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Commentary

Rethinking our chemical legacy and reclaiming our planet

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Each year, over 2,000 new chemicals are added to the tens of thousands that already flood the global market. Of these, an estimated 1% have been assessed adequately for safety, and many more are suspected to be toxic. Individual regulatory agencies lack the resources and political power to tackle this enormous challenge, signaling the need for a targeted global approach to handling chemical pollution.

By the time the average person completes their morning routine, they have interacted with many unregulated chemicals. From the plasticizers used to make our toothpaste tubes squeezable to the fluorinated compounds keeping carpets and clothing stain- and wrinkle-free, the shiny spot-free apples made possible by pesticides, and the microscopic plastic particles floating in our kitchens and living rooms, we ingest, absorb, and inhale pollutants from sunrise to sunset. However, although these compounds have escaped regulatory control, they are not necessarily benign. In fact, the opposite might be true, especially considering that we are exposed to so many different synthetic chemicals and particles simultaneously and that there is a lack of suitable global regulatory frameworks to ensure their safety.

These "novel entities" are often persistent and take up space well beyond their useful lifetime.[1] A prime example is dichlorodiphenyltrichloroethane (DDT). Prohibited in the US 50 years ago, DDT—originally used as an insecticide—is still present in seafood and dairy items, such as milk and cheese, today. Further, some plastic products take over a thousand years to break down.[2] Worryingly, no one is turning off the tap. It's estimated that over 2,000 new chemicals are introduced to the global market annually. Although regulatory agencies with the best of intentions are in place to monitor their safety, they lack the resources and political clout to tackle this enormous challenge. As a result, chemicals produced for profit are innocent until proven guilty, and those that have been in use for decades are often still referred to as "emerging" contaminants by scientists, in large part because they have not been adequately studied and not necessarily because they are new. In the US, over 80,000 chemicals have been registered for use since the Toxic Substances Control Act (TSCA) was passed in 1976, but the majority of those have not undergone regulatory testing. In fact, since its enactment, the TSCA has banned just four chemicals—yes, four. In Europe, the situation is slightly better in that REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) places more of the responsibility on industry by asking it to demonstrate that chemical risk is adequately controlled.[3] In much of the rest of the world, countries lack basic waste management, let alone the regulatory capacity to prevent pollutants from entering the environment and affecting their citizens.

If Rachel Carson, the foremother of environmental protection, were alive today, she would be appalled. Nearly 60 years ago, she voiced a scientifically grounded call for the protection of our planet from pollutants, clearly signaling that unabated use of DDT and chemicals like it, without regulation and with only profit in mind, would result in an irreparable "silent spring."

> If we are going to live so intimately with these chemicals eating and drinking them, taking them into the very marrow of our bones—we had better know something about their nature and their power.
> —Rachel Carson (*Silent Spring*)

Her insights came at a time when researchers as a group had not reached an understanding of how chemicals such as DDT elicit their effects. The eggshells of iconic birds such as bald eagles were thinning, but many didn't fully comprehend why. Today we have no such excuse. At our very fingertips we have the tools to understand how chemicals and particles interact with our cellular machinery (Figure 1) and often the ability to predict what impacts small changes in gene expression or enzyme activity might have on disease risk. For example, many papers have been published on the detrimental effects of plasticizers such as bisphenol A (BPA) and phthalates, resulting in their being banned from some products or intentionally not used in others. However, despite over two decades of research demonstrating the danger of regular exposure to plasticizers and that longer-term exposure to low levels leads to reproductive problems such as infertility and birth defects, autoimmune disorders, and the activation of signaling pathways underlying carcinogenesis,[4] these and other estrogenic chemicals are still detected and known to migrate into beverages from commonly used products such as plastic bottles,[5] and the list of bisphenols in marketed products keeps growing. The Swedish Chemicals Agency estimates that more than 200 are in circulation today.[6] This volume is so great that even with today's tools and techniques, these chemicals couldn't possibly be evaluated in a timely manner by even the largest of toxicology labs in operation, and this is but one category of chemical. For another chemical class, pesticides, reams of data describe the

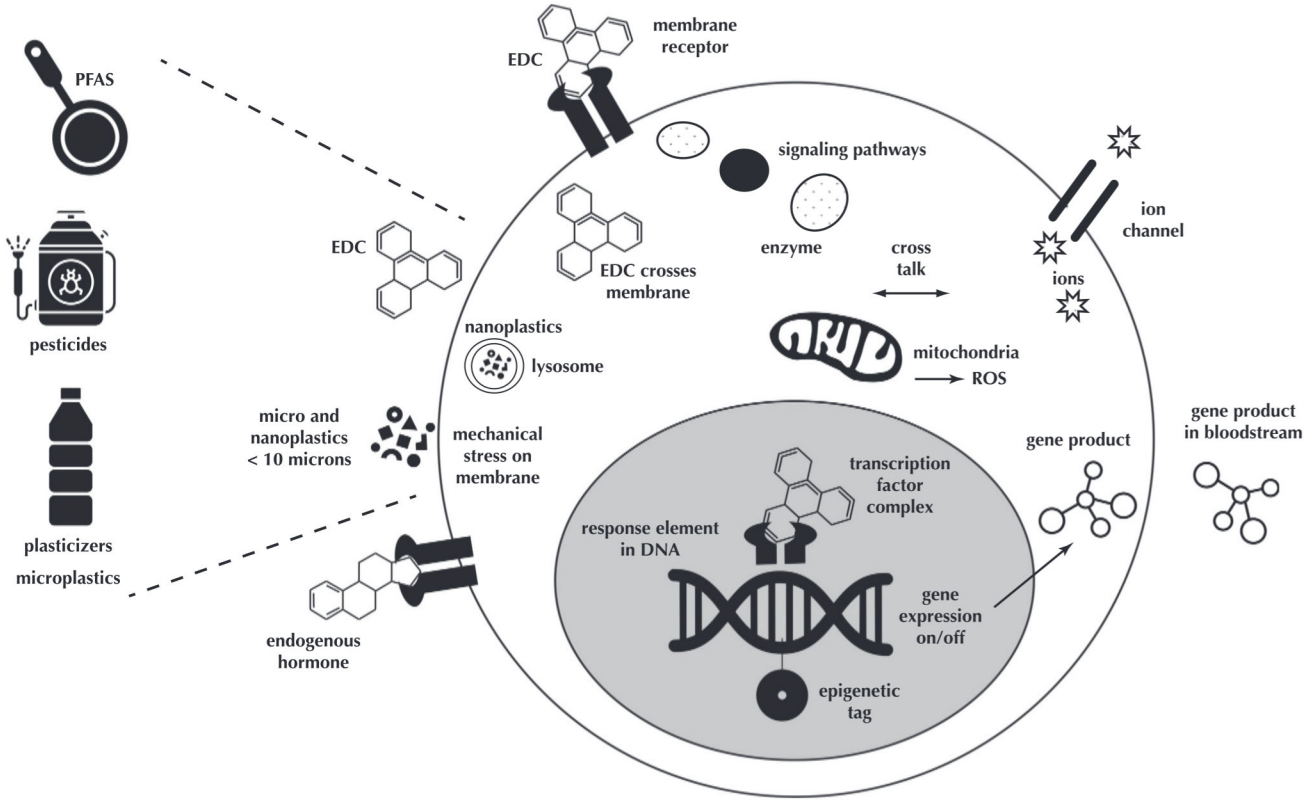

Figure 1. An overview of how chemicals interact with and disrupt cellular function

Pesticides, plasticizers, PFAS (per- and polyfluoroalkyl substances), etc., many of which are EDCs (endocrine-disrupting compounds), can leach from products or are present on food and can be inhaled in dust; microplastics are contained in or shed from products used for food or are present in the air and inhaled. These molecules and microscopic particles can thus be present in the body and interact with cells. Mechanisms include interacting with membrane receptors or eliciting mechanical stress, traversing the membrane to bind to or activate specific cellular pathways, influencing enzyme activity, causing the production of potentially damaging reactive oxygen species (ROS), and in some cases interacting via transcription factors with DNA. Some chemical exposures result in the addition or removal of epigenetic tags to or from DNA or histones. The production of gene products (RNA or protein) and their activities can ultimately be influenced by all of these processes. The author acknowledges the Noun Project for multiple individual icons in the figure.

neurotoxicological impacts of agricultural chemicals such as pesticides, which have been linked with autism in the children of farm workers exposed in early life.[7] In the US, the pesticide chlorpyrifos is now banned, but other neurotoxicants remain in use for agriculture and residential insect control. Ultimately, today's challenge isn't a lack of knowledge; instead, we lack the regulatory will and research funding to support responsible chemical use. As a result of being overwhelmed, we have effectively prioritized profit over global human health with a patchwork approach to chemical regulation that ensures protection of neither the people using these products nor the ecosystems affected by our unsustainable reliance on "better living through chemistry."

Hormonal body snatchers

We know now that thousands of chemicals, including the above-mentioned DDT, act as what are termed endocrine-disrupting chemicals (EDCs). They are similar enough to our own hormones that they can enter our bodies like an intruder with a stolen key to gain entry into our cells. These chemicals bind to receptors meant for naturally produced (endogenous) hormones that are essential to everything from growth to reproduction. EDCs interact with our DNA and alter our very composition from our cells upward, making us more susceptible to disease and a shorter lifespan. And not much is needed to cause an effect. The hormones circulating in our bloodstream activate receptors at picomolar to nanomolar concentrations, and EDCs might be able to exert their effects at the same infinitesimal doses. This amounts to approximately one drop of hormone or EDC in 20+ Olympic-sized swimming pools. Determining thresholds for EDCs is notoriously difficult because they can follow a non-linear dose response, meaning that they can cause an effect at a low dose that is not observed at higher doses, which is not surprising because this is typical of natural hormones.[8] But because established approaches for agencies such as the US Food and Drug Administration necessitate the determination of thresholds from linear dose response curves, chemicals that sometimes behave unpredictably and cause responses at extremely low levels (such as BPA) do not fit within current regulatory frameworks.[4] We are not accurately calculating the risk of exposure, and the potential repercussions are alarming.

Newborn babies enter the world pre-polluted, already affected by our synthetic lifestyles—from the microplastics embedded in their mothers' placentas[9] to potential biochemical changes in their parents' gametes (eggs and sperm). Although prenatal and gestational exposures in

women have always been a concern, sperm are also now thought to be at high risk for epigenetic reprogramming, meaning changes that occur on top of DNA without altering the DNA sequence, upon exposure to pollutants.[10] This includes a higher risk of poor embryo quality in men previously exposed to phthalates and an increased likelihood of obesity due to paternal pesticide (organophosphate) exposure.[11] Awareness that the consequences of exposure can be transgenerational should be sufficient to spark action, yet the response has been insufficient, most likely because of a lack of capacity for the longer-term testing needed.

Gaps in testing

We study only a handful of the many chemicals present in products used daily, and funding mechanisms tend to discourage the study of realistic chemical mixtures in lieu of testing one at a time to determine reference doses or safety thresholds. The phthalate bis(2-ethylhexyl) phthalate (DEHP), used in the production of the common plastic polyvinyl chloride (PVC), is a representative example.[12] The US Environmental Protection Agency's website describes studies on DEHP in multiple commonly tested mammalian species and derives a reference dose. Yet there is no acknowledgment that co-exposure to other phthalates often used in PVC-containing products is likely to be occurring. Phthalates are all likely to act via similar mechanisms and could contribute to the same adverse disease outcome.[13] Therefore, although chemicals considered EDCs might be characterized as individually "safe" at a certain level, collectively they can still have a negative impact. Again, the challenge here is in the numbers. The Endocrine Society estimates that of the over 80,000 human synthesized chemicals currently in use globally, only 1% have been assessed for safety, but thousands could act as EDCs. In reality, the safety thresholds determined for the few are undermined if one is exposed to multiple chemicals simultaneously. This is also a considerable challenge when it comes to perfluorinated chemicals, which are now detected in drinking water and military bases globally. In the US alone, over 2,800 sites across all 50 states are contaminated.[14] Although legacy perfluorinated chemicals (perfluorooctanoic acid [PFOA] and perfluorooctane sulfonic acid [PFOS]) have been phased out of production, hundreds of newly synthesized molecules of the same chemical class continue to be produced for use in everything from raincoats to food packaging and are all highly persistent because they contain one of the strongest chemical bonds in existence: carbon to fluorine. For example, the drinking-water supplies for towns along the Cape Fear River in North Carolina are contaminated with legacy and new PFAS, and some of the newer, supposedly safer chemicals are potentially more toxic than their predecessors.[15] These chemicals contaminate our food, water, and air but escape regulation because we lack the data and the regulatory teeth to limit their release.[16] As a result, people are exposed to mixtures of chemicals demonstrated time and time again to alter metabolism and immune response and act as potential human carcinogens, among other effects.

Moving forward

Recently, suggestions that we recycle plastics by converting them into fuel via costly chemical recycling approaches or use plastics as a convenient carbon sink have grown in prominence. Yet these proposals paper over the issue that plastics are contaminated with mostly unregulated chemicals—not to mention their ability to detrimentally alter the global carbon cycle.[17] By breaking plastics back down into their individual monomers to create fuels, the chemicals used in manufacturing these products would potentially be resuspended into the atmosphere and contribute to global warming and air pollution. Products created from recycled polymers could also be contaminated, and both micro- and nanoplastic particles are already known to cause health impacts.[18] Rather than using expensive technologies to recycle plastics and the chemicals they contain so we can keep creating more, we should produce far less of both.

Essentially, we have created a situation in which toxicologists and environmental chemists play the role of detective by discovering new pollutants when they end up where they shouldn't and tracing them back to the source while simultaneously discerning whether they pose a threat to human and ecological health. Grant funding is needed for this work, and obtaining that in a timely manner takes time, skill, and a dash of luck. A new approach is needed. Often when chemicals are detected, people have already been exposed for years, sometimes decades. In effect this is a form of trespassing given that many chemicals make their way into the homes and bodies of citizens without their knowledge, consent, or understanding of the implications. It is common that lower-income groups, being more likely to live near factories and landfills, are more substantially affected and receive higher exposure to pollutants. In the US, petrochemical companies are commonly located and continuing to expand along the Mississippi River corridor in predominantly African American, Native American, and Asian communities.[19] We keep repeating the same cycle of calling out companies when they pollute, slapping them gently on the wrist with a fine that is shadowed by annual profits, and then looking the other way so we can keep buying our stainproof shirts and carpets and live in pest-free homes, sometimes at the expense of poorer communities. If individuals can't afford to move or to install a reverse-osmosis filter to remove pollutants at their kitchen sink, they are held hostage by contaminants entering their home. This pattern holds both within nations and on a global scale, and it is no surprise that developing nations often become the dumping ground for richer countries and that people in poorer countries are exposed to higher levels of pollution. In fact, the growing epidemic of plastic pollution and recent refusals of difficult-to-recycle plastics from the US and Europe by countries in Asia and Africa has led to a global about-face and the new promise of a treaty from a recent meeting of the United Nations Environmental Assembly (UNEA) to limit plastic pollution by 2024.[20]

Our current approach to the manufacture and regulation of chemicals is unsustainable on a global scale, and we have already exceeded the planet's capacity to safely handle their production and disposal.[1] The decisions we make over the next several years could determine whether our children's children will be able to enjoy seafood and clean drinking water and many of the pleasures we take for granted. Humans are notably terrible at self-sacrifice for the common

good, as demonstrated by the ongoing pandemic and climate change. The resolve to deal with plastic pollution recently demonstrated by the UNEA will hopefully extend to the thousands of chemicals associated with plastics. The regulation of plastic pollution could represent a gateway to the regulation of synthetic chemical production as a whole. Prioritizing the health of our planet and its people with a global agreement on reducing chemical and plastic pollution, while acknowledging that there is no "away" for pollutants and that there never has been, is the best pathway toward a sustainable future for all of us.

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