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Manufactured Chemicals and Children's Health — The Need for New Law

The Consortium for Children's Environmental Health

Noncommunicable diseases (NCDs) are the principal causes of illness and death in children today. Their incidence and prevalence are on the rise. And emerging research links multiple NCDs in children to manufactured synthetic chemicals.[1,2]

An estimated 350,000 manufactured chemicals, chemical mixtures, and plastics are currently listed in global inventories.[3] Most are produced from fossil fuels — gas, oil, and coal. Production has expanded 50-fold since 1950, is currently increasing by about 3% per year, and is projected to triple by 2050.[4] Environmental pollution[5,6] and human exposure[7] are widespread.

Yet manufacture of synthetic chemicals and plastics is subject to few legal or policy constraints.[8,9] Unlike pharmaceuticals, synthetic chemicals are brought to market with little prior assessment of their hazard and almost no postmarketing surveillance for longer-term adverse health effects. Fewer than 20% have been tested for toxicity, and fewer still for toxic effects in infants and children.[8] Associations between widely used chemicals and disease in children continue to be discovered with distressing frequency, and it is likely that there are additional, still unknown links. Protecting children from chemicals' dangers will require fundamental revamping of current law and restructuring of the chemical industry to prioritize children's health.

NCDs IN CHILDREN AND SYNTHETIC CHEMICALS

Over the past half-century, NCD rates in children have risen sharply.[1] The incidence of childhood cancers has increased by 35%.[10] Male reproductive birth defects have doubled in frequency.[11] Neurodevelopmental disorders now affect 1 in 6 children, and autism spectrum disorder is diagnosed in 1 in 36.[12] Pediatric asthma has tripled in prevalence.[13] Pediatric obesity has nearly quadrupled in prevalence and has driven a sharp increase in type 2 diabetes among children and adolescents.[14] In adults, by contrast, illness, disability, and death due to cardiovascular disease, stroke, and many cancers have decreased.[15,16]

A large body of evidence links multiple pediatric NCDs to synthetic chemicals (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[1] This research was stimulated by studies involving children who had obvious injury from chemical exposures: an epidemic of more than 10,000 babies born with phocomelia after their mothers' ingestion in early pregnancy of the sedative thalidomide[17]; the Minamata tragedy, in which infants were born with profound neurologic impairment owing to their mothers' unwitting consumption of fish polluted by methylmercury[18]; and cases of adenocarcinoma of the vagina in young women whose mothers had taken diethylstilbestrol (DES) to prevent miscarriage.[19] In all these episodes, the mothers were physically unharmed.

Two key lessons emerged from these cases: toxic chemicals can cross the placenta, and children are far more vulnerable to toxic chemicals than adults. These findings created the intellectual foundation for the field of environmental pediatrics, also known as children's environmental health.[1]

An additional consequence of the thalidomide disaster[17] was the passage in 1962 of the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act. These amendments expanded the oversight authority of the Food and Drug Administration (FDA) for chemicals intended for use as pharmaceuticals and created requirements for manufacturers to conduct premarketing test-

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ing of new drugs for safety and efficacy and postmarketing surveillance for longer-term adverse health effects. In the wake of these amendments, the number of drugs approved by the FDA per year dropped by two thirds.[20]

GROWTH OF RESEARCH IN ENVIRONMENTAL PEDIATRICS

Research in environmental pediatrics has flourished over the past 25 years (Fig. 1). Two key catalysts of this growth were the 1993 publication of the National Research Council report, *Pesticides in the Diets of Infants and Children*,[21] which elucidated the biologic bases of children's heightened susceptibility to toxic chemicals, and the passage in 1996 of the Food Quality Protection Act (FQPA), the U.S. law on pesticides. The FQPA made protecting children's environmental health a national priority and required generation of data on chemical hazards to children, stimulating substantial expansion of federally funded research in environmental pediatrics.

This research has since documented repeatedly that even brief, low-level exposures to toxic chemicals during early vulnerable periods are linked to increased risk of disease and disability in children that can persist across the life course.[22-25] Prenatal exposures are particularly hazardous. Though "the dose makes the poison" remains a proven maxim, the timing of exposure is clearly at least as important as the dose during early human development.

Research has also revealed that toxic chemicals can produce a dose-related spectrum of injury in children. Some effects are clinically obvious, but others can be detected only with detailed evaluation. Silent brain injury with IQ loss in children exposed to low levels of lead is a well-studied example.[26]

A third discovery is that diseases associated with early-life exposures can manifest any time during the life span.[23] Some, such as anatomical birth defects, are obvious at or near birth; others don't become evident until later in childhood, adolescence, or adulthood. Delayed effects include altered sexual development,[14,27] reduced fertility,[14,27] and lifelong increased risks of asthma, obesity, diabetes, cardiovascular disease, neurologic impairment, and cancer.[1,22-25]

Because it is unethical to conduct randomized clinical trials of toxic chemical exposures, the evidence linking manufactured chemicals to NCDs in children derives largely from epidemiologic studies, with additional evidence coming from experimental studies in animals and mechanistic studies. Prospective, birth-cohort epidemiologic studies that measure chemical exposures in pregnant persons and fetuses and follow children longitudinally over many years are particularly powerful platforms for discovering associations between synthetic chemicals and disease because they link exposures to outcomes in individual children and eliminate recall bias. Such studies have revealed links between prenatal exposures to phthalates and disorders of male reproductive development[28]; between early-life exposure to dichlorodiphenyltrichloroethane and breast cancer in women[25]; between in utero exposures to brominated flame retardants, phthalates, and organophosphates and lifelong decreases in cognitive function[29]; and between early-life exposures to perfluoroalkyl and polyfluoroalkyl substances (PFAS) and immune dysfunction, dyslipidemia, and thyroid disorders[30] (see the Supplementary Appendix). Evidence for such associations is especially convincing when multiple epidemiologic studies in different populations and geographic locations yield consistent results.[26,31]

Widespread childhood exposure to a toxic chemical can damage the health, economic viability, and security of an entire society. For example, each year from the 1950s through the 1970s, about 100,000 tons of tetraethyl lead were added to gasoline in the United States to enhance automotive performance, causing massive environmental lead contamination and extensive human exposure: the population mean blood lead level was 16 to 17 μg per deciliter. The average IQ among U.S. children was reduced by an estimated 2 to 5 points,[32] the number of children with an IQ above 130 decreased by more than 50%, and the number with an IQ below 70 (the criterion used in the *International Classification of Diseases* to define intellectual disability) increased by more than 50% (Fig. 2).[33]

Diseases caused by toxic chemical exposures in childhood can lead to massive economic losses,[34,35] including health care expenditures and lifelong productivity losses resulting from reduced cognitive function, physical disabilities, and premature death. The chemical industry largely externalizes these costs and imposes them on governments and taxpayers. Recognition of their

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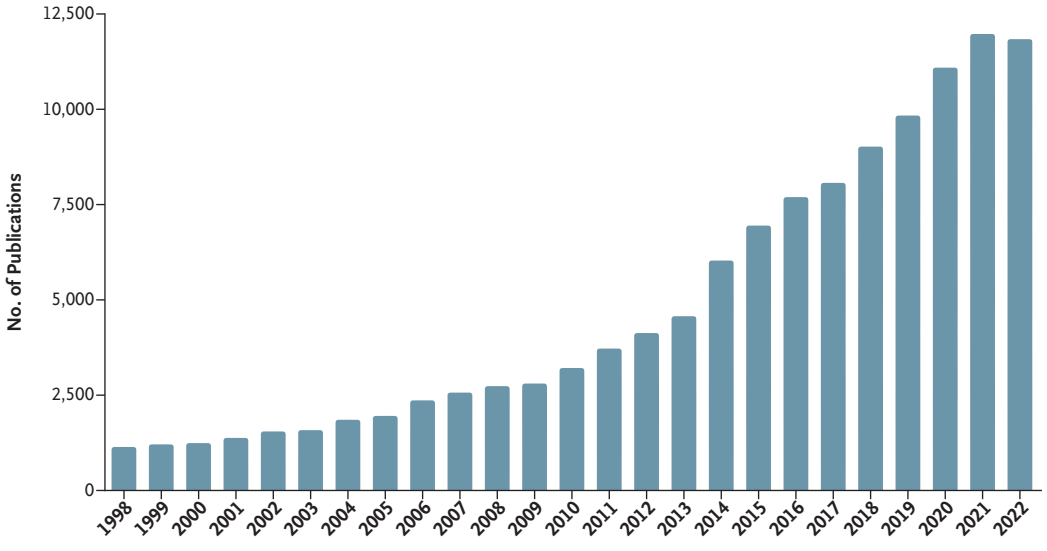

Figure 1. Number of Publications in Environmental Pediatrics Identified in PubMed by Year, 1998–2022.

magnitude has resulted in multibillion-dollar legal judgments in which manufacturers and brands have been found liable for damages caused by their products.[36,37]

Conversely, reducing toxic chemical exposures can produce major economic benefits. In the decade after lead was removed from gasoline in the United States, children's mean blood lead level fell by more than 95%, and beginning in 1980, the mean IQ of each year's birth cohort was 2 to 5 points higher than that of pre-1980 cohorts. Because each additional IQ point is associated with an increase of 1.8 to 2.4% in lifelong earning potential, the estimated economic benefit for each birth cohort is about $200 billion — a cumulative benefit since 1980 of more than $8 trillion.[32] Reduction of disease frequency following reduction of exposure is strong evidence for chemical causation.

FAILED CHEMICAL LAW

U.S. chemical law — the Toxic Substances Control Act (TSCA) of 1977 and its subsequent amendments — is based on a statutory promise to "protect public health and the environment" from "unreasonable risks" posed by chemicals.[38] In reality, however, TSCA failed to provide the Environmental Protection Agency (EPA) with the authority required to fulfill this promise.[39] The law thus effectively encourages unfettered chemical production at the expense of children's health.[9] It is broken legislation.

TSCA's flaws mean that the chemical manufacturing industry is largely free from responsibility to conduct premarketing toxicity testing of new chemicals or postmarketing surveillance for longer-term adverse events.[8,9] TSCA's fundamental assumption is that all manufactured chemicals are both harmless and beneficial, and only rarely are manufacturers required to examine potential health hazards of new or existing chemicals. Instead, TSCA places the burden on government regulators to identify potentially hazardous chemicals, undertake literature searches, conduct risk assessments, and justify any proposed restrictions using cost–benefit analyses. As a result, few associations between manufactured chemicals and disease in children have been addressed by regulatory action. Hazards that have been recognized have typically been ignored or downplayed, and the responsible chemicals allowed to remain in use with no or limited restrictions.[40,41] In the nearly 50 years since TSCA's passage, only a handful of chemicals have been banned or restricted in U.S. markets.[9]

Further tipping the scales toward unconstrained production, the government provides multibillion-dollar subsidies to U.S. chemical and plastic manufacturers.[42] In addition, manufacturers re-

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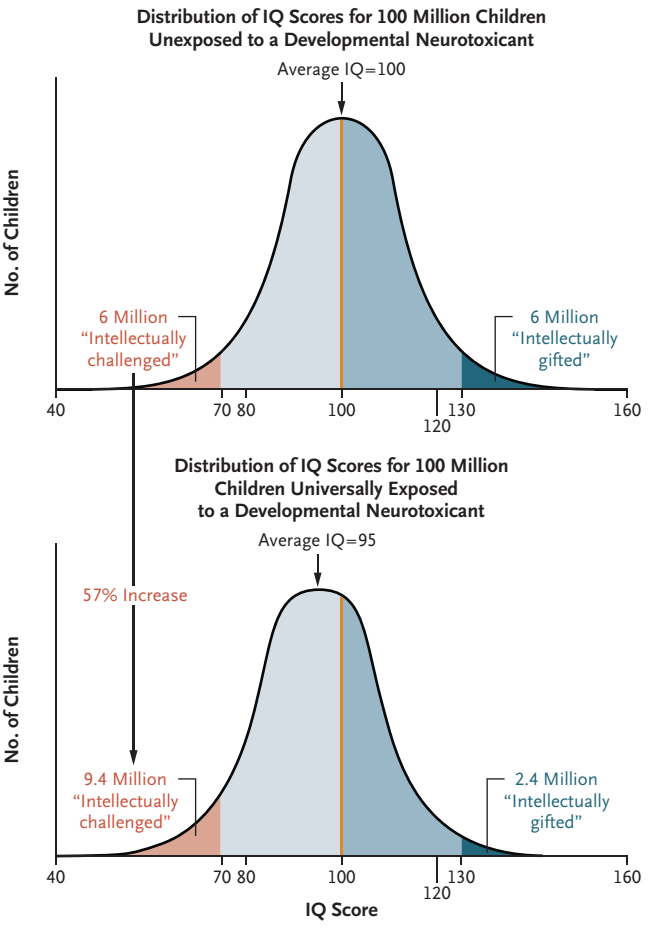

Figure 2. Societal Impact of a 5-Point Loss in Mean IQ.

Data are from Gilbert and Weiss.[33] The top graph shows the distribution of IQ scores in a population of 100 million children unexposed to a developmental neurotoxicant. The bottom graph shows the distribution of IQ scores in a population of 100 million children universally exposed to a developmental neurotoxicant causing a 5-point reduction in mean IQ.

ceive trade-secret protections allowing them to claim that virtually all information pertaining to a chemical or plastic product is secret.[9] Manufacturers have taken full advantage of this privilege, even when secrecy is not legally justified. Therefore, virtually nothing is known today about the toxicity or even the chemical composition of many chemical products sold in U.S. markets.[9]

In the European Union, chemical legislation is ostensibly more rigorous.[43] The E.U. chemicals-management law — Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) — states that it operates on the principle of "no data, no market." It requires at least some premarketing screening of new chemicals for toxicity, as well as evidence-based analyses of chemicals considered particularly dangerous. In practice, however, REACH fails to constrain chemical production. Premarketing screening in the European Union relies heavily on toxicity-testing data provided by the chemical industry, which are accepted with few quality controls. Moreover, REACH contains multiple exemptions and places a heavy burden on government regulators to prove harm. Aggressive trade-secret laws provide still further shielding.[44] The net effect is that only 73 chemicals and chemical groups have been restricted or banned in E.U. markets.

Chemical-management policies in both the United States and the European Union have two additional inadequacies. First, they consider the hazards of only one chemical at a time, which ignores the reality that children are exposed daily to mixtures of multiple manufactured chemicals that may have cumulative or synergistic effects.[45] Second, apart from the FQPA's limited requirement that the EPA consider children's vulnerabilities in setting pesticide tolerance levels, most countries' chemical laws don't generally consider children's particular sensitivities.

Thus, facing few regulatory burdens and a legal regime offering low-cost protection for its discoveries, the chemical industry has flourished. It's now the second-largest manufacturing industry globally and accounts for about 25% of the U.S. gross domestic product (GDP).[46] Under current law, it has little reason to alter its business model or invest in sustainable innovation.

A PRESCRIPTION FOR CHANGE

Safeguarding children's health against manufactured synthetic chemicals will require shifting chemical law to a more precautionary approach prioritizing health protection over unconstrained production of chemicals and plastics. Under such new laws, chemicals should no longer be presumed harmless until proven otherwise. Instead, chemicals and chemical-based products should be allowed to enter and remain on markets only if their manufacturers can establish, by rigorous, independent testing, that they are not toxic at anticipated levels of exposure. Chemical manufacturers and brands marketing chemical products should additionally be required to conduct postmarketing surveillance for longer-term adverse effects, especially in pediatric populations.

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Such a legal paradigm would align with pharmaceutical law, international law recognizing a universal right to a clean and healthy environment,[47] and guidance adopted by the United Nations Committee on the Rights of the Child affirming that the right to a healthy environment extends with particular salience to children.[48]

NATIONAL CHEMICAL POLICIES

The keystone of a new legal paradigm for chemical management would be a comprehensive approval process at the national level for all (existing and new) chemicals and plastics and all chemical uses, similar to that applied to pharmaceuticals. Chemicals, plastics, and chemical-based products would be allowed to enter and remain on markets only if rigorous, independent scientific assessment demonstrated that they were not toxic for persons of any age, especially children, at anticipated exposure levels.

To ensure that such information is trustworthy, all toxicity testing would have to be undertaken in laboratories that are free from financial conflicts of interest and not subject to contractual or other controls by industry sponsors. Manufacturers should be required to bear the cost of independent testing but not allowed to conduct it themselves.

National chemical policies should take into consideration findings from animal and mechanistic toxicology studies, which are highly predictive of human health risks, including risks to children.[49] To enable detection of a wide range of health effects, toxicologic studies need to exceed the minimal standards of Good Laboratory Practice and amplify study designs to include assessments of more recently recognized mechanisms of toxicity such as endocrine disruption. To enhance recognition of delayed consequences of early-life exposures, they should include long-term follow-up of animals exposed in utero.

GLOBAL CHEMICALS TREATY

To confront the growing global crisis of chemical pollution and its worsening effects on children's health, strengthened international efforts will be essential. A key strategy could be a legally binding global chemicals treaty developed and implemented under the auspices of the United Nations. The U.N. global plastics treaty now being negotiated may provide a model. Attempts to establish a global chemicals treaty have so far resulted only in a voluntary, multistakeholder policy framework, the Strategic Approach to International Chemicals Management, adopted in 2006, and a follow-on initiative, the Global Framework on Chemicals, adopted in 2023.

Development and implementation of a treaty will require a permanent, independent science-policy body to provide expert guidance. This body should comprise prominent scientists, including physicians, with no financial conflicts of interest.[50] It could be modeled on the Intergovernmental Panel on Climate Change or the FDA's Tobacco Products Scientific Advisory Committee, or attached to the Inter-Organization Program for the Sound Management of Chemicals. Institutional mechanisms would have to be established to ensure that the relevant U.N. agency or secretariat responds to and acts on the advisory body's recommendations.

CHEMICAL FOOTPRINT REPORTING

Chemical footprint reporting is the business sector's strategy for documenting and reducing chemical hazards[51]: chemical manufacturers and consumer brands disclose information on the potential risks posed by chemical and plastic products over their life cycle, inventorying their products to identify chemicals of high concern, restricting use of those chemicals, monitoring use reduction, and transparently reporting results.[51] Such reporting can clarify for potential investors the financial and legal risks associated with their investments. It can be required by governments, driven by shareholder resolutions, or mandated by a combination of the two.

REINVENTION OF THE CHEMICAL INDUSTRY

Ultimately, protecting children's health from manufactured chemicals will require fundamental transformation of the chemical industry's structure and business model.[52] The rigid, noninnovative, and vulnerable infrastructure of today's fossil-carbon–based industry must be replaced with a more flexible and sustainable model enabling reduced reliance on fossil-carbon feedstocks and fossil energy; development of safer, more sustainable molecules and manufacturing processes; and

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reimagined product design, delivery, and value chains for products with fewer adverse effects and the potential to become raw materials for new products at the end of their lives.

Pollution by synthetic chemicals and plastics is a major planetary challenge that is worsening rapidly. Continued, unchecked increases in production of fossil-carbon–based chemicals endangers the world's children and threatens humanity's capacity for reproduction.[11,27] Although a paradigm shift in chemicals management to prioritize human health will require profound realignment of current law, deep restructuring of the chemical industry, and redirection of financial investment on a scale similar to that of the global transition to clean energy, it is essential to preserve our "common home" and safeguard our children's future.[53] Inaction on chemicals is no longer an option.

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