle 1896–2000. 2001. (EEA report no. 22/2001) (https://www.eea.europa.eu/publications/environmental_issue_report_2001_22).
66. Food and Drug Administration. Orthophthlates for food contact use: request for information. Fed Regist 2022;87(98):31090-1 (https://www.federalregister.gov/documents/2022/05/20/2022-10532/ortho-phthlates-for-food-contact-use-request-for-information).
67. Pediatric Environmental Health Specialty Units home page (https://www.pehsu.net/).
68. UCSF Program on Reproductive Health and the Environment. Work matters: know your rights. 2024 (https://prhe.ucsf.edu/work-matters-know-your-rights).
69. UCSF Program on Reproductive Health and the Environment. Toxic matters. 2024 (https://prhe.ucsf.edu/toxic-matters).
70. Giudice LC, Llamas-Clark EF, DeNicola N, et al. Climate change, women's health, and the role of obstetricians and gynecologists in leadership. Int J Gynaecol Obstet 2021;155:345-56.
71. Lawrence F. Truth decay: when uncertainty is weaponized. Nature 2020;578:28-9 (https://www.nature.com/articles/d41586-020-00273-4).
72. Gaber N, Bero L, Woodruff TJ. The devil they knew: chemical documents analysis of industry influence on PFAS science. Ann Glob Health 2023;89:37.
73. Lamb WF, Mattioli G, Levi S, et al. Discourses of climate delay. Global Sustainability. 2020;3:e17 (https://www.cambridge.org/core/journals/global-sustainability/article/discourses-of-climate-delay/7B11B722E3E3454BB6212378E32985A7).
74. Institute of Medicine, Committee on Curriculum Development in Environmental Medicine. Environmental medicine: integrating a missing element into medical education. Washington, DC: National Academies Press, 1995.
75. Environmental Protection Agency. TRI toxics tracker (https://edap.epa.gov/public/extensions/TRIToxicsTracker/TRIToxicsTracker.html).
76. Grajewski B, Rocheleau CM, Lawson CC, Johnson CY. "Will my work affect my pregnancy?" Resources for anticipating and answering patients' questions. Am J Obstet Gynecol 2016;214:597-602.
77. Agency for Toxic Substances and Disease Registry. ATSDR case studies in environmental medicine — taking an exposure history. 2017 (http://www.atsdr.cdc.gov/csem/csem.html).
78. Corbett GA, Lee S, Woodruff TJ, et al. Nutritional interventions to ameliorate the effect of endocrine disruptors on human reproductive health: a semi-structured review from FIGO. Int J Gynaecol Obstet 2022;157:489-501.
79. National Academies of Sciences Engineering and Medicine. A class approach to hazard assessment of organohalogen flame retardants. Washington, DC: National Academies Press, 2019.
80. Intergovernmental Panel on Climate Change. Climate change 2023 synthesis report — contribution of working groups I, II and III to the sixth assessment report of the Intergovernmental Panel on Climate Change. 2023 (https://www.ipcc.ch/report/sixth-assessment-report-cycle/).