MEDICAL DISPATCH

THE PLASTIC PANIC

How worried should we be about everyday chemicals?

BY JEROME GROOPMAN

Bisphenol A, commonly known as BPA, may be among the world's most vilified chemicals. The compound, used in manufacturing polycarbonate plastic and epoxy resins, is found in plastic goggles, face shields, and helmets; baby bottles; protective coatings inside metal food containers; and composites and sealants used in dentistry. As animal studies began to show links between the chemical and breast and prostate cancer, early-onset puberty, and polycystic ovary syndrome, consumer groups pressured manufacturers of reusable plastic containers, like Nalgene, to remove BPA from their products. Warnings went out to avoid microwaving plasticware or putting it in the dishwasher. On May 6th, the President's Cancer Panel issued a report deploring the rising number of carcinogens released into the environment—including BPA—and calling for much more stringent regulation and wider awareness of their dangers. The panel advised President Obama "to use the power of your office to remove the carcinogens and other toxins from our food, water, and air that needlessly increase health care costs, cripple our Nation's productivity, and devastate American lives." Dr. LaSalle Leffall, Jr., the chairman of the panel, said in a statement, "The increasing number of known or suspected environmental carcinogens compels us to action, even though we may currently lack irrefutable proof of harm."

The narrative seems to follow a familiar path. In the nineteen-sixties, several animal studies suggested that cyclamates, a class of artificial sweetener, caused chromosomal abnormalities and cancer. Some three-quarters of Americans were estimated to consume the sweeteners. In 1969, cyclamates were banned. Later research found that there was little evidence that these substances caused cancer in humans. In the nineteen-eighties, studies suggesting a cancer risk from Alar, a chemical used to regulate the color and ripening of apples, caused a minor panic among parents and a media uproar. In that case, the cancer risk was shown to have been overstated, but still present, and the substance remains classified a "probable human carcinogen." Lead, too, was for years thought to be safe in small doses, until further study demonstrated that, particularly for children, even slight exposure could result in intellectual delays, hearing loss, and hyperactivity.

There is an inherent uncertainty in determining which substances are safe and which are not, and when their risks outweigh their benefits. Toxicity studies are difficult, because BPA and other, similar chemicals can have multiple effects on the body. Moreover, we are exposed to scores of them in a lifetime, and their effects in combination or in sequence might be very different from what they would be in isolation. In traditional toxicology, a single chemical is tested in one cell or animal to assess its harmful effects. In studying environmental hazards, one needs to test mixtures of many chemicals, across ranges of doses, at different points in time, and at different ages, from conception to childhood to old age. Given so many variables, it is difficult to determine how harmful these chemicals might be, or if they are harmful at all, or what anyone can do to avoid their effects. In the case of BPA and other chemicals of its sort, though, their increasing prevalence and a number of human studies that associate them with developmental issues have become too worrisome to ignore. The challenge now is to decide a course of action before there is any certainty about what is truly dangerous and what is not.

In 1980, Frederica Perera, a professor at Columbia's Mailman School of Public Health and a highly regarded investigator of the effects of environmental hazards, was studying how certain chemicals

in cigarette smoke might cause cancer. Dissatisfied with the research at the time, which measured toxic substances outside the body and then made inferences about their effects, she began using sophisticated molecular techniques to measure compounds called polycyclic aromatic hydrocarbons, or PAH—which are plentiful in tobacco smoke—in the body. Perera found that after entering the lungs the compounds pass into the bloodstream and damage blood cells, binding to their DNA. She hoped to compare the damaged blood cells from smokers with healthy cells, and decided to seek out those she imagined would be uncontaminated by foreign substances. "I thought that the most perfect pristine blood would come from the umbilical cord of a newborn," Perera said.

But when she analyzed her samples Perera discovered PAH attached to some of the DNA in blood taken from umbilical cords, too. "I was pretty shocked," she said. "I realized that we did not know very much about what was happening during this early stage of development."

Perera's finding that chemicals like PAH, which can also be a component of air pollution, are passed from mother to child during pregnancy has now been replicated for more than two hundred compounds. These include PCBs, chemical coolants that were banned in the United States in 1979 but have persisted in the food chain; BPA and phthalates, used to make plastics more pliable, which leach out of containers and mix with their contents; pesticides used on crops and on insects in the home; and some flame retardants, which are often applied to upholstery, curtains, and other household items.

Fetuses and newborns lack functional enzymes in the liver and other organs that break down such chemicals, and animal studies in the past several decades have shown that these chemicals can disrupt hormones and brain development. Some scientists believe that they may promote chronic diseases seen in adulthood such as diabetes, atherosclerosis, and cancer. There is some evidence that they may have what are called epigenetic effects as well, altering gene expression in cells, including those which give rise to eggs and sperm, and allowing toxic effects to be passed on to future generations.

In 1998, Perera initiated a program at Columbia to investigate short- and long-term effects of environmental chemicals on children, and she now oversees one of the largest and longest-standing studies of a cohort of mothers and newborns in the United States. More than seven hundred mother-child pairs have been recruited from Washington Heights, Harlem, and the South Bronx; Perera is also studying pregnant women in Kraków, Poland, and two cities in China, and, since September 11, 2001, a group of three hundred and twenty-nine mothers and newborns from the downtown hospitals near the World Trade Center. In all, some two thousand mother-child pairs have been studied, many for at least a decade.

This March, I visited Columbia's Center for Children's Environmental Health, where Perera is the director, and met with a woman I'll call Renee Martin in an office overlooking the George Washington Bridge. Martin was born in Harlem, attended a community college in Queens, and then moved to 155th Street and Broadway, where she is raising her five children. She entered the study eleven years ago, when she was pregnant with her first child. "I was asthmatic growing up," Martin said. "And I was concerned about triggers of asthma in the environment. So when they asked me to be in the study I thought it would be a good way to get information that might tell me something about my own health and the health of my child." She showed me a small black backpack containing a metal box with a long plastic tube. During her pregnancy, Martin would drape the tube over her shoulder, close to her chin, and a vacuum inside the device would suck in a sample of air. A filter trapped particles and vapors of ambient chemicals, like pesticides, phthalates, and PAH. "I walked around pregnant with this hose next to my mouth, but, living in New York, people hardly notice," she said with a laugh.

The Columbia team also developed a

Environmental hazards may cause lasting harm to children.

RAYMOND BIESINGER

comprehensive profile of Martin's potential proximity to chemicals, including an environmental map that charted her apartment's distance from gas stations, dry cleaners, fast-food restaurants, supermarkets, and major roadways. They took urine samples and, at delivery, blood samples from her and from the umbilical cord, along with samples from the placenta. Nearly a hundred per cent of the mothers in the study were found to have BPA and phthalates in their urine. Urine and blood samples are taken as the babies grow older, as well as samples of their exhaled breath. "We have a treasure trove of biological material," Perera said. The researchers track the children's weight and sexual development, and assess I.Q., visual spatial ability, attention, memory, and behavior. Brain imaging, using an M.R.I., is performed on selected children.

Martin was still breast-feeding her two-year-old daughter. "I bottle-fed my first child," she told me. "But when you learn what can come out of plastic bottles and all the benefits of breast-feeding—my other children were nursed." The Columbia group regularly convenes the families to hear results and discuss ways to reduce their exposure to potential environmental hazards. At one meeting, Martin found out that some widely used pesticides could result in impaired learning and behavior. "I told the landlord to stop spraying in the apartment" to combat a roach infestation, she said. On the advice of the Columbia researchers, Martin asked him to seal the cracks in the walls that were allowing cockroaches to enter, and Martin's family meticulously swept up crumbs. This approach has now become the New York City Department of Health's official recommendation for pest control. "You don't need to be out in the country and have compost," Martin said. "This has made me into an urban environmentalist."

In 2001, using data from animal studies, the E.P.A. banned the sale of the pesticide chlorpyrifos (sold under the name Dursban) for residential and indoor use. Many agricultural uses are still permitted, and farming communities continue to be exposed to the insecticide. Residues on food may affect those who live in urban areas as well. In 2004, the Columbia group published results in the journal *Environmental Health Perspectives* showing that significant exposure during the prenatal period to chlorpyrifos was associated with an average hundred-and-fifty-gram reduction in birth weight—about the same effect as if the mother had smoked all through pregnancy. Those most highly exposed to the insecticide were twice as likely to be born below the tenth percentile in size for gestational age. The researchers found that children born after 2001 had much lower exposure levels—indicating that the ban was largely effective.

For those children who were exposed to the pesticide in the womb, the effects have seemed to persist. The children with the greatest exposure were starting to fall off the developmental curve and displayed signs of attention-deficit problems by the time they were three. By seven, they showed significant deficits in working memory, which is strongly tied to problem-solving, I.Q., and reading comprehension. Another study, published this month in *Pediatrics,* using a random cross-section of American children, showed that an elevated level of a particular pesticide residue nearly doubled the likelihood that a child would have A.D.H.D.

"The size of this deficit is educationally meaningful in the early preschool years," Virginia Rauh, the leader of Columbia's research, said. "Such a decline can push whole groups of children into the developmentally delayed category."

First used in Germany, in the nineteen-thirties, bisphenol A has a chemical structure similar to that of estrogen, but was considered too weak to be developed into a contraceptive pill. Recent animal studies have shown that, even at very low levels, BPA can cause changes that may lead to cancer in the prostate gland and in breast tissue. It is also linked to disruption in brain chemistry and, in female rodents, accelerated puberty. Japanese scientists found that high levels of BPA were associated with polycystic ovary syndrome, a leading cause of impaired fertility.

Phthalates are also ubiquitous in cosmetics, shampoos, and other personal-care products. They may have effects on older children and adults as well as on neonates. A study at Massachusetts General Hospital found an association of high levels of certain phthalates with lower sperm concentrations and impaired sperm motility; young girls in Puerto Rico who had developed breasts prematurely were more likely to have high levels of phthalates in their blood. Immigrant children in Belgium who exhibited precocious puberty also showed greater exposure to the pesticide DDT, which has estrogenlike effects and has been banned in the U.S., but is still

"He's actually my co-counsel, but you may scratch his head."

used in Africa to help control malaria.

Long-term studies have provided the most compelling evidence that chemicals once considered safe may cause health problems in communities with consistent exposure over many years. Researchers from SUNY Albany, including Lawrence Schell, a biomedical anthropologist, have worked over the past two decades with Native Americans on the Mohawk reservation that borders the St. Lawrence River, once a major shipping thoroughfare, just east of Massena, New York. General Motors built a foundry nearby that made automobile parts, Alcoa had two manufacturing plants for aluminum, and the area was contaminated with PCBs, which were used in the three plants. Several Mohawk girls experienced signs of early puberty, which coincided with higher levels of PCBs in their blood.

The Albany researchers also observed that increased levels of PCBs correlated with altered levels of thyroid hormone and lower long-term memory functioning. Similar results have been found in an area of Slovakia near heavy industry. "Folks have complained about reproductive problems," Schell said, of the residents of the Mohawk reservation. "They talked a lot about rheumatoid arthritis, about lupus, about polycystic ovary syndrome. And, you know, you hear these things and you wonder how much of it is just a heightened sensitivity, but, when you see elevated antibodies that are often a sign of autoimmune disease of one kind or another, it could be the beginning of discovering a biological basis for their complaints about these diseases."

Beginning in 2003, Antonia Calafat, a chemist at the Centers for Disease Control and Prevention, and Russ Hauser, of the Harvard School of Public Health, set out to evaluate the exposure of premature infants to certain environmental contaminants. The researchers hypothesized that infants treated in the most intensive ways—intravenous feedings and delivery of oxygen by respirators—would receive the most exposure, since chemicals like phthalates and BPA can leach from plastic tubing. They studied forty-one infants from two Boston-area intensive-care units for BPA. Calafat told me, "We saw ten times the amounts of BPA in the neonates that we are seeing in the general population." In several children, the levels of BPA were more than a hundred times as high as in healthy Americans.

Calafat, who came to the United States from Spain on a Fulbright scholarship, developed highly accurate tests to detect BPA, phthalates, and other compounds in body fluids like blood and urine. This advance, she explained, "means that you are not simply doing an exposure assessment based on the concentration of the chemicals in the food or in the air or in the soil. You are actually measuring the concentrations in the body." With this technology, she can study each individual as if he or she were a single ecosystem. Her studies at the Centers for Disease Control show that 92.6 per cent of Americans aged six and older have detectable levels of BPA in their bodies; the levels in children between six and eleven years of age are twice as high as those in older Americans.

Critics such as Elizabeth Whelan, of the American Council on Science and Health, a consumer-education group in New York (Whelan says that about a third of its two-million-dollar annual budget comes from industry), think that the case against BPA and phthalates has more in common with those against cyclamates and Alar than with the one against lead. "The fears are irrational," she said. "People fear what they can't see and don't understand. Some environmental activists emotionally manipulate parents, making them feel that the ones they love the most, their children, are in danger." Whelan argues that the public should focus on proven health issues, such as the dangers of cigarettes and obesity and the need for bicycle helmets and other protective equipment. As for chemicals in plastics, Whelan says, "What the country needs is a national psychiatrist."

To illustrate what Whelan says is a misguided focus on manufactured chemicals, her organization has constructed a dinner menu "filled with natural foods, and you can find a carcinogen or an endocrine-disrupting chemical in every course"—for instance, tofu and soy products are filled with plant-based estrogens that could affect hormonal balance. "Just because you find something in the urine doesn't mean that it's a hazard," Whelan says. "Our understanding of risks and benefits is distorted. BPA helps protect food products from spoiling and causing botulism. Flame retardants save lives, so we don't burn up on our couch."

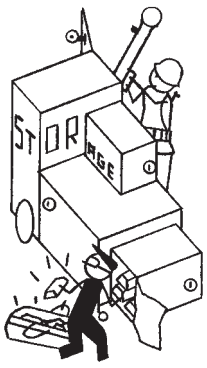
Several studies also contradict the conclusion that these chemicals have deleterious effects. The journal *Toxicological Sciences* recently featured a study from the E.P.A. scientist Earl Gray, a widely respected researcher, which indicated that BPA had no effect on puberty in rats. A study of military conscripts in Sweden found no connection between phthalates and depressed sperm counts, and a recent survey of newborns in New York failed to turn up an increase in a male genital malformation which might be expected if the effects from BPA seen in rodents were comparable to effects in humans. Richard Sharpe, a professor at the University of Edinburgh, and an internationally recognized pioneer on the effects of chemicals in the environment on endocrine disruption, recently wrote in *Toxicological Sciences*, "Fundamental, repetitive work on bisphenol A has sucked in tens, probably hundreds of millions of dollars from government bodies and industry, which, at a time when research money is thin on the ground, looks increasingly like an investment with a nil return."

With epidemiological studies, like those at Columbia, in which scientists observe people as they live, without a control group, the real-life nature of the project can make it difficult to distinguish between correlation and causation. Unknown factors in the environment or unreported habits might escape the notice of the researchers. Moreover, even sophisticated statistical analysis can sometimes yield specious results.

Dr. John Ioannides, an epidemiologist at the University of Ioannina, in Greece, has noted that four of the six most frequently cited epidemiological studies published in leading medical journals between 1990 and 2003 were later refuted. Demonstrating the malleability of data, Peter Austin, a medical statistician at the Institute for Clinical Evaluative Sciences, in Toronto, has retrospectively analyzed medical records of the more than ten million residents of Ontario. He showed that Sagittarians are thirty-eight per cent more likely to fracture an arm than people of other astrological signs, and Leos are fifteen per

cent more likely to suffer a gastrointestinal hemorrhage. (Pisces were more prone to heart failure.)

To help strengthen epidemiological analysis, Sir Austin Bradford Hill, a British medical statistician, set out certain criteria in 1965 that indicate cause and effect. Researchers must be sure that exposure to the suspected cause precedes the development of a disease; that there is a high degree of correlation between the two; that findings are replicated in different studies in various settings; that a biological explanation exists that makes the association plausible; and that increased exposure makes development of the disease more likely.



When epidemiological studies fulfill most of these criteria, they can be convincing, as when studies demonstrated a link between cigarettes and lung cancer. But, in an evolving field, dealing with chemicals that are part of daily life, the lack of long-term clinical data has made firm conclusions elusive. John Vandenbergh, a biologist who found that exposure to certain chemicals like BPA could accelerate the onset of puberty in mice, served on an expert panel that advised the National Toxicology Program, a part of the National Institute of Environmental Health Sciences, on the risks of exposure to BPA. In 2007, the panel reviewed more than three hundred scientific publications and concluded that "there is some concern" about exposure of fetuses and young children to BPA, given the research from Vandenbergh's laboratory and others.

Vandenbergh is cognizant of the difficulty of extrapolating data from rodents and lower animals to humans. "Why can't we just figure this out?" he said. "Well, one of the problems is that we would have to take half of the kids in the kindergarten and give them BPA and the other half not. Or expose half of the pregnant women to BPA in the doctor's office and the other half not. And then we have to wait thirty to fifty years to see what effects this has on their development, and whether they get more prostate cancer or breast cancer. You have to wait at least until puberty to see if there is an effect on sexual maturation. Ethically, you are not going to go and feed people something if you think it harmful, and, second, you have this incredible time span to deal with."

The inadequacy of the current regulatory system contributes greatly to the atmosphere of uncertainty. The Toxic Substances Control Act, passed in 1976, does not require manufacturers to show that chemicals used in their products are safe before they go on the market; rather, the responsibility is placed on federal agencies, as well as on researchers in universities outside the government. The burden of proof is so onerous that bans on toxic chemicals can take years to achieve, and the government is often constrained from sharing information on specific products with the public, because manufacturers claim that such information is confidential. Several agencies split responsibility for oversight, with little coördination: the Food and Drug Administration supervises cosmetics, food, and medications, the Environmental Protection Agency regulates pesticides, and the Consumer Product Safety Commission oversees children's toys and other merchandise. The European Union, in contrast, now requires manufacturers to prove that their compounds are safe before they are sold.

According to the E.P.A., some eighty-two thousand chemicals are registered for use in commerce in the United States, with about seven hundred new chemicals introduced each year. In 1998, the E.P.A. found that, among chemicals produced in quantities of more than a million pounds per year, only seven per cent had undergone the full slate of basic toxicity studies. There is no requirement to label most consumer products for their chemical contents, and no consistent regulation throughout the country. Although the F.D.A. initially concluded that BPA was safe, some states, including Massachusetts and Connecticut, either have banned it or are considering a ban. (In January, the F.D.A. announced that it would conduct further testing.)

There has been some movement toward stricter controls: in July, 2008, Congress passed the Product Safety Improvement Act, which banned six phthalates from children's toys. But so far removal from other products has been voluntary. The President's Cancer Panel report advised people to reduce exposure with strategies that echo some of what the mothers in Frederica Perera's study have learned: choose products made with minimal toxic substances, avoid using plastic containers to store liquids, and choose produce grown without pesticides or chemical fertilizers and meat free of antibiotics and hormones.

Mike Walls, the vice-president of regulatory affairs at the American Chemistry Council, a trade association that represents manufacturers of industrial chemicals, agrees that new laws are needed to regulate such chemicals. "Science has advanced since 1976, when the last legislation was enacted," he said. But Walls notes that some eight hundred thousand people are employed in the companies that the A.C.C. represents, and that their products are found in ninety-six per cent of all American manufactured goods. "The United States is the clear leader in chemistry," Walls said. "We have three times as many new applications for novel compounds as any other country in the world. We want to make good societal decisions but avoid regulations that will increase the burden on industry and stifle innovation."

Academic researchers have found that the enormous financial stakes—the production of BPA is a six-billion-dollar-a-year industry—have prompted extra scrutiny of their results. In 2007, according to a recent article in *Nature*, a majority of non-industry-supported studies initially deemed sound by the National Toxicology Program on the safety of BPA were dismissed as unsuitable after a representative of the A.C.C. drafted a memo critiquing their methods; experimental protocols often differ from one university lab to another. Researchers are now attempting to create a single standard protocol, and a bill introduced by Representative Louise Slaughter, of New York, would fund a centralized research facility at the National Institute of Environmental Health Sciences.

Other legislation aims to completely overhaul the 1976 law. "It's clear that the current system doesn't work at all," Ben Dunham, a staffer in

the office of Senator Frank Lautenberg, of New Jersey, who crafted the bill now before the Senate, told me. Henry Waxman, of California, and Bobby Rush, of Illinois, have released a companion discussion draft in the House. Lautenberg's bill seeks to allow the E.P.A. to act quickly on chemicals that it considers dangerous; to give new power to the E.P.A. to establish safety criteria in chemical compounds; to create a database identifying chemicals in industrial products; and to set specific deadlines for approving or banning compounds. The bill also seeks to limit the number of animals used for research. (Millions of animals are estimated to be required to perform the testing mandated under the E.U. law.) How much data would be needed to either restrict use of a chemical or mandate an outright ban is still unclear. Lautenberg's bill resisted the call of environmental groups to ban certain compounds like BPA immediately.

Dr. Gina Solomon, of the Natural Resources Defense Council, said that the Lautenberg bill is "an excellent first step," but noted several "gaps" in the bill: "There is what people call lack of a hammer, meaning no meaningful penalty for missing a deadline in evaluating a chemical if E.P.A. gets bogged down, and we know from history that it can be easily bogged down." The language setting a standard for safety is too vague, she added. "You could imagine industry driving a truck through this loophole."

Linda Birnbaum, the director of the N.I.E.H.S. and its National Toxicology Program, helps assess chemicals for the federal government and, if Slaughter's bill passes, could become responsible for much of the research surrounding these safety issues. Birnbaum's branch of the National Institutes of Health is working with the National Human Genome Research Institute and the E.P.A. to test thousands of compounds, singly and in combination, to assess their potential toxicity. Part of the difficulty, she points out, is that "what is normal for me may not be normal for you. We all have our own balance of different hormones in our different systems." When it comes to development and achievement, incremental differences—such as the drop of five to ten I.Q. points, or a lower birth weight—are significant. "We're all past the point of looking for missing arms and legs," Birnbaum said.

"I know of very little science where you will ever get hundred-per-cent certainty," Birnbaum says. "Science is constantly evolving, constantly learning new things, and at times decisions have to be made in the presence of a lot of information, but maybe not certainty. The problem is we don't always want to wait ten or twelve or twenty years to identify something that may be a problem."

Perera, who is keenly aware of the potential pitfalls of epidemiological research, told me that her team employs rigorous statistical methods to avoid falsely suggesting that one chemical or another is responsible for any given result. And she objects to the characterization of her research as fear-mongering. "Our findings in children increasingly show real deleterious effects that can occur short-term and potentially for the rest of the child's life," Perera said. In January, the Columbia group published data from the mothers and infants it studied following September 11th. Cord-blood samples saved at the time of birth had been analyzed for the presence of flame retardants. Each year, the children were assessed for mental and motor development. As a point of reference, low-level lead poisoning results in an average loss of four to five I.Q. points. Those children in Columbia's group with the highest levels of flame retardant in their blood at birth had, by the age of two, I.Q. scores nearly seven points lower than normal.

How do we go forward? Flame retardants surely serve a purpose, just as BPA and phthalates have made for better and stronger plastics. Still, while the evidence of these chemicals' health consequences may be far from conclusive, safer alternatives need to be sought. More important, policymakers must create a better system for making decisions about when to ban these types of substances, and must invest in the research that will inform those decisions. There's no guarantee that we'll always be right, but protecting those at the greatest risk shouldn't be deferred. ♦

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