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PFOA in People

Food wrappers may be an important, overlooked source of perfluorochemicals in humans.

Although scientists and regulators are concerned and intrigued about the presence of anthropogenic perfluorinated chemicals in the blood of people from developed countries, little is known about the source of this contamination. Research interest and controversy have focused on the presence of these chemicals in the remote Arctic, where the source of contamination is a mystery. In contrast, the problem for people is just the opposite, because these chemicals are used on everything from fast-food wrappers to stain-resistant carpet. The challenge is figuring out which sources—food, drinking water, outdoor air, indoor air, or dust—are the most important.

Corel

We all have anthropogenic perfluorochemicals in our blood, but scientists haven't found the sources.

Progress on this question has been slow. "It's been 7 years since perfluorinated chemicals came to the world's attention, and yet some of the pressing issues of human exposure sources have not been identified," says environmental chemist Kurunthachalam Kannan, who is at the New York State Department of Health Wadsworth Center and was one of the first scientists to find these chemicals in wildlife around the world.

The toxicological implications of this pervasive exposure are topics of current research. The U.S. EPA's Science Advisory Board in 2006 classified perfluorooctanoic acid (PFOA) as a likely human carcinogen. Animal studies also indicate that perfluorinated chemicals affect the liver, neonatal development, the immune system, and hormone levels (*Toxicol. Sci. 2007*, in press).

Anthropogenic perfluorinated contaminants consist of perfluorinated carboxylic acids (PFCAs), such as PFOA, and perfluorinated sulfonic acids (PFSAs), such as perfluorooctane sulfonic acid (PFOS). PFCAs are still being manufactured around the world, but PFSAs are no longer made in the U.S. and Europe. A growing body of evidence shows that direct exposure to PFOS or PFOA is not a significant source of contamination to the general population. This suggests that other chemicals capable of breaking down to form them are the sources. These indirect sources include fluorotelomer alcohols (FTOHs) that break down to PFOA and perfluorinated sulfonamides that break down to PFOS.

Two new studies illuminate an unexpected pathway by which these chemicals could enter food and people. Ongoing U.S. Food and Drug Administration (FDA) studies indicate that the perfluorinated chemicals that make food wrappers greaseproof can migrate into some foods at levels up to several hundred times higher than current FDA-approved guidelines indicate, suggesting an overlooked and potentially important source.

Among these chemicals are polyfluoroalkyl phosphate surfactants (PAPS). A new study by University of Toronto chemists Jessica D'eon and Scott Mabury published today on *ES&T*'s website (DOI 10.1021/es070126x) shows that once ingested, these chemicals are bioavailable and can be metabolized to form PFOA and other perfluorinated chemicals.

Taken together, these studies show that common assumptions about these chemicals are wrong, says Mabury. "Because these are large molecules, presumably an assumption was made that these surfactants were not bioavailable. We have shown that's wrong, at least in rats. Then, it's been assumed that they wouldn't break down—also incorrect. And now it appears that these chemicals can migrate into foods at much higher levels than previously thought," he adds.

These studies are important because "together they show that it's feasible for food contact chemicals to migrate from paper to food and to be responsible for some of the PFOA in humans," says Jon Martin, an environmental and analytical chemist at the University of Alberta (Canada).

PAPS are fluorinated surfactants that contain a long fluorinated carbon tail attached to an acidic head group. This structure is similar to that of other chemicals in this family, such as PFOA and PFOS. But unlike PFOA and PFOS, in PAPS the linkage between the fluorinated tail and acidic head is a phosphate ester linkage, which makes it vulnerable to degradation via dephosphorylating enzymes in biota.

Scientists at the U.S. Centers for Disease Control and Prevention (CDC) recently reported levels of PFOS, PFOA, and several other perfluorinated chemicals in a representative sample of the U.S. population from 1999 to 2000 (*Environ. Sci. Technol.* **2007**, *41*, 2237–2242). All 1562 blood samples, which were taken before the PFOS withdrawal, contained perfluorochemicals. Perfluorinated sulfonamides, the chemicals that break down to form PFOS, were found in more than 90% of the samples. These more detailed findings are consistent with the results of a previous CDC study of pooled blood samples.

What the rats ate

To find out whether PAPS are bioavailable and subject to metabolic breakdown, D'eon gave rats a large dose of the chemicals—200 milligrams per kilogram, or parts per million (ppm). Over the next 15 days of monitoring the rats' blood, she found first the PAPS unchanged, then several metabolic intermediates indicative of FTOH exposure, and eventually PFOA. The rats had elevated levels of these chemicals in their livers after they were killed.

Jessica D'eon

Rats that were fed PAPS converted them to other perfluorochemicals, including PFOA.

The study demonstrates that the transformation occurs, but it is too preliminary to offer quantitative information about how much gets transformed, says D'eon. In one particular dosing study, about 0.36% of the PAPS went into the blood. Then, 0.5% of this was transformed into PFOA. But, she cautions, "since this was our first study, we used a very high dose to increase our chances of seeing the breakdown products. It's quite possible that we somehow swamped the system. In other words, we might have gotten higher percentages of uptake or transformation if we had started with a lower dose," she says.

As for the study's relevance to people eating foods that come in contact with PAPS, D'eon says the data are highly suggestive. She's synthesized her own PAPS because commercial products are known to be contaminated with FTOHs. "We know that Zonyl FSE, for instance, contains 3% residual FTOH. If I had used this to dose the rats, it would be very hard to distinguish the residual FTOH from the new FTOH coming from the breakdown of the PAPS," she says. "Although I can't say for sure that commercial PAPS act the same way, I can say that the structures of my PAPS are the same as some of the known commercial materials."

Great bags of popcorn

D'eon's findings come as FDA strives to determine the implications of new research by chemist Tim Begley and colleagues at FDA's Center for Food Safety and Applied Nutrition. In 2005, they first demonstrated that perfluorinated chemicals could become concentrated in microwave-popcorn oil and migrate into foods. More recently, Kannan and colleagues analyzed the vapors that come out of a bag of cooked microwave popcorn and found a wide range of perfluorinated carboxylic acids, including PFOA (*Environ. Sci. Technol.* **2007**, *41*, 1180–1185).

Foods like popcorn that contain butter or oils with added emulsifiers may readily attract PAPS.

Begley's new work shows that FDA-approved guidelines for determining how much PAPS migrates into foods may dramatically underestimate the amount that gets into foods that involve emulsions such as butter, margarine, chocolate spread, or even oil with an added emulsifier such as soy lecithin. Because the results of these migration tests are part of the data that FDA uses to set limits on the maximum concentrations of these chemicals used on food papers, the new work could possibly lead to dramatically reduced limits for these chemicals. In addition, researchers evaluating food as a route of exposure to perfluorinated chemicals have not even tried to measure these PAPS in food yet.

Currently, about 15 different perfluorinated chemicals are approved by FDA for treating paper or other materials that contact food. The German Federal Institute for Risk Assessment (BfR) also regulates several of these chemicals. Food papers treated with PAPS include microwave-popcorn bags, bags for muffins or french fries, pizza liners, boxes for burgers and small pizzas, and sandwich wrappers. PAPS have chain lengths that range from 6 to 14 carbon atoms, and paper coatings can contain up to 0.5%, or 5000 ppm PAPS, according to a presentation Begley made at an EU food packaging meeting last year in Baveno, Italy.

FDA's approval process involves several steps. Scientists use test data to estimate the chemical concentrations that can migrate into different sorts of food. These data are combined with information about the quantities of foods that people eat. For these calculations, FDA assumes that each individual chemical accounts for the entire market, according to FDA officials, who say that this conservative assumption also simplifies calculations because it removes uncertainties about market share. Finally, FDA combines this exposure estimate with information about toxicology and sets a limit.

Typically, FDA migration tests do not use actual foods. They use substitutes or simulants that have proven to proxy well for certain types of food. For example, for a material in contact with an acidic watery food, like fruit juice, the tests use water as a surrogate. Ethanol often serves as a good proxy for fatty foods, although the tests can also use Miglyol, a fractionated coconut oil.

Many previous studies show that oil and water capture the extremes of migration for most nonpolar polymers. But Begley has found that is not the case for fluorochemicals. He conducted experiments at 100 °C with 15 minutes contact time and found that the chemicals can migrate into emulsions, such as butter, margarine, and chocolate spread, in the parts-per-million range. This may be an important route of human exposure.

Not all PAPS behave the same. For one PAP, concentrations for butter are 4.5 times higher than for water and more than 10 times higher than for oil. But for another PAP, migration into an emulsion is

800 times higher than migration into oil.

FDA takes these findings seriously and is currently evaluating their ramifications, according to an agency official. However, the problem may be small, says the official. Because most of these papers are used for fast food, the contact time between the paper and the food is usually brief.

A Freedom of Information Act request by *ES&T* reveals that none of the perfluorinated chemicals currently registered with FDA has been officially evaluated for its behavior with emulsions or emulsifiers. FDA is currently developing testing guidance that uses emulsified simulants through its Food Contact Notification program. The agency is also evaluating toxicity testing armed with the understanding that although PAPS migrate into food, it is their breakdown products that potentially could be toxic. “This situation isn’t exactly unique, but it is certainly complicated,” the FDA official tells *ES&T*.

Mabury notes that some of the intermediate products in the breakdown from PAPS to PFCAs seem to be more toxic than PFOS or PFOA. “The metabolic pathway from FTOHs to PFOA and other carboxylic acids involves several reactive intermediates. One of these that has been investigated using Daphnia turns out to be 4 orders of magnitude more toxic than the corresponding carboxylic acid. In addition, the transformation from FTOH to PFOA involves several polyfluorinated aldehydes. This family of chemicals has well-documented toxicity and carcinogenic activity. I think that, given their inherent reactivity, these transient metabolites could have greater toxicological implications than exposure to perfluorinated carboxylic acids alone,” he says.

Food surveys miss the mark

The new insights provided by Begley and D’eon suggest that the limited number of food surveys conducted on perfluorinated chemicals may have fallen short of their goal, says Mabury.

These studies attempt to replicate a country’s average diet. For the Canadian survey, researchers purchased 250 items and cooked them to reflect what people eat and how they eat it (*J. Agric. Food Chem.* **2007**, *55*, 3203–3210). Then, they concentrated the prepared foods and analyzed them for PFOS and PFOA.

The U.K. Food Standards Agency analyzed 20 composites from the 2004 U.K. Total Diet Study, including PFOS, PFOA, and other perfluorinated compounds. The study found low (nanograms-per-gram) but detectable levels of PFOS in potatoes, canned vegetables, eggs, sugars, and preserves. Only the potato composite, which included potato chips, French fries, and other potato products, contained PFOA at a detectable level.

The Canadian survey obtained similar results but came up with an estimated dietary intake that is less than the U.K. estimate. These estimates are comparable to those for exposure via drinking water, dust, treated carpet, and clothes, says Health Canada analytical chemist Sheryl Tittlemier, who led the Canadian study.

Tittlemier also has measured perfluorinated sulfonamides that can break down to PFOS. Levels were highest in fast foods in 1998 and then went down (*J. Agric. Food Chem.* **2006**, *54*, 8385–8389).

But she is not measuring PAPS, says D’eon. “Tittlemier’s work is excellent and cutting-edge, but the sulfonamides she measured are residual impurities from the food contact chemicals that got into the food; she is not measuring the actual food contact chemicals that migrated from the paper to the food. This means that current studies may be significantly underestimating human exposure to fluorinated materials via this mechanism,” she says.

Blood data

Biomonitoring studies seem to suggest that sources of PFOS and PFOA are somehow related. CDC scientist Antonia Calafat notes that CDC data from 1998 to 1999 indicate that PFOS and PFOA are pretty homogeneous across the entire population. “This suggests a common source or pathway of exposure for these chemicals,” she says. But she cautions that biomonitoring cannot differentiate between an explanation based on how people metabolize these chemicals and an explanation based on pathways or sources. CDC scientists have found that, in general, men have slightly higher levels than women and Mexican-Americans have slightly lower levels than Americans from other ethnic groups. This latter difference may be a metabolic phenomenon, Calafat says. The new data also show a correlation between increased concentrations of chemicals and higher levels of income and education, suggesting a lifestyle correlation.

A pilot study by 3M Corp. researchers suggests that the company’s phaseout of products based on PFOS chemistry, completed by the end of 2002, may already have affected levels of the perfluorochemicals in human blood just 3 years later (*Chemosphere* **2007***, 68* (1), 105–111). They compared concentrations of PFOS and PFOA in plasma samples taken from Red Cross blood donors in 2000 with samples taken 5 years later. Average concentrations of both PFOS and PFOA dropped by more than 50%, they found.

Researchers at Johns Hopkins University found PFOA in 100% and PFOS in 99% of 297 serum samples collected in 2004 and 2005 from the umbilical cords of children born in Baltimore, according to a new study (*Environ. Sci. Technol.* **2007**, DOI 10.1021/es0700911). “This study confirms that, as we might have suspected, exposure to PFOS and PFOA is fairly universal; this is of particular concern because of the potential toxicity, especially developmental toxicity, for these chemicals and the lack of information about health risks at these exposure levels. What was surprising is how strongly PFOS and PFOA are associated with each other, given that they have very different uses,” says Lynn Goldman, coauthor of the study, who is at Johns Hopkins University.

Despite the tantalizing link between PFOS and PFOA that appears to be emerging from biomonitoring studies, Calafat points out that modeling exposure through biomonitoring data is almost impossible because of too many unknowns. “Even the fate of these chemicals in the body is still too unknown. That is why we need studies that combine biomonitoring with careful analysis of sources,” she says.

Such a study is just beginning in Canada. The Chemicals, Health, and Pregnancy Study aims to find out whether perfluorinated chemicals and brominated flame retardants have an influence on thyroid hormone levels during pregnancy—an important question because thyroid hormones help to control fetal brain development.

The study, coordinated by Ph.D. student Glenys Webster at the University of British Columbia, will monitor levels of the contaminants and thyroid hormones in 150 pregnant women from the Vancouver area. In addition, scientists will measure contaminants in indoor air, clothes-dryer lint, and outdoor air. They’ll also be asking the women questions about the food they eat and other aspects of their lives. After the babies are born, the scientists will collect cord blood. Currently, no food analyses are planned.

It’s ironic that scientists know more about these chemicals in the Arctic than they do in our own backyards and houses, says Kannan. “There is a pressing [need for] funding for studies to look at human exposure pathways, including foodstuffs,” he says. —REBECCA RENNER