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Integrative Environmental Medicine

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FOREWORD

ANDREW WEIL, M.D.

An English surgeon, Sir Percivall Pott, was the first scientist to demonstrate that cancer could be caused by exposure to an environmental carcinogen. That occurred in London in 1775. Chimney sweeps of the period developed "soot wart" on the skin of the inferior surface of the scrotum; if these growths were not removed, they turned into squamous cell carcinomas that metastasized and killed. Pott correctly identified the cause as irritation from soot particles. Chimney sweeps often started work as children and therefore were in contact with soot for years. Sweat running down the body caused it to accumulate in the folds of scrotal skin. English chimney sweeps wore minimal or no clothing. German chimney sweeps wore protective garments and did not develop scrotal cancers. Pott's hypothesis was confirmed in 1922, when a carcinogen in coal soot was isolated.

One would think that environmental influences on health would have been a major focus of medical research, teaching, and practice over the years since Pott's discovery, but that has not been the case. Except for a lecture on the carcinogenic effects of tobacco smoking, my medical school education in the late 1960s included little information about environmental causation of cancer or any other diseases. Even as public concerns about air and water pollution grew in the late 20th century and scientists began to document the endocrine-disrupting, neurotoxic, teratogenic, carcinogenic, and other harmful effects of the many man-made chemicals in the environment, clinicians remained poorly informed about them, unable to respond to patients' fears and questions.

Lack of education about environmental medicine has also left physicians and allied health professionals unable to take effective political action. Too often, the lobbying efforts of polluting industries have had much greater influence on legislators and regulatory agencies than the voices of concerned citizens.

My colleagues and I at the University of Arizona Center for Integrative Medicine have made environmental health a core subject of our curriculums. As a result, a growing number of physicians, medical residents and students, and other health care professionals now have basic knowledge of the field. The publication of this newest volume in the Oxford University Press Integrative Medicine Library makes this information available to many more clinicians. Drs. Aly Cohen and Fred vom Saal have put together a thorough text that covers the main environmental chemicals that threaten human health, the sources and clinical consequences of environmental exposures, and ways to mitigate exposures. They also discuss regulatory and legislative issues surrounding these issues. I consider *Integrative Environmental Medicine* a landmark in the evolution of a field that is critically important to understanding health and illness.

PREFACE

Our environment has changed profoundly over the past 100 years. More than 87,000 new chemicals have been developed and integrated into our way of living without adequate testing to ensure safety for adults and particularly for fetuses, infants and children. Although modern materials have afforded us many advantages, we are now seeing the human health and environmental drawbacks to these conveniences. Indoor air pollution is associated with a variety of diseases, water contamination is a regular story on the evening news, and processed food contains thousands of chemicals that have never been tested for their effects on human health. Other sources for potential chemical exposure include cleaning products, food and beverage packaging, new pharmaceuticals and supplements, and personal care products that contain undisclosed, proprietary ingredients. Radiation sources are also a health concern, along with ever-expanding forms of technology and growing populations of users.

As the number and quantities of chemicals in the environment have dramatically increased since World War II, the incidence of many chronic health problems, such as type 2 diabetes, obesity, thyroid disease, asthma, allergy, autoimmune disease, autism, attention deficit hyperactivity disorder, and several cancers, have also increased. Evidence reveals that exposure to chemicals in the environment and in everyday products may increase the risk of these conditions. Add to this picture the lack of mandated chemical safety testing prior to their use in products, unknown synergistic effects of these individual chemicals mixed together or in combination with pharmaceuticals, and ineffective chemical regulation reform, and the level of concern increases dramatically. Chemicals are wrongly assumed to have the same regulatory oversight and testing as pharmaceuticals, with most consumers believing that "if it's on the shelf, it must be safe." Public ignorance about ineffective regulation and oversight exposes them to thousands of untested and unregulated chemicals on a daily basis.

Evidence presented in this book shows that contaminants are implicated in the rise in incidence of many illnesses, and there is concern that they could dismantle the infrastructure of our health care system if the disease trends

are not altered. As the burden of chronic preventable diseases continues to overwhelm health care systems around the world, clinicians and the general public need accurate information about environmental risk factors that can impact human health.

Here is the good news: There is no better time to inform and help patients make lifestyle changes and better choices. Several medical and scientific societies, led by The Endocrine Society, are working to bring the issues addressed in this book to the attention of regulatory agencies, the U.S. Congress, and EU Parliament. Health care practitioners are in a unique position to be able to convey to patients important tenets: It is possible to mitigate chemical exposures, to make healthier lifestyle changes, and to choose safer consumer products, food, and water. This information can have profound effects on the health of the population, of our offspring, and of future generations.

This book provides the latest information about environmental exposures to humans and the tools and proactive recommendations to limit adverse health effects due to exposures. It highlights the vulnerability of fetuses, infants, and children when exposures occur during critical periods of growth and development. To offer a complete picture, we describe the history of the chemical revolution in the 20th century, legislative issues related to modern chemicals, the unique toxicologic problems related to exposure to chemicals known as endocrine disruptors, and the current diseases linked by epidemiologic and experimental animal studies to various exposures. Throughout the text and especially in Chapter 14, we share important tools, resources, and practical information to empower clinicians to inform their patients about making practical lifestyle changes to reduce exposures to environmental hazards.

In keeping with the philosophy of integrative medicine, which is healing-oriented medicine that takes account of the whole person (i.e., body, mind, spirit) and all aspects of lifestyle, our focus is on prevention rather than management of symptoms. In line with this philosophy, we embrace the "precautionary principle," which states that when an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause-and-effect relationships are not fully established.

As co-editors of this text, we have chosen authors who are leaders in their respective areas, share a common interest in experimental and clinical research, and have a strong desire to educate health practitioners and the public. This book represents a unique collaboration of researchers and clinicians who have joined together to provide the most up-to-date information for clinicians and those seeking a deeper knowledge of their diseases.

We have divided the text into three sections: (1) history and overview of chemicals, (2) sources and clinical aspects of environmental exposures to

chemicals and radiation, and (3) regulatory and legislative issues, exposure mitigation, and resources for clinicians and patients.

In Section 1, Chapter 1 begins with an overview of the chemical revolution that occurred over the 20th century, leading to the development of tens of thousands of chemicals currently in commercial use without adequate premarket testing. Chapter 2 discusses our love affair with plastics since World War II. An astounding approximately one trillion pounds of plastics are produced globally every year. We describe the lifecycle of plastics, including invention, manufacture, use, and disposal by consumers and industry, highlighting the environmental and human health consequences. Chapter 3 describes how common environmental chemicals can hijack the endocrine system to disrupt normal physiology and homeostasis, particularly during critical periods of human development.

In Section 2, Chapters 4 and 5 focus on sources of pollution and the importance of clean indoor air, water, and food for optimal health. Chapter 4 focuses on the relationship between dust and mold in the home and respiratory diseases, including the consequences of exposure to toxic chemicals that bind to dust. Chapter 5 covers chemical pollutants in water and water contamination events that have unveiled serious problems with drinking water systems in the United States. Chapter 6 shows that diet and the chemicals in processed food and the environment need to be considered in order to maintain a healthy gut microbiome and reduce inflammatory diseases. Chapter 7 discusses commonly used medications, including acetaminophen and antidepressants, that have the unexpected capacity to exacerbate the harmful effects of chemicals that leach our of products found in virtually every home. Chapter 8 describes the pervasiveness of pesticides and their effects on the development of neurodegenerative disease, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS). Chapter 9 describes the precipitous rise in antimicrobial cleaning chemicals used in households, schools, and workspaces, including medical offices and hospitals, as well as the consequences of antimicrobial resistance. Chapter 10 explains the health risks associated with electromagnetic radiofrequencies, WiFi, cell phone, and tablet use, with an important focus on childhood exposures.

In Section 3, Chapter 11 focuses on the failure of regulatory bodies to properly vet food additives that affect the safety of all processed food, the health effects that have been elucidated, and the need for a rational approach to identifying and regulating these chemicals. Chapter 12 describes the unique properties and health hazards of endocrine-disrupting chemicals found in a wide range of common household products. This class of environmental toxicants disrupts hormones whose actions are mediated by receptors in specific target tissues that respond to very low concentrations, rather than being

acute systemic toxicants that are hazards only at high doses. Chapter 13 brings to light innovations for remediation of existing polluted environments and the "green chemistry" strategy for developing chemicals that are not a risk to human health. Chapter 14 outlines best practices for clinicians to screen for chemical exposure in patients and describes tools, practical tips, online resources, and proactive lifestyle recommendations for reducing exposure and increasing elimination of harmful chemicals found in everyday life.

We hope this book affords clinicians and the public an increased awareness of environmental medicine and its critical contribution to disease prevention and management. By providing helpful resources such as smart phone apps, links to websites, and printable clinician and patient information (see Chapter 14), our aim is to facilitate a change in health outcomes for patients, their families, and the global population. We hope you will feel enlightened and empowered and possibly respond with a call to arms, no matter where on the path you may be starting your journey.

Aly Cohen and Fred vom Saal

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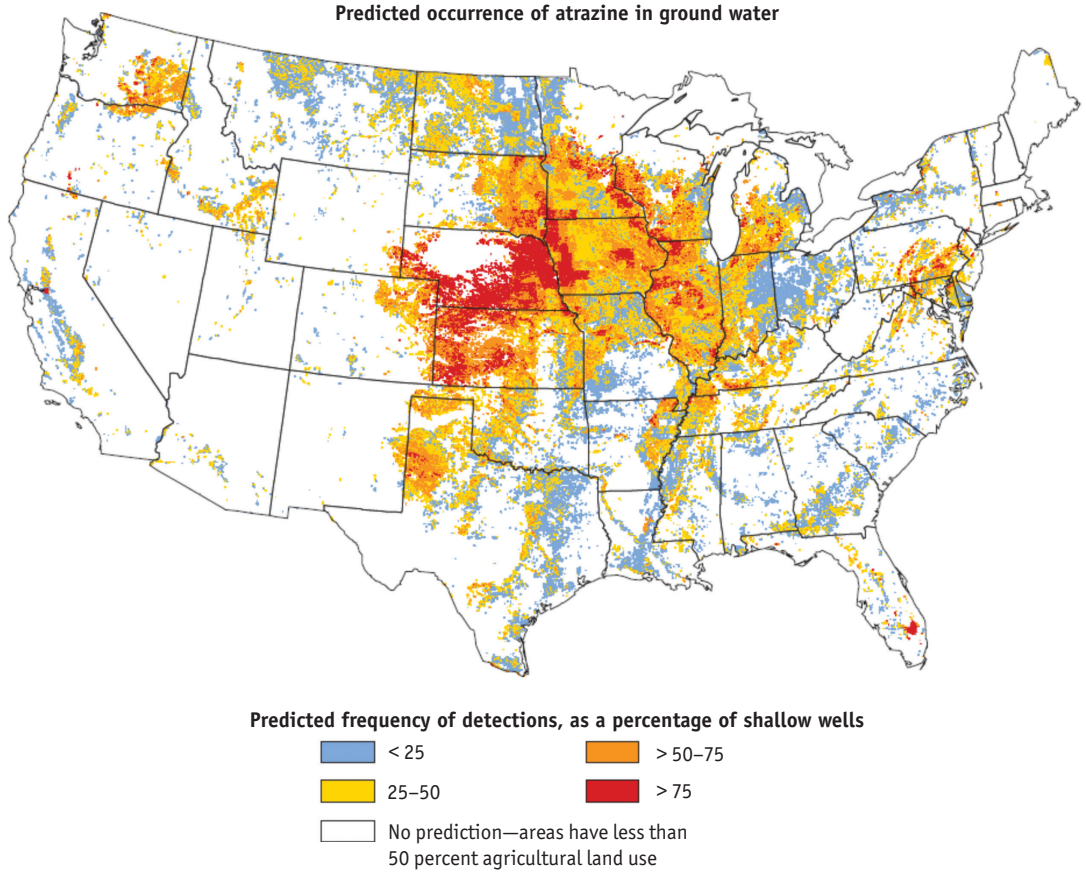

FIGURE 5.3. Map shows where the herbicide atrazine has been detected in shallow drinking water wells in the United States. Adapted from Gilliom, R.J., Barbash, J.E., Crawford, C.G., et al. 2006. *The Quality of Our Nation's Waters—Pesticides in the Nation's Streams and Ground Water, 1992–2001.* U.S. Geological Survey Circular 1291. https://pubs.usgs.gov/circ/2005/1291/pdf/circ1291.pdf.

SECTION 1

History and Overview of Environmental Chemicals

1

The Age of Chemicals in the 21st Century: New Inventions, New Problems

CAROL F. KWIATKOWSKI

Key Concepts

- Humans are exposed on a regular basis to many types of chemicals, including pesticides, metals, industrial products and byproducts, plastics, and antimicrobials.
- Exposure to very low concentrations of chemicals, particularly endocrine disruptors, can have detrimental and lasting effects that may not manifest for years.
- The effects of exposure during prenatal and childhood development can be permanent and can persist for multiple generations.
- Several medical societies recommend avoiding or reducing exposure to chemicals implicated in adverse health conditions, even in the absence of definitive scientific evidence proving cause and effect.
- Governments should correct deficiencies in safety testing protocols, require that chemicals be tested before use in consumer products or at least prohibit substitution of a harmful chemical with one that is untested, and promote the development of safer alternatives and green chemistry.

Introduction

The 20th century was filled with tragic incidents of chemical exposures that killed or sickened hundreds of human and animal victims. These events capture the attention of the media and the public and may be addressed by swift government action. However, behind each major news event

is a little-known story of damage that erodes the health of millions who are exposed in a less dramatic manner, day in and day out, to the same chemicals that led to the newsworthy tragedies. These and similar chemicals are present in our air, water, and soil, and we are exposed in our homes, work places, and play areas. We eat, drink, and breathe them; we rub them on our skin.

The warning signs of chemical exposures are not posted on office or bathroom walls; they are not even listed on the containers that hold the chemicals. For the most part, evidence of the existence of these chemicals and their potential damage to our health and that of future generations lies buried in the annals of academic libraries. Although public awareness is growing, government response has been too slow, and generation after generation continues to be exposed.

This chapter provides examples of pesticides, metals, air pollutants, flame retardants, plastics, antimicrobials, and other common contaminants encountered by most humans in the developed world on a daily basis. Exposure to these chemicals has been documented in numerous academic studies[54] and in data collected through the U.S. Centers for Disease Control and Prevention (CDC) National Biomonitoring Program. The program assesses more than 300 environmental chemicals by sampling blood, urine, breast milk, and other biologic specimens in the general population. Most people have numerous detectable chemicals in their bodies, and some have hundreds. Socioeconomically stressed communities have higher levels of exposure to many environmental chemicals. Even people living in remote areas where chemicals are not used or manufactured can have high levels due to transport of chemicals by wind and water and through the food web.

Children typically have higher levels of chemicals in their bodies than adults because children spend more time closer to the ground, where chemicals settle; they have more hand-to-mouth behavior than adults; they have greater food and water intake per unit of body weight; and their immature immune and metabolic systems do not process chemicals as well as adult systems do. They are also born "prepolluted" with chemicals that cross the placenta. One biomonitoring report identified as many as 232 chemicals in the umbilical cord blood of minority newborns.[21] Breast milk and baby formula are other early sources of contaminants in young children.

Chemical impacts on the endocrine system are of particular concern because many synthetic chemicals can disrupt hormone function at very low concentrations, within the range of human exposure.[55] Adverse effects from exposure that occurs in utero can be permanent. Laboratory research on the effects of prenatal and early postnatal exposure to low concentrations of chemicals can be seen in an online learning tool developed by The Endocrine Disruption Exchange (TEDX).[4,52] The timing of chemical exposure in each rodent study is mapped to a timeline of events in human prenatal development, showing adverse effects on the central nervous system, the male and female reproductive systems, and the endocrine and immune systems.

Despite these facts, the toxicologic tests used by government regulatory agencies do not routinely assess sensitive end points related to the endocrine system; they do not include the effects of exposure to low chemical concentrations; and they do not include examination of immediate or long-term effects due to exposure during critical periods in development. Therefore, we cannot rely on safe exposure levels set by the government to protect people from harm, particularly fetuses, infants, and children. This is alarming given the dramatic growth in synthetic chemical production in the United States over the past century, as shown in Figure 1.1.

Mirroring this growth is an increase in the prevalence and/or incidence of many diseases in which environmental chemicals are implicated. Examples include infertility, hypospadias, cryptorchidism, childhood cancer, autism, attention deficit hyperactivity disorder (ADHD), diabetes, and obesity. Birth rates and sex ratios have also been affected. In one heavily polluted First Nation community living along the Great Lakes in eastern Canada, the proportion of male births over a 5-year period declined from 0.54 to 0.35.[33] Many population statistics attest to major changes in chronic disease rates over the past century. It is time for individuals to become aware of changes they can make to avoid harmful chemical exposures and

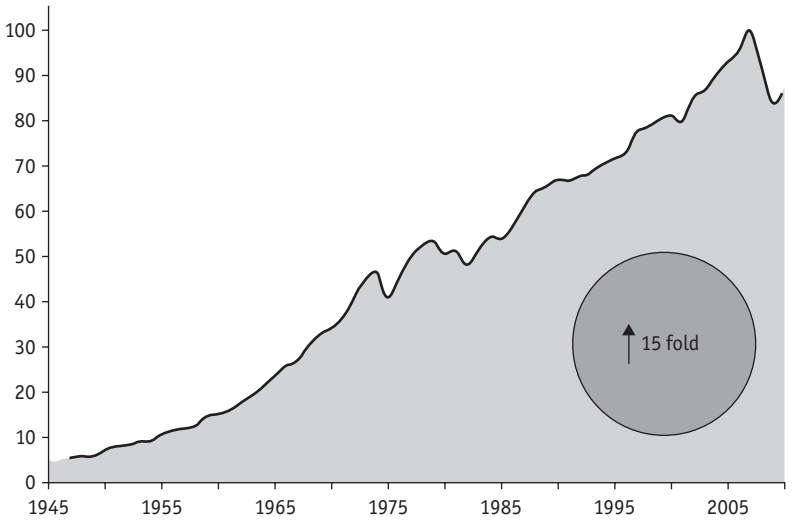

Figure 1.1. Chemical production in the United States, 1945–2007. Federal reserve data on chemical production is only offered as relative production, which is unit-less. A specific reference year is chosen and values are calculated relative to that year's production. In this particular data set 2007 is the reference year and is assigned a value of 100. Data from: U.S. Federal Reserve Board, Division of Research and Statistics. Reprinted with permission from the University of California San Francisco Program on Reproductive Health and the Environment.

for governments to take a precautionary approach to regulating chemicals in order to protect the public health.

Chemicals of Concern

After World War II, chemists, having excelled at developing agents of chemical warfare, began synthesizing compounds (e.g., polymers, resins, plastics, lubricants, solvents, surfactants) for the purpose of improving modern living. The conveniences offered by these products were welcomed by consumers, and it did not take long before these chemical compounds pervaded almost every aspect of daily life. Man-made chemicals are found in clothing, cosmetics, fragrances, furniture, building materials, electronics, cleaning products, and toys, as well as food and water.

Table 1.1 provides a categorization scheme designed to organize chemicals according to their use (e.g., household chemicals, personal care products), function (e.g., flame retardant, solvent, antimicrobial), and type of chemical (e.g., metal, biogenic compound). In the following sections, selected chemicals are described to illustrate the history, exposure routes, and health effects of several chemical categories.

PESTICIDES

Pesticides are unique in the chemical pollution realm because they are specifically designed to kill living organisms, usually by means of acute neurotoxicity (see Chapter 8). Unfortunately, their use results in collateral damage to humans, wildlife, and the ecosystem.

Like many modern chemicals, the pesticide dichlorodiphenyltrichloroethane (DDT) was developed in the early 20th century. Initially used to fight insect-borne diseases such as malaria, it was quickly adopted in agricultural and household use for general pest control. Rachel Carson's 1962 book, *Silent Spring*, raised widespread public concern about the use of DDT and other pesticides because of their effects on the nervous system and liver and their roles as carcinogens and mutagens.[8] A decade later, the U.S. Environmental Protection Agency (EPA) cancelled the use of DDT in the United States, although it is still used in other countries to fight malaria and other insect-borne diseases.[18]

Today, hundreds of pesticides are registered by the EPA to kill weeds, insects, rodents, mites, fungus, and more. A common insecticide is chlorpyrifos, which the EPA cancelled for all home uses in 2000 and recently proposed

Table 1.1. Chemical Categories

Category	*Description*
Household Product Ingredient	Chemicals found in items such as appliances, vehicles, building materials, electronics, crafts, textiles, furniture, and household cleaning products.
Personal Care Product/ Cosmetic Ingredient	Chemicals found in products such as cosmetics, shampoos, lotions, soaps, deodorants, fragrances, and shaving products.
Food Additive	Antioxidants, dyes, and compounds used in food processing, and as components in food packaging.
Flame retardant	Chemicals used to prevent fires.
Plastic/Rubber	Components, reactants, or additives used in the manufacturing of rubbers or plastics.
Pesticide Ingredient	Insecticides/acaricides (miticides), herbicides, fungicides, rodenticides, and other biocides, including chemicals described as 'inert'.
Antimicrobial	Chemicals that prevent the growth of and/or destroy microorganisms.
Biogenic compound	Naturally occurring or biologically derived chemicals such as phytoestrogens, flavonoids, monophenols, mycochemicals and phenolic acids.
Industrial Additive	Chemicals such as preservatives, antioxidants and surfactants used in such things as glue, plastic, rubber, paint, and wood products.
Solvent	Chemicals used to dissolve other chemicals.
Metal/Metallurgy	Elements or chemicals used in the extraction, processing, or manufacturing of a metal or metal-containing product, including welding.
Byproduct/Intermediate/ Reactant	Chemicals used in the synthesis of other compounds, and/or unwanted byproducts such as impurities and contaminants, including combustion byproducts.
Medical/Veterinary/Research	Chemicals used in hospitals, medical supplies, and equipment, in laboratories or as reagents, and pharmaceuticals.
Metabolite/Degradate	Breakdown products of other chemicals.

to cancel for all food-related uses.[20] Chlorpyrifos is an example of a pesticide that can have numerous effects on brain development and function and to which almost everyone is exposed.[12]

People are often exposed to several pesticides at once. A graphic example of the neurodevelopmental effects of exposure to pesticides can be seen in Figure 1.2, in which artwork created by exposed children clearly demonstrates an impaired ability to draw a person.[25] Wildlife is also exposed to mixtures of pesticides, such as from sewage effluent or agricultural runoff in rivers and lakes. Intersex fish (e.g., males with testicular oocytes) have been found in numerous water bodies in the United States.[30] Alligators living in lakes that are highly polluted by pesticides have been shown to have smaller gonads and reduced testosterone levels compared with alligators living in unpolluted water.[26] Wildlife share the same water, air, and soil as humans, and the effects of chemical exposure on animals may serve as harbingers of the health effects in humans.

Pesticides have transgenerational effects. When exposure occurs during pregnancy, three generations are exposed at once: the mother, the fetus, and the fetal germ cells. Furthermore, research on laboratory animals has demonstrated effects of pesticides on subsequent generations that were not directly exposed. The effects were most strikingly shown in studies of vinclozolin (a fungicide). Three generations after exposure, descendants

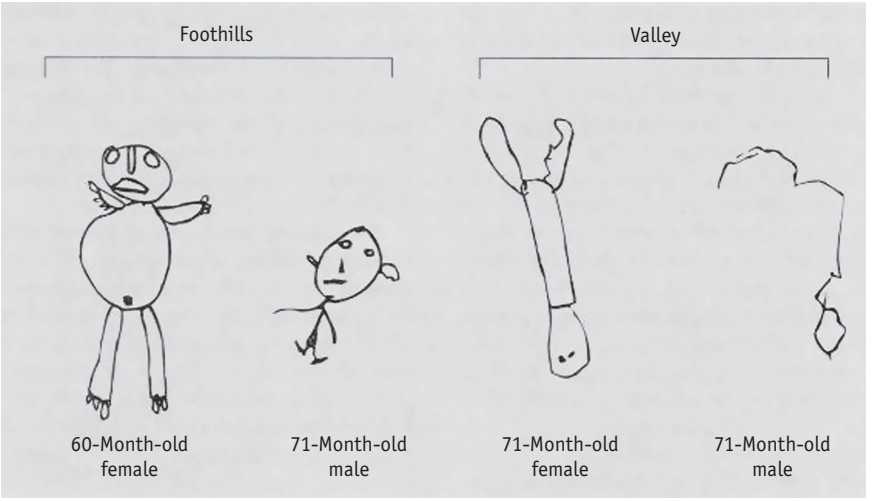

Figure 1.2. Representative drawings of a person by 5-year-old children who were unexposed (i.e., in the foothills) or exposed (i.e., in the valley) to pesticides.
From Guillette, E.A., Meza, M.M., Aquilar, M.G., Soto, A.D., & Garcia, I.E. 1998. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. *Environ Health Perspect.* 106:347–353.

displayed effects on metabolic activity, brain development, and behavior, including altered responses to stressful environments in adolescence.[13] These effects would be extremely difficult to study in humans.

Pesticide exposure can lead to effects that do not manifest until years later. Laboratory research on early life exposure to several different pesticides has revealed links to Parkinson's disease through alterations in the neurochemicals that affect locomotor activity.[46,53]

Despite growing interest in organic practices, pesticides are considered to be essential to modern agriculture. It is unlikely that the use of chemicals in large-scale farming will be eliminated in the near future. It is therefore imperative that governments develop ways of identifying the safest alternatives and continue to raise public awareness about the best ways to reduce exposure.

METALS: LEAD

Exposure to lead has been known since ancient times to have adverse health effects. Nevertheless, people have used it in everything from water pipes to paints to cosmetics. In the early 1970s, the EPA began phasing lead out of gasoline, in which it was used as an additive to boost octane levels; this process took more than 25 years to complete. In an effort to reduce childhood exposures, lead was also removed from household paint, although exposure is still a problem in older houses. Aging infrastructure can create new public health emergencies, as was shown in Flint, Michigan, where a switch to a more corrosive water source (i.e., a river) in 2014 caused lead to leach from pipes into drinking water. The incidence of elevated blood lead levels in children doubled as a result.[27]

Although regulatory efforts have been successful at lowering the levels of lead in blood, continued scientific research has made it clear that there are no safe levels of lead exposure. Even minute amounts encountered during development can cause devastating and permanent damage to the growing child. Although some of the effects of this *legacy chemical* are fairly well known, others are not. The CDC's Agency for Toxic Substances and Disease Registry (ATSDR) provides a long list of adverse outcomes in numerous physiologic systems as a result of acute and chronic exposures.[2]

SOLVENTS: BTEX

BTEX is an acronym for the aromatic hydrocarbons benzene, toluene, ethylbenzene, and the xylene isomers. BTEX are acquired during the extraction of

fossil fuels and then refined and used as feedstock for the synthesis of thousands of other chemicals. When lead was banned as a fuel additive, BTEX hydrocarbons were the chosen replacement chemicals, and today they comprise up to 28% of high-octane gasoline.[39] They are also used in the production of numerous consumer and industrial products, including adhesives, detergents, solvents, paints, and pesticides. They are in such items as cleaning products, wall paint, glue, nail polish, and air fresheners.

According to the EPA, toluene is among the top 10 chemicals used in consumer products, and ethylbenzene is among the top 10 for children's products, including toys, furniture, playground equipment, and plastic and rubber products.[19] As a result, indoor air has become polluted, and concentrations of BTEX indoors can be four to six times higher than in outdoor air due to the off-gassing of household products and building materials. Although BTEX chemicals can be controlled by limiting their use as gasoline additives, there is currently little awareness of the issue and few regulatory approaches for cleaning up indoor air.

A review of BTEX exposure in humans at ambient (low) concentrations found effects in the respiratory, immune, cardiovascular, and reproductive systems.[6] Many of the studies were conducted in children exposed prenatally or during early childhood.

New sources of exposure are potentially affecting millions of people in the United States and other countries. A relatively new approach to extracting fossil fuels called hydraulic fracturing (i.e., fracking) has brought raw and refined petrochemicals into people's neighborhoods and backyards. During hydraulic fracturing, complex mixtures of chemicals combined with water and sand are pumped into the ground at high pressure to release the desired methane. BTEX and other toxic chemicals come up with the methane and are released into the air near homes, schools, and urban centers. They can also contaminate ground, surface, and drinking water sources. Research is beginning to emerge, and epidemiologic studies have reported adverse developmental outcomes (e.g., congenital heart failure, increased preterm births) associated with living in close proximity to hydraulic fracturing sites.[9,34,47]

INDUSTRIAL BYPRODUCTS: DIOXINS

Dioxins are the byproducts of numerous industrial operations. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic and best-studied form of dioxin. Although dioxins are not intentionally produced, they enter the air from thousands of sources, including incinerators that burn medical, municipal, and hazardous wastes; chemical processing facilities that use

chlorine to make products such as pesticides and plastics; and metal refining and smelting operations.

Before industrialization and the introduction of chlorine, dioxins existed naturally only in very small amounts, but they are now found everywhere in the world. Transported through the air, they do not react with oxygen or water and are not broken down by bacteria. They are among a list of chemicals known as *persistent organic pollutants* (POPs).

When dairy cows and beef cattle eat feed crops containing settled airborne dioxins or are given feed that contains dioxins from other animal fats, these chemicals become concentrated in the fat of the animals. Humans ingest dioxins primarily in fatty foods such as beef, dairy products, and fish, but they also occur in lesser concentrations in other foods. Dioxins accumulate in human fatty tissue, with a half-life of 7 to 12 years. Children, nursing infants, workers exposed occupationally, people who eat fish as a main staple of their diet, and people who live near industrial sites where dioxins are released may be highly exposed.

Perhaps the most famous dioxin incident occurred in 1976, when a chemical plant in Seveso, Italy, exploded, releasing a cloud of dioxins that quickly settled over the town and surrounding areas. Animals began to die immediately. A 2010 *TIME* magazine article,[14] which listed the incident as one of its top 10 environmental disasters, described a man's cat dying and the tail falling off. Two days later, there was nothing left but the skull. People quickly began to get sick, many with the signature symptom of dioxin poisoning, a skin disease known as chloracne. It was weeks before the town was evacuated and the area quarantined. Long-term health studies have found evidence of cardiovascular and respiratory disease, diabetes, and cancer among affected individuals.[5]

The EPA has studied dioxins at length and recognizes that they can cause cancer, interfere with the endocrine system, lead to reproductive and developmental problems, and damage the immune system. Because they alter the fundamental ways in which cells develop and grow, they can lead to a broad spectrum of physiologic effects. Importantly, effects can occur within the range of exposures in the general population. Children are particularly susceptible, and human perinatal exposure has been associated with impaired brain development; endocrine, liver, and lung dysfunction; and other adverse outcomes.[51]

PERFLUORINATED COMPOUNDS

Perfluorinated compounds (PFCs) are a group of chemicals that have been made since the 1950s for specific uses in industrial and consumer products.

They also occur as byproducts and breakdown products of other fluorinated chemicals. The two most widely studied PFCs are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), which have been used in many applications. PFOS has been used in nonstick cookware; stains and water repellants for apparel, carpets, and furniture; food packaging; paints, cosmetics; shampoos; and denture cleaners. PFOA has been used in breathable waterproof fabrics, insulations for electrical wiring, and foam-based fire extinguishers.

PFCs are found ubiquitously in human populations and other species, even in remote locations far from manufacturing or use of PFCs. This widespread detection has been attributed to their resistance to biodegradation and their bioaccumulative properties. It is thought that most human exposure occurs through food and drinking water. Crops grown in PFC-contaminated soil can take up and accumulate these compounds. Exposure to PFC-contaminated air or house dust and direct contact with PFC-containing consumer products are other potential sources of exposure.

PFCs are primarily found in the kidney and liver. PFOA and PFOS have long half-lives in humans, ranging from 2 to 9 years for PFOA and up to 21 years for PFOS. They cross the placenta and have been measured in maternal and cord blood and in breast milk. Laboratory studies indicate that PFCs interfere with reproduction and development and may cause cancer.[1,32,57] Despite the known toxicities of PFCs, enactment of regulations to control their production and use has been difficult, and voluntary action by industry to remove them from consumer products has led to substitution with other harmful chemicals.

FLAME RETARDANTS

California's fire safety regulation TB117, enacted in 1975, led to the use of large quantities of flame-retardant chemicals in consumer products across the United States. These products include furniture foam, carpet padding, electronics, and building insulation. Many products used for babies and children are made with foam that contains flame retardants, including car seats, crib mattresses, and nursing pillows. The chemicals migrate out of the foam and are a common component in house dust[62] (see Chapter 4).

Although some may consider flame retardants a necessary evil, their purpose of delaying or preventing the ignition and spread of fire has been challenged, and their toxicity to the health of firefighters who inhale toxic gases is a serious concern.[45] Further, they have been associated with numerous adverse effects in humans and laboratory animals, including decreased

fertility, altered neurodevelopment, lowered IQ, hyperactivity, and hormone disruption.[29,35,43]

Some flame retardants have been banned due to their toxicity, but because they are extremely long lasting in the environment and bio accumulate, the risks of exposure remain. Laboratory research into one common replacement chemical identified it as an endocrine disruptor and an obesogen at low, environmentally relevant levels.[36] In a bit of good news, the flammability standard for TB117 was revised in 2013 in a manner that allows many products to meet the standard without the use of harmful chemicals.

PLASTICS: BISPHENOL A

In contrast to legacy chemicals such as lead and PFCs, bisphenol A (BPA) is perhaps the most widely studied *emerging chemical*, a term used to describe chemicals of emerging concern. Manufacturers began using BPA in industrial and commercial products in the 1950s, although it had been shown in the 1930s to have the efficacy of an endogenous estrogen in animals. Its hardness and clarity made it appear to be the ideal plastic for everything from baby bottles and eyeglass lenses to airplanes and automobiles. It is used as an epoxy resin in food and beverage can linings, water pipes, dental sealants and fillings, and adhesives. It is speculated that the widest source of human exposure may come from its use as a coating on thermal receipt paper, from which it readily migrates onto hands and into mouths. BPA is metabolized and excreted quickly, but exposure is so prevalent that it is found in almost everyone tested and in many different bodily fluids.[10]

BPA has become an iconic chemical to demonstrate the issue of endocrine disruption, particularly with regard to prenatal exposure. Millions of dollars in government research funds have been spent studying BPA alone. Hundreds of studies have been published identifying adverse health effects, including effects at low, environmentally relevant levels.[38,40,56,59] Outcomes include impaired male and female reproduction, metabolic disease, altered immune function, and adverse effects on brain development and behavior.

Despite these findings, industry pushback has stalled national regulations that would reduce the production or use of BPA (see Chapters 11 and 12). Worldwide BPA production is almost 5 million tons, and its functional and economic qualities make industry reluctant to replace it. Cities and states in the United States have been more proactive than the federal government, and public concern has been perhaps the most effective at motivating industry to create BPA-free products. Unfortunately, replacement of BPA with chemicals such as bisphenol S (BPS), bisphenol F (BPF), and 4-hydroxyphenyl

4-isoprooxyphenylsulfone (BPSIP) may not be any better in terms of health. However, the replacements are so new that little is known about their potential health effects. This is an example of the pervasive issue of *regrettable substitution*, in which chemicals with health concerns are replaced by chemicals we know nothing about.

PLASTICS: PHTHALATES

Phthalates are plasticizers added to make plastics such as polyvinyl chloride (PVC) softer and more flexible. They are also commonly used to make fragrances last longer. Several types of phthalates are used, and many are produced in volumes of tens of millions of pounds. Common uses are in food packaging, fragrances, personal care products (e.g., soap, shampoo), and numerous household products such as garden hoses, detergents, shower curtains, and toys. They are also in building materials, paints, and adhesives.

Because phthalates are not bound to the plastics in which they are mixed, they are readily released by leaching or evaporation. As plastics age and break down, the release of phthalates accelerates. Leaching also increases from contact with fatty foods and oily substances. Some phthalates are detected in almost every person tested, and sometimes they are found at very high levels.[10]

Diet is the primary route of exposure for phthalates, likely because the FDA has approved 30 phthalates for use as food additives (including in packaging), although some of the approved phthalates are now regulated in children's products. Skin absorption is an important route of exposure that has not been well studied. Absorption can occur through the use of men's and women's personal care products, sunscreens, and insecticides. Potential sources of inhalation include breathing fragrances and hair sprays and baking modeling clay. A major concern about phthalates is their use in medical devices such as fluid bags and tubing, particularly in neonatal care units.

Like BPA, phthalates are commonly recognized by the scientific community as endocrine disruptors. Prenatal phthalate exposure in humans has been correlated with effects in baby boys including incomplete testicular descent, increased risk of hypospadias, and shorter anogenital distance, which is a marker for androgenic effects.[50] There is also evidence for effects on neurodevelopment, pointing to cognitive and behavioral outcomes including ADHD-like behaviors.[17] In adult men, altered sperm, increased abdominal obesity, and insulin resistance have been shown.[28,48]

Worldwide, various phthalates have been banned by countries, states, and cities for specific uses (e.g., in children's toys that can be placed in the mouth), but they are typically replaced by other phthalates that have undergone little

scientific research on their health effects. An expert panel was convened by the U.S. Consumer Product Safety Commission to review the full range of phthalates in children's products. Their 2014 report concluded that eight phthalates had sufficient data to confirm they should be banned from children's products at levels greater than 0.1%.[11]

Although we are continuously exposed to mixtures of many different phthalates, regulations typically focus on individual chemicals. Further, although phthalates have been shown to be harmful during prenatal development, regulations have focused on children's products, ignoring the potential effects of fetal exposure through the maternal diet. More effective regulations are needed to reduce phthalate exposure.

ANTIMICROBIALS: TRICLOSAN

Triclosan is one of the most commonly used synthetic broad-spectrum antimicrobial agents. It is used primarily to prevent the growth of bacteria (see Chapter 9). It is widely used in hospitals and in many consumer products such as liquid soap, deodorant, cosmetics, toothpaste, and clothing. It is also used in durable items such as toys, cutting boards, and fitness mats. Although the FDA requires over-the-counter drugs and cosmetics to be labeled if they contain triclosan, this does not apply to other items. Triclosan is registered with the EPA as a pesticide and is used as a preservative to prevent bacterial deterioration in many commercial and consumer products (e.g., adhesives, fabrics, vinyl, plastics, sealants).

Triclosan is readily absorbed through the skin and has been found in serum, in breast milk, and as metabolites in the urine of 75% of Americans.[7] Although it is not generally regarded as toxic, numerous laboratory studies attest to its endocrine-disrupting properties, which affect the estrogen, androgen, and thyroid systems.[23,31,37,41,49] Triclosan is also thought to be adding to the increase in antibiotic-resistant bacteria. For many consumer products containing triclosan (e.g., soaps, body washes), there does not appear to be any added health benefit compared with regular soap and water. Triclosan is a common pollutant in surface water (i.e., rivers and streams), sewage sludge, and sediment, potentially affecting aquatic ecosystems and wildlife.

Summary

The recitation of adverse environmental effects of chemicals could continue for many pages, describing the exposure routes and health impacts

of fragrance ingredients, food additives, mercury, arsenic, and much more. However, the point has been made that we live in a world infused with man-made chemicals. Exposure at very low concentrations can have detrimental and lasting impacts that may not manifest for years, making it very difficult to connect cause and effect. Moreover, the effects of exposure during prenatal and childhood development can be permanent and can persist for multiple generations. The urgency with which we must begin to address these problems cannot be overstated.

Looking Forward

Scientists are beginning to weave together research to explain the unacceptable prevalence of chronic conditions that are disabling society. They are telling the story in terms such as *adverse outcome pathways*. These are models that attempt to connect events at the molecular level (e.g., hormonal changes) through the subsequent cellular and organ responses to adverse outcomes for the whole being.[58] New, high-volume in vitro test methods and in silico computational models are being developed, and many more chemicals are being screened and identified as having endocrine activity.[22] Methods are being advanced to systematically review animal and human epidemiologic data to definitively identify the hazards associated with environmental chemicals[42] (see Chapter 13).

New approaches are being developed to estimate exposure to chemical mixtures that attempt to reflect real-world chemical body burdens.[16] They include characterization of the *exposome*, the totality of exposures humans experience throughout their lives.[60] Green chemistry approaches, in which chemicals are "benign by design," may provide incentives for industry to create products without harmful chemicals.[44] However, we are many years away from positive health impacts of these new scientific developments in the real world.

For most chemicals, no information about health effects exists. For those that have proved harmful, protective health measures continue to be delayed by arguments that regulatory and other preventive actions should not be initiated until definitive proof of cause and effect is demonstrated. However, the standard of proof—randomized clinical trials—is unethical in environmental health research. There is already enough evidence that the chemicals of concern are toxic, thus they cannot be administered to humans. However, if they are unethical to administer in a clinical trial, why are we allowing them to be released into the environment? The current U.S. approach of allowing chemicals to be brought to market without appropriate safety testing is

untenable. Europe is one step ahead in that legislation has been passed to require chemicals to be tested for adverse health effects before market entry.

Health care professionals in the 21st century who treat patients with cancer, diabetes, obesity, reproductive problems, thyroid conditions, and developmental and behavioral disorders must become educated about indoor and outdoor environments and the potential sources of chronic and long-term chemical exposures that affect their patients.

Medical professionals can provide a tremendous service to improve public health by educating patients about how to reduce exposures to potentially harmful chemicals. Numerous professional societies have issued statements advocating for preventive measures even in the absence of scientifically established cause and effect (i.e., the *precautionary approach*). They include The Endocrine Society,[24,61] the American College of Obstetricians and Gynecologists,[3] the American Society for Reproductive Medicine,[3] and the International Federation of Gynecology and Obstetrics.[15] Health care professionals are encouraged to incorporate these recommendations into patient care practices for children and adults. In the face of uncertainty, preventive action should be the norm, and the medical community has a critical role to play in helping patients learn how to avoid unnecessary chemical exposure.

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2

The Plastic Age: Worldwide Contamination, Sources of Exposure, and Human Health Consequences

CHARLES MOORE AND SARAH S. MOSKO

Key Concepts

- We live in the plastic age, but most people are ignorant about the material that they use most in their daily lives.
- Manufacturers of plastic products divorce themselves from the issue of recovery of the material after its useful life, which can be as brief as a few minutes, resulting in vagrant plastic waste.
- Plastics often are made from harmful chemicals, a percentage of which are still free monomers after polymerization. Many chemicals are added to convert plastic resin feedstocks into useful products and can leach into the things they contact.
- All shapes, sizes, and colors of plastic debris have amassed in the world's oceans, where they adsorb and absorb harmful chemicals from seawater due to their lipophilic and hydrophobic qualities, providing a vehicle for the entry of toxic chemicals into the ocean food web.
- Increasing numbers of animal studies in the past decade have documented developmental derailments, including endocrine disruption and cancers, that are attributable to fetal and postnatal exposure to certain plastic monomers (e.g., bisphenol A, styrene) and plastic additives (e.g., phthalates, brominated flame retardants) at environmentally relevant doses.
- Human studies have revealed that fetuses and infants are exposed to an alarming number of industrial chemicals in utero and through breast milk and that some of these chemicals are associated with ubiquitous plastics.
- The list of human health problems that correlate with exposure to chemicals in plastics reads like a catalog of modern Western diseases.