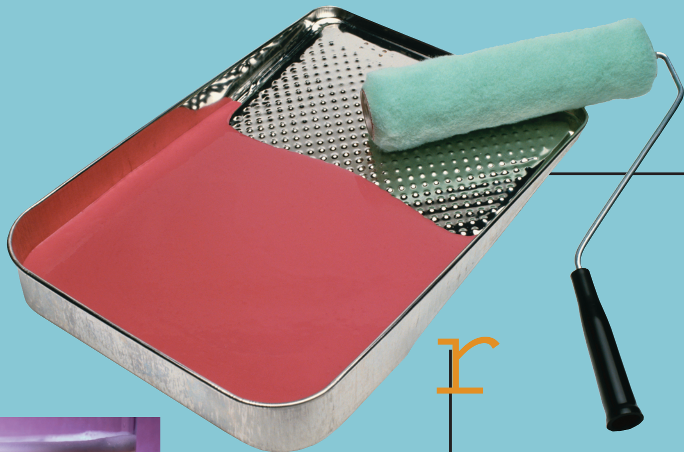
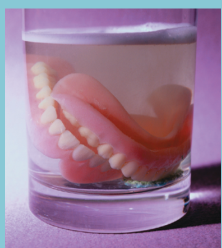
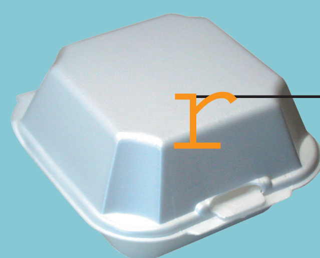
GROWING

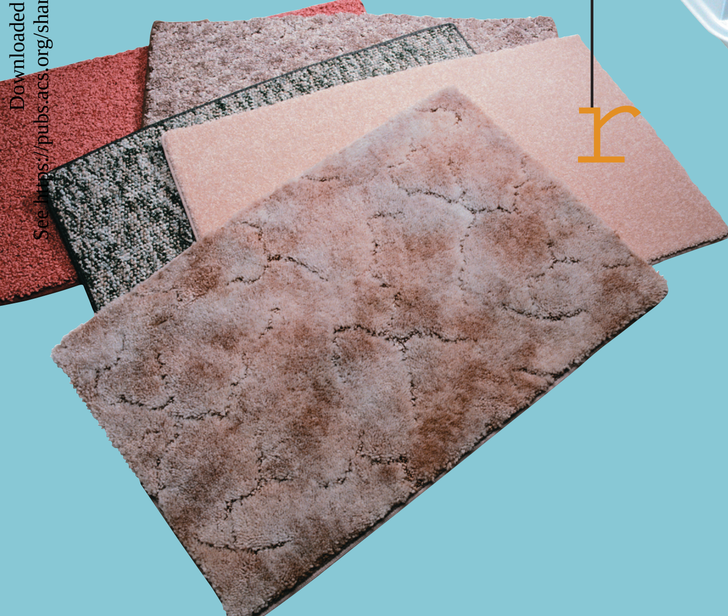


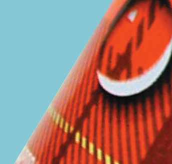


Evidence of toxic effects and environmental impacts has sent researchers scrambling to obtain more data.

REBECCA RENNER







CONCERN OVER

PERFLUORINATED CHEMICALS

The world was caught off-guard last May, when St. Paul, MN–based 3M Corp. announced that it would phase out a group of perfluorinated chemicals used in its popular Scotchgard fabric protector and other products. The meticulous and the messy rushed to stockpile Scotchgard. Manufacturers that use these chemicals to make everything from paper plates and microwave popcorn bags to semiconductor coatings and airplane hydraulic fluid worried about the consequences to their businesses.

All of the fluorochemicals set for phaseout either use perfluoro-octane sulfonate (PFOS) in their manufacture or breakdown to PFOS, a chemical that behaves in the environment like a persistent organic pollutant (POP), but seems to lack most of the important characteristics of more familiar POPs such as DDT or polychlorinated biphenyls (see sidebar on page 156A) (*1*, *2*). As a result, environmental scientists and regulators are racing to answer questions about environmental exposures, fate, transport, and toxicity, in part to determine if PFOS or the perfluorinated compounds are causing adverse effects in the environment.

Big unknowns

The winds move POPs around the world because they are semivolatile. PFOS has a very low vapor pressure, but it still moves around the world, turning up in the blood of people and animals from areas far

A fluorochemicals primer

Fluoro-organic chemicals are compounds in which one or more carbon–hydrogen (C–H) bonds is replaced by the carbon–fluorine (C–F) bonds, to which the chemicals owe many of their unique properties. Stable and chemically inert (the C–F bond is thermodynamically one of the strongest known), the chemicals repel water and oil, reduce surface tension better than other surfactants, and work well under harsh conditions.

In perfluorinated chemicals, all of the C–H bonds are replaced by C–F bonds (*1*). In PFOS ($C_8F_{17}SO_3H$), a reactive sulfonyl group provides a link to other functional groups, such as free acids, metal salts, sulfonyl halides, and sulfonamides. In a proposed Significant New Use Rule, EPA seeks to bring fully fluorinated alkyl sulfonate-containing compounds having 4–10 carbons under regulatory control (*2*). This proposal covers all of the compounds that 3M is phasing out.

PFOS and related fluoro-organic chemicals have been used since the 1950s in soil- and stain-resistant coatings for fabrics, carpets, and leather, as well as in grease- and oil-resistant coatings for paper products. Specialized industrial uses, accounting for about 1.5 million pounds, include fire-fighting foams, mining and oil well surfactants, acid mist suppressants for metal plating and electronic etching baths, alkaline cleaners, floor polishes, photographic film, denture cleaners, shampoos, and ant insecticide.

Surface treatments constitute the largest volume of PFOS production: 5.1 million pounds in 2000. Scientists and regulators believe that they present the greatest potential for widespread human and environmental exposure. This category includes protection of clothing, upholstery, and carpets (2.4 million pounds). Applications are performed at textile mills, leather tanneries, finishers, and carpet manufacturing facilities. The Scotchgard market also allows for such treatments at home. Paper mills applying PFOS chemicals to protect paper products accounted for ~2.7 million pounds in 2000 (*7*).

3M is phasing out its U.S.$300 million-dollar business in fluorochemicals that use PFOS in their manufacturing process or that are precursors to PFOS. According to Michael Santoro, 3M environment director, the company is forging ahead with development of a nonfluorinated Scotchgard, which should be on the market this year.

removed from where it is manufactured or used. PFOS has been found in blood samples taken from people living in China, as well as in albatross, polar bears, and other life forms inhabiting remote areas (*3, 4*). Most POPs accumulate in fats. But as an exceedingly effective surfactant having both lipophobic and hydrophobic properties, PFOS doesn't accumulate in lipids. So, octanol–water partitioning, the standard predictor of bioaccumulation in animals, is meaningless for PFOS. Instead, this ionic, polar surfactant binds to blood proteins and accumulates in the liver and gall bladder. Recent animal tests have also raised concerns about its potential developmental, reproductive, and systemic toxicity.

Does PFOS cause adverse effects at current levels in the environment? "Wait and see" is the attitude of most academic researchers and regulators, who say that too many unanswered questions remain. "The environmental behavior of the fluorinated surfactants is very different from most organic compounds because of their unique properties. Currently, we do not understand the properties of these surfactants or their environmental fate well enough to determine what impacts they may have, particularly in areas where they may concentrate or accumulate," says Thomas Cahill, who studies their fate and transport at Trent University in Peterborough, Canada.

3M, however, contends that the picture is already clear and that PFOS does not cause adverse effects (*5*). "We've done over 700 different studies related to human health and environmental effects," says 3M Environment Director Michael Santoro. "We've compared the results of those tests to the actual monitoring data, and based on this comparison, we conclude that there are no adverse effects to wildlife at the levels found in the environment," he says, and notes that additional studies are under way to confirm this conclusion.

Richard Purdy, an independent toxicologist who previously spent 19 years with 3M, has a diametrically opposed viewpoint. The highest concentrations found in animal tissue (6 ppm for minks and eagles) are only about 10 times lower than the highest adverse effect level concentrations determined from toxicity tests (58 ppm), he says, noting that this safety margin is too low considering the variability in species' sensitivities. Purdy presented his analysis at the Society for Environmental Toxicology and Chemistry (SETAC) meeting in November 2000 (*6*).

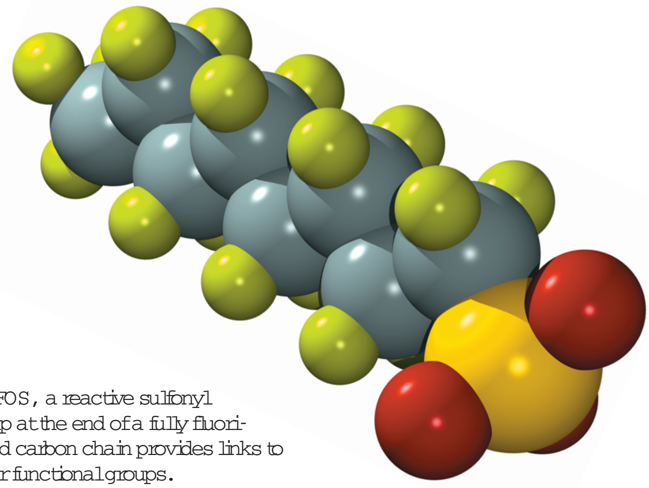
Although Purdy stands alone in this assessment, scientists and regulators say that despite 3M's PFOS phaseout, they cannot breathe a collective sigh of relief about PFOS and other fluorochemicals. "There are huge gaps in our knowledge—specifically, around what the fluorine atom itself does to environmental fate, disposition, and persistence of these compounds," says University of Toronto chemist Scott Mabury.

Moreover, no one knows whether PFOS is the only compound in this class with troublesome environmental and toxicological properties. This question is important because although 3M is the major manufacturer of compounds that break down to PFOS, other companies make fluorochemicals having similar properties and applications; however, they use a different synthetic procedure, a telomerization process (Figure 1). Few data are available on these other fluorochemicals, but environmental chemists familiar with organofluorine compounds worry that they could have similar environmental fates based on their structures. "We believe that fluorochemicals need to be investigated because many are partially perfluorinated, which will influence their environmental behavior and contribute to their overall persistence—indeed, potential degradation products may differ little, or not at all, from products withdrawn by 3M," says Mabury, who also notes that from 1988 to 1997, the average global consumption of fluorinated polymers rose by almost 220%.

Warning signs

Historically, research on POPs focused principally on chlorinated compounds, even though other halogenated compounds, including fluorinated compounds, were also found to be persistent and bioaccumulative in the environment. Scientists assumed that because many of these compounds are incorporated into polymers, they should not readily travel in the environment and accumulate in living organisms.

But, in 1976, Donald Taves, a research physician at the University of Rochester in New York, who was investigating water fluoridation, chanced upon organic fluorine in human blood and speculated that there could be "widespread contamination of human tissues with trace amounts of organic fluorocompounds derived from commercial products" (*7*). The chance discovery raised 3M's awareness of the issue. But the unique characteristics of PFOS did not really become evident until three years ago, when improvements in analytical methods gave 3M the necessary tools to determine that the persistent compound was present at low levels in humans and in animals far from any sources.



In PFOS, a reactive sulfonyl group at the end of a fully fluorinated carbon chain provides links to other functional groups.

Searching for sources

Now, in order to characterize potential environmental threats, scientists are searching for PFOS sources. If manufacturing is the principal source, then when 3M stops making PFOS, its release to the environment should be markedly reduced. However, if PFOS is coming from landfills or existing products, there could still be a significant problem. Also, there may be environmental processes that can concentrate PFOS to harmful levels.

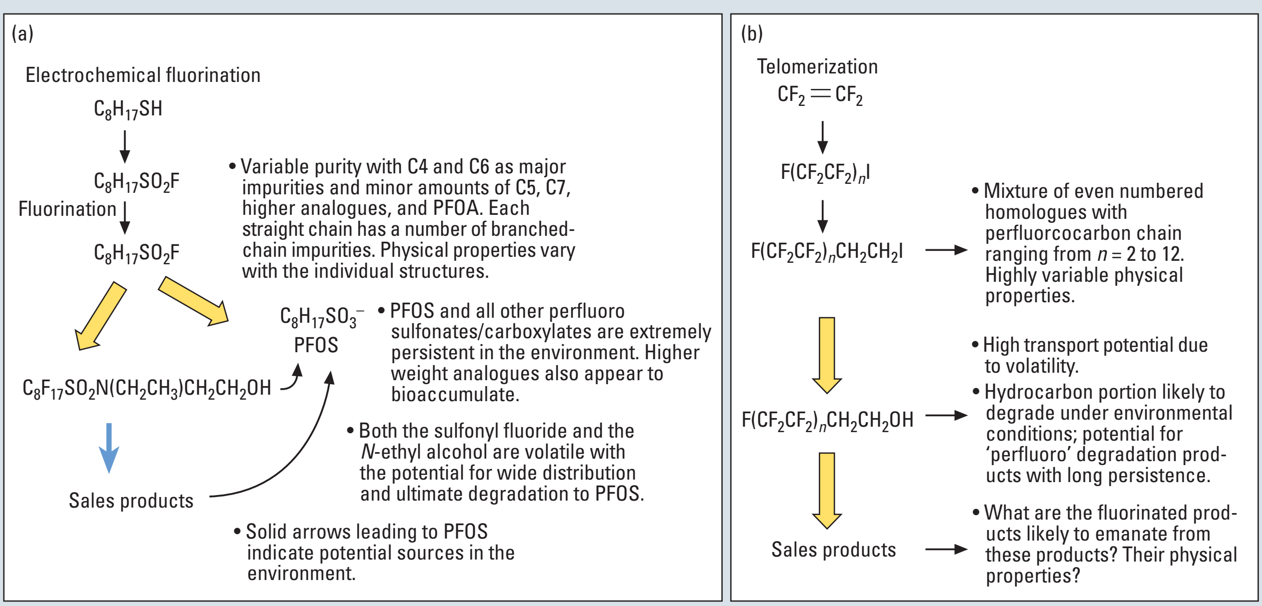
Thanks largely to 3M, there is already a sizable body of information concerning PFOS—at least three research groups partly funded by the company are working on these problems. 3M has shared research results with EPA, and the agency has made the information publicly available. Although research papers are still in the pipeline, some answers are already emerging (*1, 2, 8*).

Kurunthachalam Kannan and John Giesy's group at the Department of National Food Safety and

FIGURE 1

The electrochemical fluorination and telomerization process

(a) 3M's electrochemical fluorination process produces a mixture of branch- and straight-chained molecules. (b) The telomerization process primarily produces straight-chain products.



Source: Scott Mabury, University of Toronto.

“The monkey and rat test results were scary. The monkeys all died, and with the rats, the pups died.”

Toxicology Center at Michigan State University (MSU), in East Lansing have analyzed more than 2000 tissue samples from all over the world that are archived in laboratory freezers. According to Kannan, although the archived samples have limitations—they were not collected with a particular problem in mind—they provide a beginning framework for estimating fluoro-organic chemical contaminant levels in the environment and for searching out patterns to identify environmental sources and sinks.

PFOS contamination levels are greatest in fish-eating animals living in continental areas. The MSU researchers have found up to 6 ppm in North American mink and eagles. Contaminant levels are lower in samples obtained from coastal areas and are least in oceanic areas, he says. Besides PFOS, Kannan and Giesy find other fluorinated compounds in samples taken from animals at continental sites, so they believe that these samples are closer to the original source of contaminant release.

That source is unlikely to be attributed to direct releases of PFOS during production, according to Cahill and fellow fate and transport modelers Ian Cousins and Donald Mackay at Trent University. Because PFOS is unlikely to move into the atmosphere, they believe that a volatile precursor or precursors is the culprit. It’s also possible that a volatile fluorochemical is released from materials in landfills. To explore these hypotheses, they are measuring the physical properties of PFOS and likely precursors. The researchers are also developing fate and transport models to account for PFOS’s peculiar behavior, including its remarkable persistence. According to Mabury, PFOS does not show the slightest sign of degradation when boiled in nitric acid for an hour.

Differences and similarities

3M’s compounds differ from other fluorocompounds, in part, because of the electrochemical fluorination process that 3M has used for more than 40 years to produce them. Anhydrous hydrogen fluoride and hydrocarbon stock are dissolved in hydrofluoric acid, and an electric current is passed through the media. Perfluorination occurs when all the hydrogen molecules are replaced by fluorine. Because the process is difficult to control, it also produces small amounts of residual compounds as byproducts. These may be some of the precursors observed moving through the environment. One active area of 3M research focuses on how long these residuals last in a particular form. “This whole area of chemistry is complex. That is what has made it such a challenge,” says Santoro.

3M is the only major company known to use the electrochemical fluorination process. The other major manufacturers of fluorinated surfactants use a telomerization process: DuPont (United States), Atofina (France), Clariant (Germany), Asahi Glass (Japan), and Daikin (Japan) make fluorochemicals by reacting tetrafluoroethylene with other fluorine-bearing chemicals. The process yields even, straight-chain alcohols, $F(CF_2CF_2)_nCH_2CH_2OH$, which can be converted into final products. DuPont’s product line averages 7–8 carbons and can be pure compounds but are generally mixtures, according to Stephen Korzeniowski, a DuPont business manager. Last July, the five companies formed a consortium to investigate the environmental fate, transport, and effects of their products.

Although there is little hard evidence currently concerning the environmental behavior of these telomerization-based fluorochemical products, environmental chemists familiar with the compounds believe they need to be investigated further, because based on their structures, they may have similar environmental characteristics.

Stanford University environmental chemist Craig Criddle, who is familiar with the compounds produced by the telomerization process, speculates that their environmental behavior may be similar to that of PFOS. “3M’s process is a little messier, but the telomerization process is not so fundamentally different. You are still left with that fluorocarbon tail,” he says. Korzeniowski notes, however, that in the three or four years that DuPont has been doing employee monitoring, no elevation of fluorotelomer levels has been found in the blood of workers directly involved in their production. For PFOS, elevated levels in 3M workers were one of the early clues that a problem might exist. But, says Korzeniowski, “PFOS seems to behave differently from our products.”

As to the environmental fate of the fluorotelomers, Korzeniowski says that DuPont and other manufacturers have begun a research program to study degradation products. "Scientific information and studies on these materials are too limited to say whether they break down or not," he says.

Of rats and monkeys

If the environmental behavior of PFOS is initially surprising, so too is its toxicity. Laboratory toxicity tests on rats and monkeys, conducted over a year ago, first raised concerns about PFOS's potential developmental, reproductive, and systemic toxicity. These issues are currently being pursued by scientists in academia and by EPA.

"The monkey and rat test results were scary. The monkeys all died, and with the rats, the pups died," says an anonymous EPA official familiar with the tests. The tests also revealed that liver enlargement and reduced serum cholesterol levels are early responses to PFOS exposure. Other adverse effects include changes in liver enzymes, weight loss, convulsions, and death. In Rhesus monkey studies, no monkeys survived beyond 3 weeks into treatment at 10 mg/kg/day dosing or beyond 7 weeks into treatment at doses as low as 4.5 mg/kg/day. At doses as low as 0.75 mg/kg/day, cynomolgus monkeys also died after first becoming listless and uninterested in food. There were also changes in the monkeys' livers and significant reductions in blood cholesterol (*9*).

Postnatal deaths and other developmental effects were reported at low doses in offspring in a two-generation reproductive toxicity study in rats. At the two highest doses of 1.6 and 3.2 mg/kg/day, pup survival in the first generation was significantly decreased. All first-generation offspring at the highest dose died within a day after birth, and almost one-third of the first-generation pups in the 1.6 mg/kg/day dose group died within 4 days after birth. The no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) for the second-generation offspring were 0.1 and 0.4 mg/kg/day, respectively, based on reductions in pup weight compared to controls. Reversible delays in reflex and physical development were also observed in this study, raising concerns about the possible developmental neurotoxicity following PFOS exposures (*10*).

This is the same two-generation rat study that Purdy uses to argue that PFOS is an environmental problem. At the NOAEL of 0.1 mg/kg/day, the PFOS concentration in the rat liver was 15 ppm. The LOAEL associated with a decrease in weight was 58 ppm, corresponding to a dose of 0.4 mg/kg/day. The greatest concentration found in mink liver, 6 ppm, is about threefold less than this NOAEL and 10 times less than the LOAEL. Mink could be more or less sensitive to PFOS than rats, so accepted practice is to address this uncertainty by applying a safety factor of 10-fold, says Purdy. This analysis suggests that PFOS in the environment is already causing adverse effects, he says.

Like a lock and key

The structure of fluorinated organic compounds is what explains their toxic action, according to MSU biochemist Brad Upham, who studies how disruptions in normal cell behavior can cause cancer. "Compounds like PFOS are chemically inert, and since they don't react with DNA, the accepted assumption is that they aren't toxic," he says. But their structures fit like keys into some of the body's natural locks that control a variety of processes. PFOS moves through the body by binding to blood proteins and subsequently accumulates in the liver and gall bladder. Scientists speculate that the body recognizes PFOS as a bile acid and continues to recycle it as it does with authentic bile acids. This recycling process, called enterohepatic circulation, begins when the liver uses cholesterol to make bile acids, which aid digestion by emulsifying fat in the gut. Once their work is through, the acids are recycled back into the liver. Such behavior is seen with some drugs, but it is novel for an environmental residue, according to Charles Auer, director of EPA's Chemical Control Division.

Other perfluorinated fatty acids, such as perfluorooctanoic acid (PFOA) and PFOS, are known to promote liver cancer in rats even though they do not damage DNA, the mechanism usually associated with cancer development. Perfluorinated fatty acids also cause an increase in the enzyme peroxisome, which is involved in fat oxidation. In 1998, Upham and colleagues found that the chain length of perfluorinated fatty acids determines whether they can affect an important mechanism of normal cell behavior, gap junction intercellular communication (*10*).

According to Kannan, chemicals that bind to protein, like PFOS and other similar organofluorine compounds, could potentially open many cellular locks. This is because there are two very different sites for toxic action. First, when PFOS binds to protein, it may block, or replace, natural compounds that should bind to that protein and that perform important signaling duties in the body. Second, protein-binders like PFOS accumulate in physiologically important organs, in this case the liver and gall bladder, where they can potentially interfere with organ functions.

Giesy and his colleagues are searching for other cellular locks that can be opened with organofluorine keys. At the SETAC annual meeting in November, they showed that PFOS exposure weakens cell membranes, making it easier for environmental contaminants to enter the cell (*11*). PFOS caused the effect, but other fluorinated organics with a similar structure yet different carbon–fluorine chain lengths did not.

Mindful that concern is focused on environmental effects, Giesy's group is trying to determine whether organofluorine compounds elicit the same response in all species. In May, Giesy and colleagues will present data at the SETAC European meeting in Madrid, Spain, indicating that the inhibition of gap junction intercellular communication by perfluorinated compounds is neither species- nor tissue-specific (12).

Where to draw the line?

Risk assessors from the United States, the United Kingdom, Canada, Japan, and other Organization for Economic Development and Cooperation (OECD) member countries are assessing issues related to PFOS in the environment. The countries are working together as part of a special OECD initiative to evaluate PFOS, and OECD is working with the United Nations Environment Programme to expand the assessment to include environmental impacts in countries beyond the OECD.

One big issue of concern is determining the range of these compounds that are problematic to the environment. "We don't know how big the class is," says Auer. Chain length is an important consideration, he says. "We need to find out where we get a tailing off in accumulation and where we get a change in toxicity." EPA has already started to review information about PFOA as the next step in its evaluation of flourinated surfactants.

Much has been learned since Taves's early work and 3M's recognition of the environmental problem. Purdy worries, however, that we cannot yet rest, happy in the knowledge that the system worked. "We introduce new chemicals at a vast rate, often with very little understanding of their environmental impact. We picked up PFOS more thanks to luck than judgment," he warns.

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Rebecca Renner is a contributing editor of ES&T.