# An Emerging Concern: The Health and Environmental Implications of Chemical Persistence

*A white paper examining what is currently known about the impact of chemical persistence in the environment from pharmaceuticals, agriculture, manufacturing and other sources*

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# An Emerging Concern: The Health and Environmental Implications of Chemical Persistence

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## ABOUT THE AUTHOR


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# I. INTRODUCTION

We are living in a chemical world. An estimated 10,000 pharmaceutical compounds are on the market today, and several decades of research studies have revealed that low levels of many of these compounds and their metabolites are turning up in the environment. In 2002, a study published by the U.S. Geological Survey revealed that water collected from streams and rivers contains pharmaceuticals and other chemicals; since then, additional studies have turned up similar results.[1] The concern is that some of these compounds "are not passive, benign travelers in the environment but instead bioaccumulative, persistent, and toxic to wildlife—and possibly humans," writes Sara Everts in a 2010 feature story for *Chemical & Engineering News (C&EN)* titled, "Drugs in the Environment."[2]

As analytical technologies have improved dramatically over the years, scientists have become able to detect trace amounts of chemicals in environmental samples. The data from these analyses is raising many questions about the long-term effects of chronic, long-term exposure to a complex concoction of both man-made and naturally occurring chemicals on humans, wildlife, and ecosystems. Among the troubling findings reported thus far: birth control hormones can feminize fish, anti-inflammatory drugs can kill vultures, anti-depressants can slow fish and frog development, and, perhaps most notably, antibiotics can promote the evolution of multi-drug-resistant superbugs.

The U.S. Environmental Protection Agency (EPA) has coined a phrase for the thousands of compounds for which the environmental and health impacts are largely unknown: *chemicals of emerging concern*. The list is long, including pharmaceuticals and personal care products; agricultural chemicals such as pesticides, fertilizers, and hormones; chemicals used in plastics and other everyday products; metals; nanomaterials; and more. And although the EPA has a list of pollutants that may make water unsafe—including eight hormones and one antibiotic—it does not currently regulate even a single human pharmaceutical in drinking water.

But some scientists argue that until more data come in, "it is presumptuous to take action on a problem that might not be widespread," Everts writes. "Yet among those who advocate taking a precautionary approach, there is a growing dialogue about what might be done to minimize the impact of [chemicals] in the environment."

When the Toxic Substances Control Act was signed into law in 1976, all chemicals that were on the market at that time were grandfathered in, deemed safe for use unless they would later be found to pose an "unreasonable risk to health or to the environment." For all new chemicals entering the market thereafter, chemical producers have been required to submit information to the EPA, including chemical identities, names, molecular structures, categories of use, byproducts of the manufacturing process, disposal methods, and environmental and health effects. Additional information regarding chemical risks can be obtained by the EPA or by voluntary industry efforts, but the law has been scrutinized by environmental and health advocates, since it does not *require* companies to generate or report information regarding a chemical's toxicity. The lack of chemical hazard information has proved problematic in the face of recent chemical spills. "Companies are not mandated to submit hazard information they have to the Environmental Protection Agency, except when the data suggest the possibility of substantial risk," write Jeff Johnson and Cheryl Hogue in a *C&EN* report on a chemical spill in Charleston, West Virginia,[3] where thousands of gallons of a coal-processing liquid (4-Methylcyclohexanemethanol) were released into the Elk River, contaminating the water supply for 300,000 people.

This report will review what is currently known about the environmental and health impacts of a variety of chemicals and materials used in widespread applications every day across the globe, highlighting the areas where more research is needed and the role chemists can play in the development and safe use of chemicals and other materials.

## II. PERSONAL CARE PRODUCTS

### Antibiotics and Antibacterial Agents

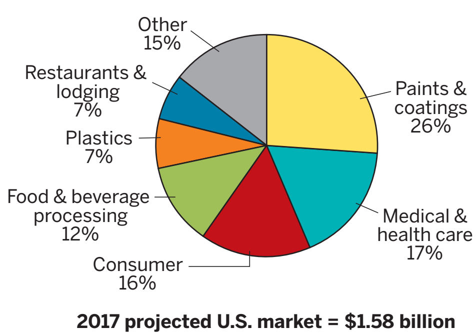
In the 1940s, the era of antibiotics was launched with the discovery of penicillin, which has been widely recognized as "one of the greatest advances in therapeutic medicine," according to an ACS Commemorative Booklet on the topic.[4] A *New York Times* report on penicillin in 1940 called the drug "the most powerful germ killer ever discovered."[5] Not long after its discovery, researchers would learn that bacteria can evolve resistance to drugs over time. Today, the arms race against antibiotic-resistant bacteria is arguably one of the most pressing challenges in medicine.

The overuse of antibiotics and other antibacterial agents is presumed to be the driving force behind so-called superbugs—bacteria that have acquired resistance to multiple antibiotic compounds. Research has found that rates of antibiotic-resistant infections correlate with levels of antibiotic consumption, leading scientists to suspect that the prescription of antibiotics for treating viral infections is part of the problem.[6] An estimated one-half of all antibiotics used in the U.S. are used in agriculture. Farmers feed antibiotics to animals as a prophylactic to prevent bacterial infections before they arise, and also to promote growth—a practice that has been criticized by environmentalists.[7]

Antibiotics that are consumed by humans and animals can promote the development of antibiotic-resistant strains of bacteria, which can eventually find their way into the environment. Several recent studies support the notion that treated wastewater released into water sources may be driving the spread of antibiotic resistance:

- In a 2011 study, researchers at the University of Minnesota, Twin Cities, found that when municipal wastewater gets released into rivers and streams, genes encoding antibiotic resistance can be detected downstream from the treatment plant. The concern is that the drug-resistant strains may be able to pass along resistance genes to bacteria in the environment, although that was not directly observed in this study.[8]
- Researchers at the University of Kansas found that soils contaminated with metals boasted bacteria with higher levels of resistance than non-contaminated soils.[9] Although the mechanism is not clear, soil surrounding wastewater treatment plants tends to have higher levels of metals, which may explain why release of treated wastewater into the environment may encourage the spread of antibiotic resistance.
- In a study performed in Colorado in 2012, researchers sampled water downstream of animal feeding facilities and wastewater treatment facilities and found a spike in antibiotic resistance genes in those locations compared to samples collected elsewhere.[10]

In addition to their use in medicine and agriculture, antibacterial compounds are pervasive in many personal care products, including hand soap, dish detergent, toothpaste, and cosmetics.




Disinfectant and antimicrobial chemicals are used in a wide variety of U.S. industries.

Credit Source: Freedonia Group

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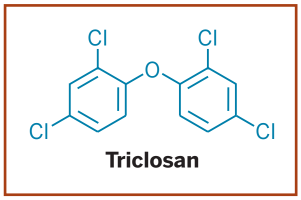
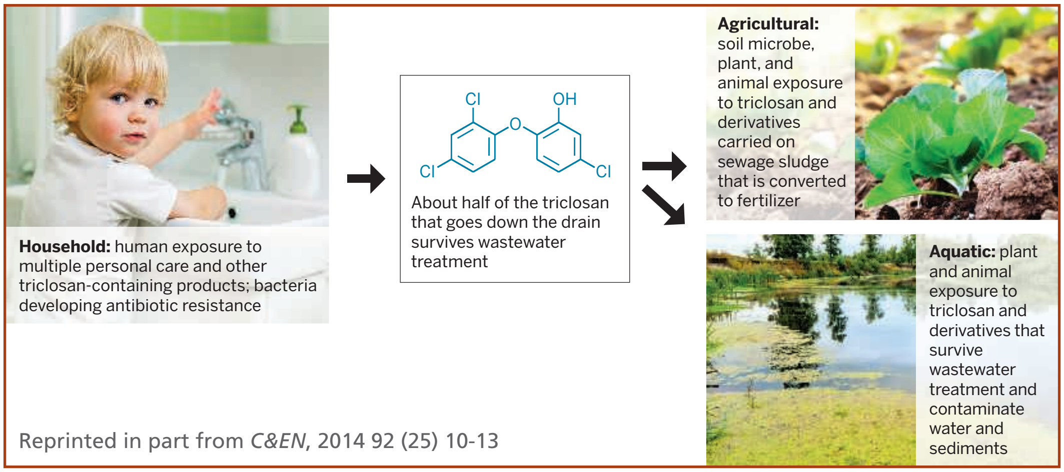
One such compound is triclosan, which was first patented in the 1960s and has been found to be present in three-quarters of urine samples collected from a representative sample of the U.S. population.[11] Some scientists have expressed concern over triclosan's toxicity, ineffectiveness as an antibacterial agent, and potential contribution to the problem of antibacterial resistance, which has brought the compound to the attention of regulatory agencies. In 2008, the EPA concluded that the level of exposure most people have to triclosan through various routes—such as washing with antibacterial hand soap, breathing in the compound in dust, and consuming it in small amounts in food—is within safe limits.




In studies with mice and fish, triclosan has been found to hinder muscle contraction. Data from other studies suggest triclosan is able to disrupt signaling of the endocrine system. Although the body is able to detoxify low levels of triclosan, Margaret O. James of the University of Florida told *C&EN* that the greatest concerns are for pregnant women, since the hormonal environment is critical for proper development of the fetus.[11]

Once triclosan gets washed off hands and goes down the drain, its effects continue to be felt. A 2007 study by Arizona State University researchers found that wastewater treatment removes only about half of the triclosan present; a small fraction (about 4%) gets discharged with water, and the rest remains with sewage sludge. The U.S. Geological Survey found triclosan in the top five for organic wastewater contaminants, present in 60% of stream water samples collected from 30 states in 1999 to 2000.[11] But the impact of those low levels of triclosan on aquatic organisms remains unclear.

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Triclosan, along with hundreds of other chemicals present in sewage, makes its way into the environment through the application of sewage sludge on farmland—a controversial practice that is at the center of an ongoing debate among scientists, farmers, concerned citizens, health advocates, and regulatory agencies. Each year, an estimated 8 million tons of so-called biosolids are applied to U.S. land. Studies have found that chemicals present in the sludge may work their way down into the soil, and may also get incorporated into the edible portions of crops.[12-14]

**FOUND IN THE DIRT**

**Some of the synthetic compounds found in a wheat field spread with biosolids**

| CHEMICAL | USE |
|---|---|
| Bisphenol A | Thermal receipt paper, plastics |
| HHCB | Fragrance in consumer products |
| Nonylphenol ethoxylates[a] | Nonionic surfactants in detergents |
| Triclosan | Antibacterial soaps |
| Warfarin | Anticoagulant drug |

**a** Includes breakdown product nonylphenol.
**HHCB** = hexahydrohexamethylcyclopenta-2-benzopyran.
**SOURCE:** *J. Am. Water Resour. Assoc.* 2014, DOI: 10.1111/jawr.12163

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A 2008 study by researchers in Colorado found that earthworms living in soil to which biosolids have been applied are able to take up pharmaceutical residue, including the antibiotic thrimethoprim.[15] Although the amounts are small, the concern is that the uptake into earthworms can lead to a potential pathway up the food chain.[13] But the EPA has not yet established limits for the thousands of pharmaceuticals and other chemicals that are known to be present in sludge because, according to the agency, the risks of these compounds to human health or the environment are largely unknown.

A review of triclosan's safety profile in plastics and other products by the EPA is ongoing, and the U.S. Food and Drug Administration (FDA) has proposed regulations that would require products containing triclosan to show clinical benefit, such as a reduction in bacterial infections. So far, one state – Minnesota – has signed into law a ban on products containing triclosan as of January 1, 2017.[16] With more regulatory action potentially on the horizon, companies such as Johnson & Johnson and Procter & Gamble have already begun removing triclosan from their products.[11]

## Natural and Synthetic Hormones

In the 1990s, reports began cropping up with data suggesting that estrogen and estrogen-like compounds that are present in sewage effluent can distort normal male development. A team of U.K. scientists were the first to take note that male fish downstream from wastewater treatment facilities were becoming feminized: expressing proteins associated with egg production in female fish and even developing early-stage eggs in their testes. The phenomenon was linked to estrogenic compounds, which include the natural hormone 17β-estradiol and the synthetic compound 17α-ethynylestradiol. These compounds, and their metabolites, do not completely break down during wastewater treatment.[13]

More recent studies have revealed additional effects on fish and wildlife. In 2010, a team of U.K. researchers found that estrogen can also impact female fish by changing their courting behaviors—which can lead to alterations in the population's genetic makeup.[17] Another 2010 study conducted in Sweden found that rainbow trout treated with sewage effluent accumulate the birth-control drug levonorgestrel in their bloodstream at levels that were four times higher than the human therapeutic concentration.[18]

But there is some evidence that the effects of hormones on wildlife populations can be reversed. From 2001 to 2003, researchers poured small amounts of 17α-ethynylestradiol into an experimental lake in Canada, and they found that the fathead minnow population crashed due to reproductive failure, which caused the animals that rely on the minnows for food to also suffer while the minnow's prey—zooplankton and insects—thrived.[19] Then the researchers observed that three years after the team had stopped adding the hormone to the lake, the minnow population was able to rebound and recover their original population size.[8]

## Other Pharmaceuticals

The list of pharmaceutical compounds that have been discovered in the world's water sources and elsewhere in the environment is long. In 2013, a team of Wisconsin researchers analyzed samples from the water and sediment of Lake Michigan and found evidence of roughly 30 pharmaceuticals and personal care products.[20] Of the compounds detected, 14 were present at levels considered to be of medium or high risk to the environment, based on data from the EPA. At the top of this list was metformin, which is the most widely prescribed antidiabetic drug in the world, with 76.9 million prescriptions in 2014 in the U.S. alone.[19] A 2014 study conducted in Germany revealed that metformin was present in water samples collected from all across the country, and was even present in tap water at concentrations higher than levels deemed safe by an international Rhine River Basin agency.[21] Studies investigating the effect of metformin on fish have revealed that male minnows are feminized and produce fewer offspring after being exposed to levels comparable to those of wastewater treatment facilities.[22] University of Wisconsin-Milwaukee researcher Rebecca Klaper told *The Scientist* that metformin is stable against common wastewater treatments, including UV light irradiation, and that technologies for filtering out chemicals like metformin are prohibitively expensive.[19]

In sediment cores obtained from a lake in Sweden, researchers have detected the antianxiety drug oxazepam. Interestingly, the concentration of the drug deposited in the lake bed over three decades correlated tightly with the number of prescriptions written for the drug.[19]

There are many unanswered questions about the effects of long-term exposure to low levels of biologically active compounds, such as subtle but significant effects on an organism's development and behavior. The antidepressant fluoxetine, or Prozac, can slow the development of frogs and fish. The anticonvulsant carbamazepine affects the emergence of insects that fish depend on for food.[19]

Another class of drugs that have come into the spotlight in environmental studies are psychotropic drugs, such as selective serotonin re-uptake inhibitors (SSRIs), which are used to treat depression and anxiety disorders. Sertraline, or Zoloft, is one such SSRI, which has been found to cause juvenile perch to experience a decrease in appetite.[23] The effect was non-lethal, but researchers point out that a decline in feeding could impact the reproduction and life span of the population of fish in the wild.[19] In a separate study, the psychiatric drug oxazepam, which accumulates in insects, was found to accumulate in fish and alter their behavior, causing them to eat more quickly and leave their schools more often.[24]

The effects of drugs in the environment are not limited to aquatic life. In the 1990s, millions of vultures in India and Pakistan died after eating livestock carcasses that contained the anti-inflammatory drug diclofenac, which is used to treat lameness and fever.[25] The birds died from acute kidney failure and visceral gout. The antidepressant fluoxetine, or Prozac, has also been found to persist in the environment and capable of altering birds' eating behavior.[26]

In addition to shedding light on the environmental effects of chemical contaminants, researchers in the field are beginning to make strides toward understanding what the impact of continual, sustained, low-dose exposure to pharmaceuticals could be on human health. An Australian research team published a study in 2006 that showed a low-concentration mixture of 13 different pharmaceutical drugs can inhibit the growth of human embryonic kidney cells grown in the lab. The doses used in this study, however, were representative of those found in the environment, not in drinking water.[27] In light of the many unanswered questions about long-term health consequences, some scientists, such as Dana W. Kolin, a research hydrologist at the U.S. Geological Survey, say policy and regulatory decisions should wait. "We need to determine which compounds or sets of compounds are the worst players, and then we need to make the decision whether these things need to be removed before they get into the environment," Kolpin told *C&EN* in 2008.

In the meantime, some of the discussion has shifted toward better sewage treatment methods to remove contaminants from the water before their release into the environment. Since sewage treatment plants were not originally designed to remove synthetic substances, new technologies would need to be put in place—such as ozonation and nanofiltration—to remove the myriad chemicals from wastewater. These technologies can be energy-intensive and costly, and no single method has been found to remove all bioactive agents.[13,19] So it's an open question whether the benefits outweigh the costs, and it's a question that is very difficult to address without complete knowledge of the effects on human health and the environment.

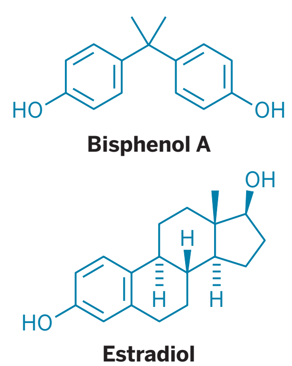
The skills of synthetic chemists will be critical in the development of new "green" chemical techniques. Some environmentally conscious researchers are making efforts to create new pharmaceuticals that are "benign by design"—meaning they are stable for as long as is necessary to elicit their desired effects, and then are readily degraded once the job is done. In 2000, a team led by Klaus Kümmerer of Leuphana University of Lüneburg, Germany, reported that a derivative of the anticancer drug ifosfamide was still as potent as an anticancer agent as the original molecule, even though a portion of the molecule that makes it highly stable had been swapped out with a sugar.[28] If similar efforts were made by pharmaceutical companies to create more environmentally friendly drugs, progress could be made toward solving the problem of highly stable, bioactive molecules persisting in the environment for long periods of time.

At the 2010 International Conference on Sustainable Pharmacy in Osnabrück, Germany, delegates—including representatives from industry, academia, government, and non-governmental sectors—brainstormed ideas for regulatory incentives that could encourage researchers in various industries to develop more environmentally friendly drugs.[2] Several suggestions emerged in the discussion, including providing patent prolongation for newly approved drugs with better environmental profiles, and offering companies designing "green" drugs fast-track vouchers for FDA priority review, which could translate into millions of dollars in revenue by getting a blockbuster drug to market sooner.

## III. PLASTICS AND EVERYDAY PRODUCTS

### Endocrine-Disrupting Compounds: Bisphenol A and Related Molecules

Several compounds used in plastics have come into the spotlight in recent years due to concerns over their adverse effects on human health and the environment. Perhaps the most notorious of these chemicals is bisphenol A (BPA), which has faced scrutiny from consumer and environmental advocacy groups that cite evidence in the literature to suggest it is capable of mimicking or interfering with the body's hormones.




BPA's phenol rings and bridging isopropylidene group are reminiscent of the multiring steroidal structure of estradiol and other estrogens.

Reprinted in part from: *C&EN*, 2011 89 (23) 14-19

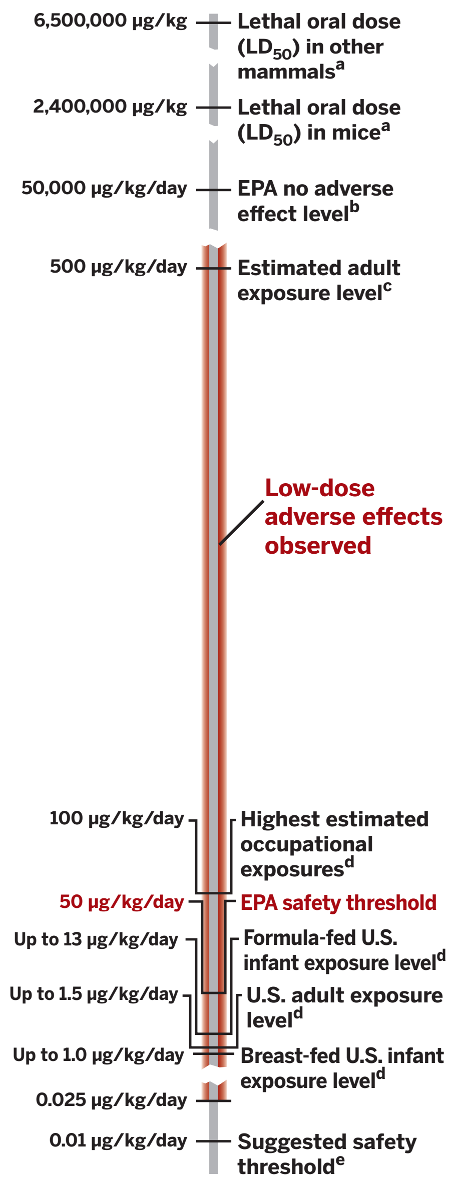
BPA is used in polycarbonate plastics, epoxy resin food-can liners, and thermal receipt paper. It has many attractive properties, including its versatility, shatter resistance, and low cost. In recent years, there has been much debate over whether the use of BPA, and other so-called endocrine disruptors, should be restricted, or even entirely banned. As *C&EN*'s Stephen K. Ritter put it in a 2011 cover story on the issue, "There are no simple answers."[29]

The debate over BPA's toxicity remains open-ended. On one side, both industry and academic scientists cite research studies that suggest that the levels of BPA most people are exposed to are not high enough to cause harm. On the other side, advocacy groups and some scientists argue that even in the absence of a scientific consensus on BPA's safety, there is sufficient evidence to warrant regulatory action to prevent potential harm.

Which side has the scientific evidence on their side? That's not a simple question, because the results of seemingly similar studies have arrived at, in some cases, completely opposite conclusions. The evidence from research studies performed thus far were summarized in the 2011 *C&EN* cover story:

- BPA displays acute toxicity at high doses (thousands to millions of micrograms per kilogram body weight).
- At low doses (from 0.025 to 500 micrograms per kilogram body weight), things aren't as clear. In humans, BPA binds weakly to the primary estrogen receptor; as the dose increases, different genes are switched on and off. This is what makes it difficult to take data from high-dose studies and extrapolate down to determine what a safe low dose would be. In fact, BPA has a toxicity profile that is counter-intuitive: the worst effects are seen at the highest and lowest doses.
- A large-scale BPA study commissioned by the chemical industry in 2002 found that no adverse effects were found in rats who were dosed with low levels of BPA. But the study was criticized for using a strain of rats that some believe is insensitive to these low doses.

## SENSE OF SCALE




**a** Acute toxicity, where a single dose is lethal to half of the animals treated. **b** EPA estimate of lowest toxicity; the safety threshold is set 1,000 times lower than this value. **c** Daily intake determined by some endocrinology researchers. **d** National Toxicology Program estimated daily intake; formula-fed infant value assumes using polycarbonate baby bottles and formula packaging containing BPA, which have now been phased out. **e** Tolerable daily intake suggested by a group of endocrinologists.

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- A follow-up study in 2008 used mice instead of rats, and came to a similar conclusion: no adverse effects from low-dose exposure to BPA. But that study was criticized for the use of an animal feed that contained a class of naturally occurring estrogen-like compounds known as phytoestrogens, which could mask BPA's effects.

- In 2008, a major epidemiologic study was published in the *Journal of the American Medical Association*, which made the connection between levels of BPA in the urine of human research subjects and the occurrence of heart disease and type 2 diabetes. A follow-up study a few years later arrived at a similar conclusion. But these observational studies are not able to prove causation. For obvious ethical reasons, a randomized controlled trial on the effects of BPA on humans cannot be performed.

- Two studies performed on rhesus monkeys arrived at completely opposite conclusions. One study found that monkeys metabolize BPA differently from rats but at rates similar to humans, which led the researchers to conclude that toxic effects observed in rats could over-predict toxicity in humans. The other study concluded monkeys and mice both metabolize BPA at similar rates as people do, concluding that it is reasonable to extrapolate health effect studies performed in animal models to humans.

In 2010, the EPA added BPA to a list of chemicals under consideration for regulation under the Toxic Substances Control Act. Then in 2012, the FDA concluded that science does not support a ban on BPA used in food packaging. And yet a few months later, the FDA banned the use of BPA in baby bottles and children's drink cups,[30] followed by a 2013 ban on BPA used in infant formula cans.[31] Both Europe and China have invoked similar bans. In 2014, the FDA concluded its four-year review of BPA and reaffirmed its previous position that BPA levels currently found in food are safe.

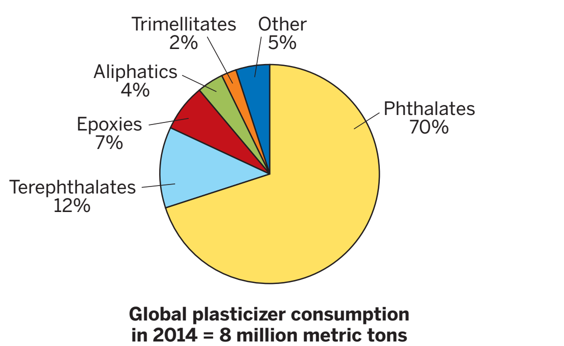
The search for replacements that perform as well as BPA and are not too expensive has been a challenge to the chemical industry.[32] Many BPA replacements, such as bisphenol S (BPS) and bisphenol F (BPF), have structural similarities to BPA, raising concerns that they may have similar toxicity and adverse health impacts as BPA. A study performed by University of Texas's Cheryl Watson found that picomolar concentrations of BPS can disrupt normal functioning of cultured rat cells.[33] "[Manufacturers] put 'BPA-free' on the label, which is true," Watson told *Scientific American* in 2014.[34] "The thing they neglected to tell you is that what they've substituted for BPA has not been tested for the same kinds of problems that BPA has been shown to cause. That's a little bit sneaky." A 2015 study published in *Proceedings of the National Academy of Sciences* found that low doses of both BPA and BPS cause alterations in brain development in zebrafish, which is linked to hyperactivity.[35]

BPS and BPF have been detected, along with BPA, in dust samples collected from home and office settings in four countries.[36] BPS has also been found in BPA-free paper products, leading some toxicology researchers to call for more research on the health effects of BPS and other BPA replacements.[37]

A computer model developed by researchers at the FDA makes it possible to predict whether a BPA substitute has potential for having endocrine-disrupting effects by assessing how well the compound orients itself with the human estrogen receptor.[38] But others argue that there is an urgent need to increase regulation of chemicals on the market because current regulations make it possible for one harmful chemical to simply be replaced by another.

## Other Chemicals Used in Plastics and Household Products

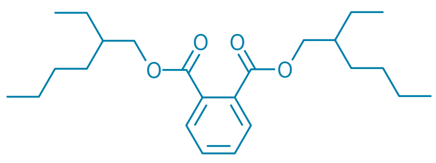
Phthalates are a group of chemicals that serve as plasticizing agents, providing flexibility and durability to dozens of everyday products. They appear in food packaging and cosmetics, as well as medical devices, flooring, roofing, and coatings on wires and cables. The potential of phthalates was first discovered in the late 1920s by Waldo Semon, a B.F. Goodrich chemist who mixed polyvinyl chloride (PVC) together with solvents including dibutyl phthalate, yielding a plasticized PVC that would quickly make its way into many commercial applications.[39]




SOURCE: IHS Chemical

Reprinted in part from *C&EN*, 2015 93 (25) 15-16

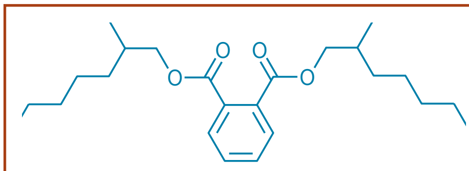
Phthalates fall into two general categories of compounds: low-molecular weight (three- to six-carbon backbone) and high-molecular weight (greater than six carbons in the backbone). A 2009 report from the Centers for Disease Control and Prevention found measurable levels of many phthalate metabolites in almost every person tested—and although simply having detectable levels in the body does not automatically imply adverse effects, environmental and consumer activists have expressed concern over possible health implications.[40] Some phthalate molecules—in particular, the lower-molecular weight forms—have been implicated in medical conditions in humans (so-called high phthalates, on the other hand, have lower volatility and fewer concerns over toxicity and migrating out of materials).[41] For example, in a 2007 study of 1,451 men in the U.S., researchers determined that concentrations of three phthalate metabolites found in urine correlated with both waist size and insulin resistance, a condition that can lead to the development of type 2 diabetes.[42] Exposure to di(2-ethylhexyl) phthalate (DEHP) has been linked to sperm malformation and abnormal hormone levels in men, as well as pregnancy loss in women.[43] And in a 2014 study involving 500 U.S. couples hoping to become pregnant, researchers proposed the first potential mechanism that may explain how exposure to phthalates may impair fertility—the plasticizing agents are correlated with cellular oxidative stress, which is a possible cause of fertility issues such as impaired sperm quality.[43] The study revealed that women had higher urine concentrations of all but one phthalate metabolite, which may be explained by greater exposure to phthalates that are present in cosmetics, including lotions, liquid foundations, and nail polish.




**Di(2-ethylhexyl) phthalate (DEHP)**

U.S. lawmakers placed a ban on the use of low-molecular weight phthalates in toys and child-care articles in 2008, and similar bans were implemented in Europe. Then in 2015, the European Union effectively banned the low-molecular weight phthalate DEHP in all but approved uses. China, which has a large share of the total global market and produces many of the vinyl products used in households around the world, still uses DEHP, which explains why it remains the most commonly used phthalate worldwide.[39] In a 2015 issue of *C&EN*, Michael McCoy writes: "The synthetic materials made possible by phthalates have become essential to a successful modern society. Society is now trying to decide if that success has come at too great a cost."[40]

As a result of regulatory changes and a growing demand from consumers for phthalate-free products, chemical industries have been actively seeking out alternative plasticizing agents. Some have replaced low-molecular weight phthalates with high phthalates, most commonly diisononyl phthalate (DINP), while others are looking to non-phthalate plasticizers, including those based on renewable materials.[41] Environmental groups are also taking action, urging home improvement retailers to tell suppliers to remove phthalates from vinyl flooring. Some companies, including Apple, have voluntarily eliminated phthalates from cables. The Consumer Product Safety Commission has proposed an expansion on the restrictions on phthalates in child care products in the U.S.[40]




**Diisononyl phthalate (DINP)**

Found in many household products, fluorochemicals have been found to be linked to cancer[44] and the disruption of sexual development in lab animals. Long-alkyl-chain fluorocarbons, in particular, are known to be extremely stable, which also enables them to persist in the environment. "Low levels of the compounds have contaminated nearly every corner of the food chain, from herring to humans," Stephen Ritter wrote in a July 2015 *C&EN* article, describing the end of a nine-year volunteer stewardship program launched by the EPA to eliminate the production and use of one such chemical, perfluorooctanoic acid (PFOA), along with its precursors and analogs.[45] PFOA and related compounds are used to render surfaces repellent to water, soil, and oil, and have found applications in nonstick cookware, pizza boxes, stain-resistant carpet, breathable rain jackets, and airplane hydraulic fluid.

Over the years, the chemical industry has voluntarily taken steps toward replacing long-chain fluorochemicals with short-chain analogs that are less bioaccumulative, and thus expected to be less toxic.[46] But some scientists and advocacy groups say the short-chain compounds should be discontinued as well. In 2015, more than 200 scientists signed a policy document called the Madrid Statement, emphasizing the need for scientists, industry, governments, and consumers to share information and work toward limiting the use of fluorochemicals and developing safer alternatives. "The goal should be to introduce nonpersistent alternatives that still provide the exquisite surface properties that fluorochemicals are known for but that can fully degrade in the environment," as stated by environmental chemist Scott Mabury of the University of Toronto.[45]

Earlier this year, the FDA announced that three perfluoroalkyl ethyl-containing substances could no longer be used to coat paper that comes into contact with food sold in the U.S.:[47]

- Diethanolamine salts of mono- and bis (1H, 1H, 2H, 2H perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range $C_8$-$C_{18}$ and the salts have a fluorine content of 52.4% to 54.4% as determined on a solids basis;
- Pentanoic acid, 4,4-bis [(γ-ω-perfluoro-$C_{8\text{-}20}$-alkyl)thio] derivatives, compounds with diethanolamine; and
- Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[(γ, ω-perfluoro $C_{4\text{-}20}$ alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide.

The prohibited substances are commonly used in microwave popcorn bags, fast-food wrappers, and pizza boxes, but have not been made in the U.S. since 2011. However, the food packaging could be imported from other countries. The decision was spurred by new toxicity data that the FDA says show "there is no longer a reasonable certainty of no harm from the food-contact use" of these substances. Environmental groups welcomed the ban but said additional steps are needed to prohibit the use of other perfluorinated compounds that are structurally similar to the banned chemicals and yet are still used in food-contact applications.

## Flame Retardants

Brominated flame-retardant chemicals are commonly used in the polyurethane foam innards of upholstered furniture. Fire-safety scientists say the chemicals, which have been used for decades, have saved the lives of tens of thousands of people who have been victims of home fires. But advocacy groups and some scientists have expressed concern over the chemicals, which have demonstrated neurological and other health effects, as well as endocrine disruption,[48] and have been appearing in outdoor air samples[49] as well as in all U.S. coastal waters.[50] Arlene Blum is the founder and executive director of the Green Science Policy Institute in Berkeley, California, and is responsible for a movement to overhaul sections of California's strict fire-safety laws. Blum points to the nearly 4,000 peer-reviewed papers on flame-retardant chemicals' toxicity, emphasizing risks to children, who might be at the highest risk for damage to their physical and intellectual development. Plus, Blum contends in *C&EN*, the chemicals do not work as advertised, and there are other ways to prevent deaths from furniture fires—such as improved building codes, reduced cigarette smoking, and increased use of sprinkler systems.[48] But industry scientists counter that exposure does not equal risk, and that simply detecting a chemical in human blood does not mean the substance is present at high enough levels to cause harm.

Some flame-retardant industries have begun phasing out polybrominated diphenylethers (PDBEs), and replacing them with either organophosphate esters or new formulations that contain other brominated chemicals, including 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylheyl)-tetrabromophthalate (TBPH). But a 2013 study found that the level of organophosphate flame retardants—which have been implicated in cell-based studies as carcinogenic and neurotoxic—are present at 100- to 1,000-times higher levels than the brominated compounds they are replacing.[49] Research on TBB and TBPH suggests they may also have environmental risks, such as the ability to build up in fish and damage their DNA. And a 2011 study also found that in air samples in the Midwest, levels of TBB and TBPH doubled every 13 months between 2008 and 2010.[51]

For nearly 40 years, the federal government has failed to implement a national fire protection standard for industries related to household furniture, so California's Technical Bulletin 117 (TB 117) describes what has become the de facto national standard for fire protection. Under TB 117, each furniture component must pass two tests that examine how quickly the material burns when ignited by a smoldering cigarette or open flame.[48] In 2013, a proposed revision would replace the open flame test with a test that would evaluate a material's resistance to ignite in the presence of a smoldering cigarette. The move, which has been applauded by Blum as a "a win-win-win for fire safety, health and environment," would eliminate the need for flame retardants in furniture. But fire safety scientists and the chemical industry say the move would remove an important layer of fire protection for California residents.[52]

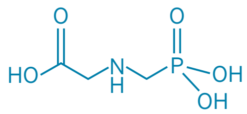
Scientists at the National Institute of Standards & Technology are also taking steps toward the development of safer flame retardants. In a 2014 study, they describe a new coating for foam material that they found reduced the rate of heat released from the foam by 77% compared to foam with no flame retardant. The coating is composed of clay, a fiber chitosan derived from crustacean shells, and DNA from herring sperm.[53] Another research team at Texas A&M University is developing an environmentally friendly flame retardant in which a cotton substrate is coated with a layer-by-later assembly of positively and negatively charged substances. The resulting material was found to be resistant to ignition under high heat; and instead of disintegrating in the presence of a flame, the material develops only a char, and retains 41% of its weight.[54]

## IV: AGRICULTURE

In agriculture, chemicals such as pesticides and fertilizers are applied to farmland to battle pests and provide nutrients that boost crop yields. In livestock, hormones and antibiotics are used to combat illness and support animal growth. Agriculture in the U.S. is now a $3 trillion industry,[55] which has brought along enormous benefits for society. At the same time, the many and varied chemicals that have been used to increase productivity have come with consequences to the environment and to human health. For example, some harmful pesticides have been banned after studies revealed the health hazards resulting from chronic or acute exposure, while countless others remain the subject of debate today.

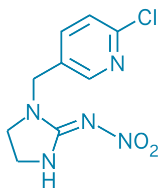
Rachel Carson, a marine biologist and conservationist, is credited for catalyzing new regulations and laws that began emerging in the 1970s. In her book, *Silent Spring*, she drew attention to the impact of dichlorodiphenyltrichloroethane (DDT) and other pesticides on the environment and human health.[56]

In the years following the publication of Carson's book, the EPA conducted a review of the evidence, concluding that some pesticides—including DDT, aldrin, dieldrin, chlordane, and heptachlor—posed unreasonable risks, and called for cancellation or suspension of their sale and use. Since then, other pesticides—including both insecticides and herbicides—have been subject to more stringent regulatory oversight and action. Much of the action taken against pesticides has been made in response to studies of acute toxicity, which assess the immediate health consequences in response to high levels of exposure, although scientists have begun to recognize the need for research on the health effects of long-term exposure to low levels of pesticides.[57]



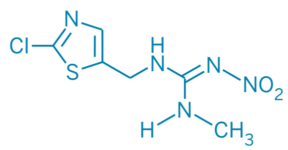
Glyphosate

The herbicide glyphosate grew in popularity after biotech crops, engineered to be resistant to glyphosate spraying, hit the market in the 1990s. Glyphosate has long been considered to be more environmentally benign than other pesticides. But in 2015, a report from the International Agency for Research on Cancer (IARC) concluded that glyphosate, which is sold by biotech firm Monsanto as Roundup, is "probably carcinogenic to humans," namely being linked to non-Hodgkin's lymphoma. Monsanto and other biotech firms say they disagree with IARC's conclusion, saying the agency ignored some of the most relevant data.[58]



Imidacloprid

The class of pesticides known as neonicotinoids have received, arguably, the most attention from the public in recent years. In the early 2000s, the use of neonicotinoids rose as restrictions were implemented for carbamates and organophosphates after studies raised concerns over their effects on human health.[57] But a large body of research studies on neonicotinoids over the past couple of decades have suggested that the chemicals can adversely affect the behavior of bees and other pollinators that play a critical role in agriculture. Bees are likely exposed to neonicotinoids through dust particles that slough off of pesticide-coated seeds during planting time, and through the nectar and pollen of neonicotinoid-treated crops.[59] In a 2013 study, researchers found that bees treated with realistic doses of neonicotinoids—imidacloprid and clothianidin—were not able to forage efficiently.[60] A 2015 study revealed that bees are attracted to the pesticides, which subsequently alter their behavior and growth in a crop field.[61]



Clothianidin

To help minimize honeybee losses, seed industries are seeking new methods to reduce the amount of pesticide-laden dust that is generated during planting.[62]

A survey conducted by the U.S. Department of Agriculture found that from 2014 to 2015, U.S. beekeepers lost 42% of their honeybees—the second highest loss ever recorded. Among scientists, there is disagreement over whether this phenomenon—which has been named "colony collapse disorder"—can be concretely linked to neonicotinoids, or if other factors may be at play. A 2015 effort led by the U.S. EPA and Department of Agriculture is aimed at developing a national pollinator health strategy to help protect pollinators from harmful pesticides.[63]

In contrast with pesticides, fertilizers seek to boost crop yields by providing the macronutrients necessary for plant growth, which include nitrogen, phosphorus, potassium, calcium, magnesium, or sulfur.[64] The primary problem with the use of fertilizer on farmland is a phenomenon known as nutrient runoff—when excess nutrients make their way into rivers and streams, where they cause algal blooms. These blooms can make waterways impassable, introduce toxins into water supplies, and produce oxygen-depleted "dead zones" where fish and aquatic species cannot survive.[65] The ongoing battle to reduce the size of the dead zone in the Gulf of Mexico has made slow progress—in 2015, the hypoxic area encompassed nearly 6,500 square miles, which is larger than the state of Connecticut, and three times higher than the goal that was set by the EPA and other agencies in the Gulf Hypoxia Action Plan for 2008.[66]

Another approach to fertilizing farmland involves the application of so-called "biosolids," or processed sewage sludge, to farmland. Currently, more than half of the roughly 6.5 million dry metric tons produced annually is used to treat about 1% of available farmland.[67] The practice is lauded by some as a way to return nutrients to the soil, rather than burying them in landfills. But the controversy over the use of biosolids stems from the fact that they are a complex mixture of beneficial nutrients and hundreds of other chemicals, including pharmaceuticals and personal care products. When applied to land, they have a possible route into the food chain, with unknown consequences to the environment and human health. In one research study on a field to which biosolids had been applied, about a dozen "chemicals of emerging concern" were found to have migrated as far as 50 inches into the soil, and some were taken up into wheat plants.[68] Although the EPA has limits in place for 10 contaminants in biosolids (nine heavy metals and fecal coliform), it does not currently regulate the hundreds of other chemicals that have been found in treated sewage sludge, and sewage treatment plants are not required to test for their presence or remove them.

# V: NANOPARTICLES AND ADVANCED MATERIALS

For centuries, humans have used nanomaterials without knowing it. For example, stained-glass windows that get their color from nano-sized particles of gold and silver.[5] In recent decades, scientists have increasingly looked to nanoscience for the development of new materials with interesting optical, physical, and electronic properties for applications ranging from biosensing and therapeutics to personal care products.

In conjunction with advances in the field of nanoscience has come increasing concern over the impact of nanomaterials on human health and the environment. According to a 2011 report in *C&EN*, more than one thousand products containing nanomaterials are now on the market – in sunscreen, food packaging, and cosmetics.[69] Research studies have found that in the environment, man-made nanomaterials can be transferred from one organism to another, and can increase in concentration as they move up the food chain, in a process known as "biomagnification."[70] Nanomaterials can negatively impact fish reproduction and disrupt cell membrane functioning,[71] and there is a growing concern that chronic exposure to low levels of nanoparticles can have cascading effects on aquatic life.[69] In pregnant mice, nanoparticles have been shown to be able to cross the placental barrier and cause neurological damage to offspring, among other pregnancy complications.[72]

Several research studies involving nanoparticle uptake in humans have revealed the ability of the light-reflecting nanoparticles that are commonly used in sunscreen to penetrate the outer layer of people's skin and eventually enter the bloodstream, albeit at low levels.[73] However, the authors did not confirm whether the nonradioactive zinc isotope that was detected in the blood stream was in nanoparticle form or had broken down into soluble zinc ions. Research on pigs, which have skin that is believed to behave like human skin, has found that zinc oxide nanoparticles did not travel past the topmost layer of skin—known as the stratum corneum. Titanium dioxide nanoparticles, however, penetrated about halfway through the 20 to 30 layers of skin that comprise the stratum corneum. Whether nanoparticles in sunscreens and cosmetics penetrate the skin or simply get sloughed off over time along with dead skin cells is still up for debate.[73] Although funding for nanotechnology safety research increased from $34.8 million to $117 million between 2005 and 2011, technological developments are still currently outpacing studies on safety.[69]

## Mining

In 2011, the EPA found more than 4 billion pounds of toxic chemicals were disposed of or released into the environment by U.S. facilities, down 8% from the previous year. Nearly half of the total toxic releases originated from the mining of metals, such as copper, lead, and gold.[77]

Coal mining and the burning of coal in power plants are other sources of toxic chemical releases into the environment. Coal naturally contains small concentrations of arsenic, barium, beryllium, boron, cadmium, chromium, thallium, selenium, molybdenum, and mercury. Upon burning, the metals become concentrated in coal-ash residue—at levels four or more times those in natural coal. Each year, 131 million tons of coal ash is generated by 460 coal-fired power plants in the U.S.[78]

Efforts have been made by government and industry to reduce air pollution from coal-fired power plants—but they come with tradeoffs. Instead of disposing coal ash, industries create massive holding ponds for containing the ash, which can be taken and processed to create material for reuse in various applications, such as structural fill and road base, or applied to farmland to "amend" the soil.[78]

But structures for confining coal ash sludge can falter, posing a risk to nearby residents. In 2008, some 5.4 million cubic yards of coal-ash sludge broke through a dam at a coal-fired power plant in Tennessee and flowed through farmland and into nearby rivers, covering an area of more than 275 acres with a 6-foot-deep mass of toxic sludge.[78] "Despite the amount of ash and the potential for problems, no federal regulations control the fate of ash from coal-fired power plants," Jeffrey Johnson wrote in a *C&EN* article about the incident. "Instead, a hodgepodge of state regulations and power-plant economics determines whether the ash and other combustion wastes are stored in a wet or dry state or whether they wind up in a landfill, mine, wetland, quarry, as construction fill, spread on farmland, or in a product."

In some regions of the U.S., traditional underground coal mining has been replaced with mountaintop-removal mining, which involves blasting through rock with explosives. People living or working near such mines have been found to have higher rates of lung cancer.[79] Research on cultured human lung cells has shown that when the cells are exposed to airborne particulates collected from locations near a mountaintop removal site, the cells adopted cancer-like properties. Upon injection into mice, the exposed cells promoted three to four times more tumor growth than cells treated with particulates collected from non-mining sites.[79]

Also during mountaintop-removal mining, waste rock and coal residues are often disposed of in nearby river valleys, where minerals can leach into the water, altering the salinity and levels of trace metals. Mining activity has thus been implicated in water pollution, which is suspected to be driving the disappearance of certain sensitive insect species.[80]

## Hydraulic Fracturing

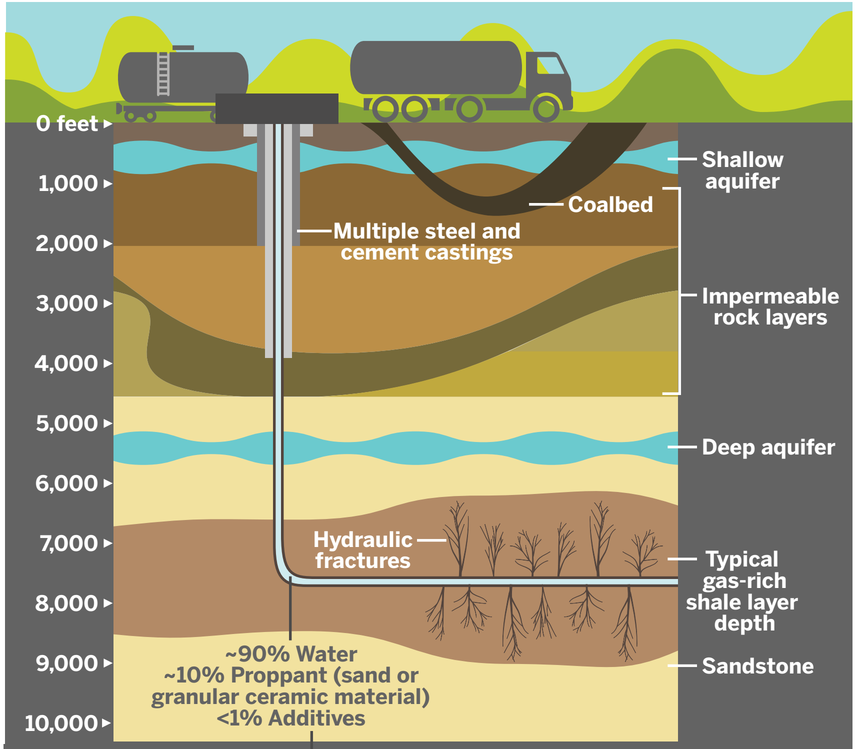
The hydraulic fracturing industry is another sector of the energy industry that has environmentalists concerned. More commonly known as "fracking," the process involves the injection of water and additives deep underground to enable the retrieval of oil and natural gas. The wastewater that is generated by fracking operations has caused problems for sewage plants. A 2013 study revealed that the sewage plants are not able to handle the high levels of contaminants in the water, and that treated wastewater flowing out of the plants and into the environment still contained elevated levels of chemicals from natural gas production.[81]

When it comes to treating the liquid that comes from fracking wells, scientists are exploring methods for removing harmful contaminants. "But figuring out the composition is no easy task," Celia Henry Arnaud wrote in a 2015 *C&EN* feature story. "The fracking wastewater is a complex mixture of organics, metals, and radioactive materials. Some of these substances get put into the water as fracking fluid additives, some are formed during degradation or transformation reactions, and some come from underground geologic formations. Many researchers are working to identify these components and their relative concentrations."[82]

In 2011, the EPA announced plans to collect data on fracking fluids and make the data available to the public.[83] A 2015 draft report concluded that fracking has had no "widespread, systemic impact" on water resources, but that in specific situations the technique can indeed pose water quality risks.[84] These include situations where wells are poorly constructed and fracking fluids are spilled or not treated adequately before disposal. In 2014, companies in the hydraulic fracturing industry joined forces with the American Chemical Society's Green Chemistry Institute® (GCI) to create a forum—known as the ACS GCI Hydraulic Fracturing Roundtable—to improve fracking's environmental footprint.[85]

Forum members have been collaborating to prioritize chemical and engineering research needs aimed at minimizing the long-term environmental impacts of the method and glean the most economic benefit from the technology.

**THE ANATOMY OF A FRACKING OPERATION**




**Common Water-Based Fracking Fluid Additives**

| Ingredient | Example | Function |
|---|---|---|
| Acid | Hydrochloric acid | Clear debris from well bore |
| Thickener | Guar gum | Increase viscosity of fluid to disperse proppant |
| Friction reducer | Polyacrylamide | Aid flow of fluid deep underground |
| Scale inhibitor | Ethylene glycol | Prevent carbonate/sulfate deposits |
| Corrosion inhibitor | Methanol | Protect steel casings |
| Biocide | Glutaraldehyde | Prevent microbial fouling |

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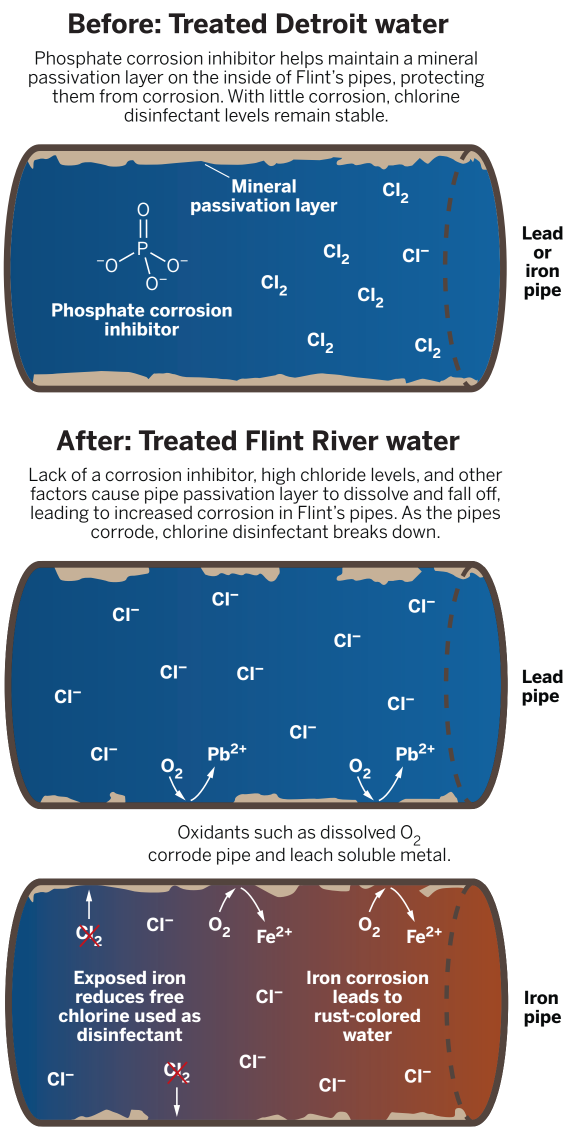
## Lead

Lead contamination was launched into the media spotlight in 2015, when data collected by researchers at Virginia Tech revealed that city pipes in Flint, Michigan, were leaching high levels of lead into the city's drinking water supply.[86] The problems were found to have begun in 2014, when the city of Flint changed its water source from Lake Huron—water treated and provided by the Detroit Water & Sewerage Department—to the Flint River. The chemistry of the river water was not optimized to control corrosion of lead pipes—specifically, the city failed to add phosphate to the water, which would have interacted with lead to form largely insoluble lead phosphates that would add to the pipes' passivation layer instead of flowing out of residents' faucets.

Flint has since switched back to the Detroit water, but Michael Torrice reports in *C&EN* that it will be months before the pipes regain their passivation layers that will prevent lead from continuing to leach into the water.[86]

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### Methylmercury

Oceans near industrial sites have been found to have elevated levels of methylmercury, a neurotoxic and persistent chemical that is formed when certain strains of bacteria methylate oxidized mercury. Methylmercury becomes increasingly concentrated as it moves up the food chain[74] and has been found to accumulate in snow around oil sands production sites in Canada, which holds one of the largest known oil reservoirs in the world.[75]

The risk of mercury to wildlife is challenging to assess.[76] Mercury is known to be taken up by fish and then passed on to birds that feed on those fish. In birds, mercury can disrupt reproduction. Ecologists have typically monitored mercury levels in birds by analyzing their blood and feathers, although a 2013 study revealed that those levels don't correspond with levels found in eggs, suggesting that scientists cannot assume tissues can be used interchangeably to assess mercury risk.

## VII: CONCLUSION

Chemists play myriad roles in both the development of new chemicals, the detection of contaminants in the environment, and the study of downstream effects on human health and the environment. One way to reduce chemical persistence would be to create compounds that are "benign by design"—meaning they are stable enough to be used in their desired applications but are likely to degrade rather than accumulate in the environment. Advocates for this approach say regulatory action and financial incentives will be needed to get chemical companies to create more environmentally friendly chemicals for pharmaceutical and industrial applications.[2]

But even if new chemicals are required to meet these criteria, what would be done about the thousands of other persistent, bioaccumulative compounds already in widespread use? That's a topic that remains the center of debate. While some scientists and environmental advocates push for stricter regulations and requirements for safety testing prior to widespread use, others argue that such actions are unnecessary and would hamper scientific progress and innovation.

In the meantime, ongoing research on all fronts is yielding new information on the impacts of the thousands of chemicals on the market today. The results of these efforts will continue to inform the debate over what can be done to best support scientific progress while minimizing negative impacts on human health, wildlife, and the environment.

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