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. Chemical pollution is estimated to be responsible for at least 1.8 million deaths each year. 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.

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. Many fossil fuel–derived chemicals (petrochemicals) interfere with the function of the endocrine system. 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). Exposures have been linked to multiple adverse human health conditions, including cancer, neurodevelopmental harm, and infertility.

Fossil-fuel consumption and petrochemical production are more than 15 times higher than they were in the 1950s. Over the past 7 decades, the prevalence of multiple chronic health conditions and attributable deaths has been increasing in the United States and globally. 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%. 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.

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 (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. Producing plastic and plastic-related chemicals can be more lucrative than selling methane and ethane for fuel, heat, or electricity.

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. As part of petrochemical growth, plastic production is predicted to grow by a factor of almost 3, from more than...
400 million metric tons to 1100 million metric tons by 2050. 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).

Recognition of environmental contributors to disease has increased among some clinicians, particularly specialists in obstetrics and gynecology, pediatrics, and endocrinology. 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.” 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. 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). 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.

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. 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...
underestimate human effects, since they do not represent the full range of human variability or vulnerability to chemical exposures. 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.

Systematic reviews, sometimes including meta-analyses, adhering to recommended methodologic practices, are considered the highest quality method for evaluating and synthesizing environmental health evidence. 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. 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). 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, 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). 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. PBDEs can alter thyroid hormone levels during pregnancy. Thyroid hormones are critical for brain development, and even small decrements in maternal thyroid hormone levels, including subclinical decrements, are associated with adverse neurodevelopmental outcomes in offspring, including lower IQ levels.

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. BPA is listed as a developmental and re-
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). 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. Finally, there is evidence that the effects of EDCs can be transmitted to subsequent generations through alterations to the epigenome.

**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). 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. 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.” 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. EDCs can migrate from myriad sources and aggregate in dust; people are then exposed through inhalation, ingestion,
 tion, or dermal absorption. A systematic review identified more than 40 chemicals in household dust, many of them EDCs, including flame retardants, phthalates, and PFAS. 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.

**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. 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). This represents a fraction of potential EDC exposures, since standard detection technology measures less than 1% of total chemicals in use. 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, 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.)

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. 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. In addition, there is limited suggestive evidence of increased risks of gestational hypertension and preeclampsia, breast and testicular cancer, and thyroid disease and dysfunction.

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. 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).

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. As noted above, exposure to BPA, the most well-known compound in this class, has multiple adverse effects on health. 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.

**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. 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.64,65 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.”66

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 inequities27 (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 1980s64 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>
<thead>
<tr>
<th>Chemical Class and Examples</th>
<th>Major Exposure Sources</th>
<th>Health Effects</th>
<th>Specific Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFASs: PFOA, PFOS, PFHxS, PFBS, PFBA†</td>
<td>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</td>
<td>Decreased infant and fetal growth, dyslipidemia, decreased antibody response to vaccines in children and adults†</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Ortho-phthalates: DEHP, DBP, BBP, DEP, DINP</td>
<td>Food, personal care products (e.g., fragrances), food packaging materials, building materials (e.g., PVC flooring), industrial facility releases</td>
<td>Male reproductive toxicity (e.g., sperm effects), decreased anogenital distance, preterm birth, metabolic disorders (e.g., insulin resistance, diabetes)44</td>
<td>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.</td>
</tr>
<tr>
<td>Flame retardants: PBDEs, organophosphate ester flame retardants (OPFRs)</td>
<td>Consumer products (e.g., electronics, furniture, mattresses, children’s products), personal care products (e.g., nail polish), plastics, industrial facility releases, legacy environmental exposures</td>
<td>Impaired neurodevelopment41</td>
<td>Altered thyroid function in newborns, reproducitvity45 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</td>
</tr>
<tr>
<td>Bisphenols: BPA, BPS</td>
<td>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</td>
<td>Adverse effects on ovarian development and function, female reproductive toxicity, impaired neurodevelopment, metabolic abnormalities, immune system abnormalities45</td>
<td>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).46</td>
</tr>
<tr>
<td>Heavy metals: lead, cadmium, mercury, arsenic</td>
<td>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</td>
<td>Impaired neurodevelopment, male reproductive toxicity (e.g., impaired semen quality, fertility effects), female reproductive toxic effects, cancer, immunosuppression47,48</td>
<td>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 10.49</td>
</tr>
<tr>
<td>Pesticides: organophosphate pesticides, neonicotinoids, pyrethroids, DDT</td>
<td>Food and drinking water, insecticides, rodenticides, herbicides, spray drift from use in agricultural fields</td>
<td>Impaired neurodevelopment (e.g., lowered IQ), reduced sperm quality25</td>
<td>Increased susceptibility to childhood cancers (e.g., leukemia and brain tumors), increased susceptibility to testicular cancer, impaired fetal growth3,42,3</td>
</tr>
</tbody>
</table>
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).

**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. 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) — 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 exposures.

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. The feasibility of some recommendations, however, varies according to economic status and other factors (e.g., buying pesticide-free organic...
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 SOCIIETAL INTERVENTIONS**

People can reduce exposures to some chemicals through individual actions,4,7,8 but most exposures are beyond individual control. For example, although washing fresh produce is recommended...
The New England Journal of Medicine

The New England Journal of Medicine

Downloaded from nejm.org by Sarah Banapur on April 3, 2024. For personal use only.

No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.


54. Environmental Protection Agency. IRIS toxicological review of formaldehyde.