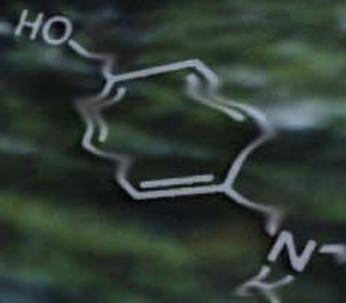


Analyzing the **Ignored Environmental Contaminants**

**The U.S. Geological Survey reports
some of the first monitoring data on
pharmaceuticals and other emerging organic
wastewater contaminants in U.S. streams.**

BRITT E. ERICKSON





As analytical chemists develop new tools for detecting organic wastewater contaminants, the number of compounds they find in the environment continues to grow. Low levels of reproductive hormones, steroids, antibiotics, and numerous other prescription and nonprescription drugs, as well as some of their metabolites, have been detected in European waters and, more recently, in U.S. streams. Along with pharmaceuticals, products used in everyday life, such as detergents, disinfectants, fragrances, insect repellants, fire retardants, and plasticizers, are turning up in aquatic environments.

Because little is known about the toxicity of these emerging contaminants at low levels and on non-target organisms, it is difficult to predict what health effects they may have on humans and aquatic organisms. “There is so little known about even the potential for effects from these substances in the environment, [let alone] real effects,” says Christian Daughton, chief of the Environmental Chemistry Branch at the U.S. EPA’s National Exposure Research Laboratory in Las Vegas, Nev., who has developed an extensive Web site (1) to catalyze research on pharmaceuticals and personal care products in the environment. For the most part, these substances are not bioaccumulative, but even if they do break down rapidly, their continual input into the environment gives them a persistent quality.

Pharmaceuticals and other everyday products have probably been in the environment for as long as they have been in use, but only recently have analytical methods been developed to detect them at the low levels—less than 1 microgram per liter ($\mu\text{g/L}$)—typically found in the environment. Most of the data on these substances in the environment have come from Europe, and until recently, little has been known about the prevalence of such compounds in U.S. waters. Researchers at the U.S. Geological Survey (USGS), however, have been working to change that.

USGS begins monitoring

In the March 15 issue of *ES&T* (pp. 1202–1211), Dana Kolpin and his USGS colleagues report some of the first monitoring data in the United States for these emerging wastewater contaminants. The study is the first in a series of USGS reports on the topic and looks at 95 contaminants from industrial, human, and agricultural wastewater sources, in 139 U.S. streams during 1999–2000. Data from the stream study are available on the Web in a companion USGS Open-File Report (2).

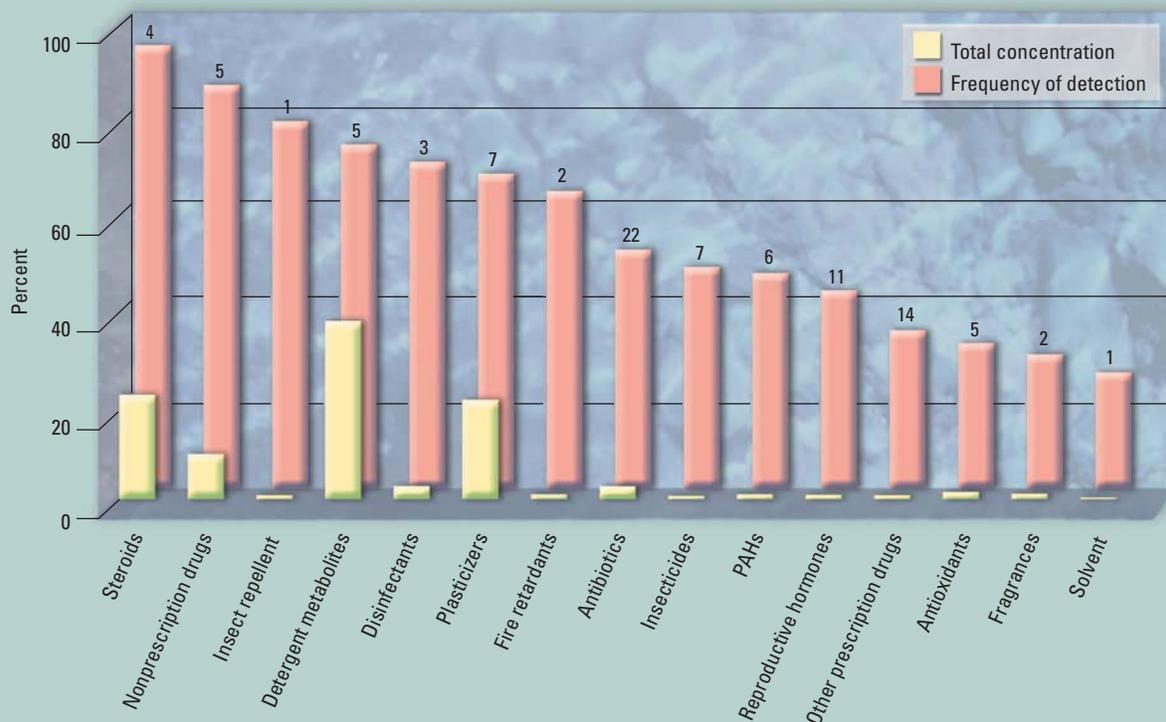
For the most part, the USGS stream study focuses on sites susceptible to contamination, such as those downstream of urban areas and livestock production. However, approximately eight less developed sites were also chosen to obtain data “on the other end of the spectrum”, says Kolpin, a hydrologist who organized the sample collection. In the less developed sites, the researchers found a lot fewer compounds, at lower concentrations, but there were a few things that turned up, including caffeine and the active ingredient in antibacterial soap, triclosan. “It is hard to get totally away from any human activity,” says Kolpin.

The results of the study should not be considered representative of every stream in the United States, emphasizes Kolpin, because it is biased toward streams where contamination is likely. Nonetheless, numerous

FIGURE 1

Organic wastewater contaminants by general use category

Emerging organic contaminants in U.S. streams, as reported by the U.S. Geological Survey, can be broken down into 15 categories. Orange bars show frequency of detection, and yellow bars show the percent of the total measured concentration. The number of compounds in each category is shown above the orange bars.



Source: Adapted from Kolpin et al. (*Environ. Sci. Technol.* 2002, 36, 1202–1211).

compounds were detected in most of the streams that were sampled. As shown in Figure 1, the most frequently detected compounds included steroids, insect repellent, caffeine, triclosan, the fire retardant tri(2-chloroethyl)phosphate, and the detergent metabolite 4-nonylphenol. Concentrations of individual compounds were typically much less than 1 µg/L. Three classes of compounds—detergent metabolites, plasticizers, and steroids—had the highest concentrations.

“What was unusual was that we found as many compounds as we did,” says Kolpin. Although they anticipated finding mixtures, the researchers were surprised to find as many as 38 of the 95 targeted compounds in a single water sample. The average number of compounds in a given sample was seven. Such complex mixtures present great challenges to toxicologists. Little is known about the individual toxicity of these compounds, let alone potential interactive effects, such as synergism or antagonism.

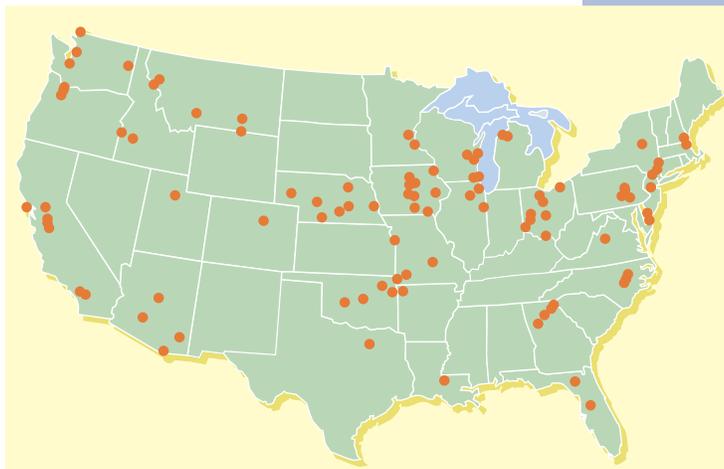
The USGS stream study provides a single snapshot of how prevalent these emerging contaminants are at multiple sites, but it does not address the temporal aspect. “We thought it would be better to take one sample at a lot of sites, rather than sample a lot of times at a smaller set of sites,” says Kolpin. Contaminants like pesticides are known to vary seasonally, so the next step is to look at the concentrations of these emerging contaminants over time. Such studies will give the researchers a better idea of the fate and transport of the contaminants, as well as help pinpoint their primary sources.

Future USGS reports will include groundwater and source water studies, and a follow-up stream report will be published that takes a closer look at land use, comparing, for example, what was found at agricultural versus industrial sites, says Kolpin. In the stream and groundwater studies, not all sites were sources of drinking water. So last summer, with money from the EPA, USGS researchers sampled about 80 sites that were all drinking water sources. The source water study targets nearly the same suite of compounds as the stream study, with a few additional compounds. Data from that study have yet to be published.

Limited analytical methods

When USGS began discussing the topic of pharmaceuticals and other organic wastewater contaminants in the environment at an internal workshop in September 1998, there were “limited to no current methods for looking at these emerging compounds,” recalls Kolpin. The research chemists at the meeting each took a particular class of compounds, such as hormones or antibiotics, and set out to develop analytical methods. “We were sending them water samples at the same time they were developing methods,” he says. For some of the compounds, particularly the antibiotics, the USGS researchers used European methods as a starting point. Altogether they developed five new analytical methods, which are described in the *ES&T* paper.

There were a few compounds, including roxarsone, an arsenic-containing feed additive used to promote growth in poultry, polybrominated diphenyl ethers, which are found in flame retardants, and the



The U.S. Geological Survey monitored 139 streams for the presence of a variety of pharmaceuticals and other organic wastewater contaminants. Site locations are shown in the map above.

antibiotic amoxicillin, that the USGS researchers wanted to look for, but they did not have good analytical methods. Although methods do exist for analyzing each of those compounds individually, the key is to develop methods in which 20–30 compounds can be determined in a single analysis, explains Kolpin. “If each compound had its own method, it would be so inefficient and expensive,” he says.

The 95 targeted contaminants in the USGS stream study were chosen from a large number of potential compounds “based on usage, toxicity, potential hormonal activity, and persistence in the environment,” the researchers report in the *ES&T* paper. “But ultimately, the bottom line was, did it work with the method being developed,” says Kolpin.

Picking priority pollutants

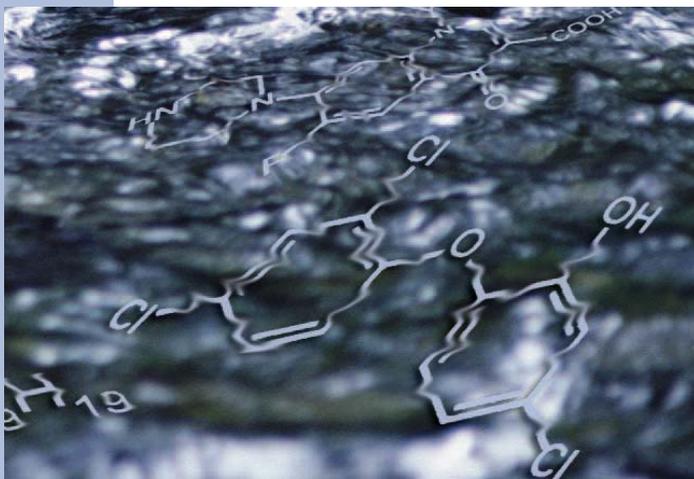
When it comes to deciding which of these emerging organic wastewater contaminants to monitor, the situation is remarkably reminiscent of the mid-1970s. At that time, as a result of a lawsuit, EPA had to decide which compounds, from a list of thousands of industrial wastewater pollutants, to regulate. In the end, 129 so-called priority pollutants were chosen. They were called priority pollutants rather than toxic pollutants because, much like today, there were few toxicological data available, according to Bill Telliard, director of analytical methods for EPA’s Office of Water.

In the 1970s, EPA based its decision on the availability of reference standards, how much of a compound was manufactured, and in how many locations the compound was found, recalls Telliard, who was a key player in the priority pollutant decision-making process. When it came to deciding where to set the limits for the 129 pollutants, “for the most part, it came down to method detection limits,” says Larry Keith, who developed gas chromatography/mass spectrometry (GC/MS) methods for semivolatile organic compounds in the 1970s. Most organics could be reasonably analyzed by GC/MS at the 10-ppb level in water, so that is where the limit was set, he says.

“For so long, our research priorities have been focused on the compounds that we counted as priority pollutants,” says Lynn Roberts, a professor of environmental chemistry at Johns Hopkins University’s Department of Geography and Environmental Engineering. Roberts, like many other researchers, is now shifting her attention to these emerging organic contaminants that have largely been ignored for many years.

Roberts’ group is computing the usage of the top 200 human prescription drugs in the United States, in order to predict their environmental concentrations and hence prioritize analytes for their own method development efforts. “We are trying to take the approach of looking for drugs that, by virtue of their likely abundance in the environment and their likely human or aquatic toxicity, could represent an environmental problem,” she says.

Usage data for pharmaceuticals and other emerging organic contaminants, however, are difficult to obtain, because a lot of it is proprietary. To compute usage, Roberts’ group uses two different approaches—one based on the number of prescriptions issued for a particular drug and the other based on sales. There is not perfect correspondence between the two methods. “We feel the sales results are likely to be more reliable, but they may not include many large-volume generic drugs,” says Roberts. “Estimating usage from the number of prescriptions issued is fraught with more uncertainty because one drug can be prescribed for several purposes—a low dose for one purpose and a high dose for another purpose,” she explains. In addition, the duration of prescriptions varies.



European researchers began looking for pharmaceuticals and other emerging organic contaminants in the environment several years before U.S. researchers. Thomas Ternes of the EWSE Institute for Water Research and Water Technology in Wiesbaden, Germany, began monitoring for pharmaceuticals in German waters in 1994. His list of targeted compounds was based on the quantity of a drug that was manufactured (>10 tons/yr in Germany), and availability of analytical methods and reference standards. “For most of the human pharmaceuticals, we have no risk assessment and no ecotoxicological data. So you have

no chance of predicting effects,” he says. Ternes and his colleagues are currently trying to develop new treatment techniques for removing pharmaceuticals from wastewater and drinking water, using new combinations to get maximum removal.

Environmental risk assessment

One of the differences between the European Union and the United States is that when it comes to environmental risk assessment, the Europeans tend to use more precaution. In a 2001 discussion paper (3), the European Agency for the Evaluation of Medicinal Products proposes that an environmental risk assessment be required for human-use medicinal products, if the crude predicted concentration in surface water is >0.01 µg/L.

In the United States, environmental risk assessments are required for new human-use drugs if the predicted concentration at the point of entry into the aquatic environment is ≥1 µg/L. That level was set in 1997, when the U.S. Food and Drug Administration (FDA) revised the National Environmental Policy Act of 1969 to reduce the number of environmental impact statements and risk assessments it received (4).

FDA chose the 1 µg/L level because there weren’t any known effects that occurred under 1 µg/L in historical toxicity data submitted to the agency as part of environmental assessments. Effects data typically include 1–3 acute toxicity studies in aquatic organisms, says Nancy Sager, associate director of the Office of Pharmaceutical Science in FDA’s Center for Drug Evaluation and Research. “The end points we look at are no-observed-effect concentration and EC₅₀ or LC₅₀,” she says. LC₅₀ is the concentration that is lethal to 50% of the test organisms, and EC₅₀ is the concentration that is expected to cause one or more specified effects in 50% of the test organisms.

The tests are suited for acutely toxic substances, and different mechanisms of action may be unmasked at low exposure levels, says EPA’s Daughton. There really aren’t any tests that are run for the more subtle effects, like behavioral changes, he says. For example, selective serotonin reuptake inhibitors, which are drugs commonly prescribed for depression, eating disorders, obsessive compulsive disorder, panic disorder, and premenstrual syndrome, “are known to affect spawning behavior and many other behaviors in fish and all sorts of aquatic life,” says Daughton. “If you start affecting serotonin levels, there is a potential for all sorts of things to happen.” But there are no monitoring data to show whether any of them occur in the environment, he adds.

“It’s dangerous to try to set fairly high arbitrary cutoffs as triggers for environmental risk assessments because there are substantial class-to-class variations in drugs’ ability to elicit biological responses,” says Roberts. An alternative might be to set cutoffs within different therapeutic classes, she says. But even within such groups, drugs can act in very different ways, with potentially different biological receptors and chemical potency. “Perhaps this should argue for more stringent cutoffs than 1 µg/L, such as the EU’s proposed cutoff for triggering environmental assessments,” she says. “Concentration is only part of it,”

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—Lynn Roberts, Johns Hopkins University

agrees Daughton. "You have to know the potency as well. Some of these genotoxic drugs are worrisome at any measurable concentration," he says.

Metabolites and degradation products

To understand the full picture, we need to look at both the parent compounds and their degradation products, says USGS's Kolpin. "In groundwater, pesticides are known to transform into compounds that are much more persistent and mobile than the parent compounds," he says. Sometimes, these breakdown products are less toxic, but other times, they are just as toxic or more toxic than the parent compound. In general, human drugs are metabolized to more polar compounds, says Ternes. "The more polar metabolites pass through water treatment plants with high probability," he says.

"Although EPA hasn't yet included pharmaceuticals [or their metabolites] on its list of potential new drinking water contaminants, the agency is starting to consider herbicide degradates," says Roberts. Many herbicide degradation products seem to have equivalent toxicity to the parent herbicide, she says. Metabolites and degradation products are difficult to monitor because there are no reference materials for most of them. Roberts and her group have been synthesizing their own reference materials for many previously unstudied herbicide degradation products. When they started looking for such compounds in the environment, not surprisingly, they found many of them. "As any analytical chemist knows, what you see depends on what you look for," she says.

Tracers

Even if these emerging organic contaminants turn out not to be health threats, they could end up serving as environmental tracers. The presence of caffeine, for example, indicates there has been some sort of human input, says Kolpin. USGS is working on a collaborative effort with EPA to see if any of these compounds are good chemical indicators of fecal waste, he says. Traditionally, bacterial indicators, such as *Escherichia coli* and *Enterococci*, have been used to test water quality at bathing beaches. These bacterial indicators, however, require at least 24 hours to obtain data, and they do not discriminate between animal and human fecal sources. In addition to caffeine, the researchers are examining the use of other pharmaceuticals and detergent components, such as surfactants and fluorescent whitening agents, as indicators of human fecal material.

Pharmaceuticals and other emerging contaminants may also help geologists date sediments. "Each compound has an actual date when it was introduced into commerce. So if you find it in a sediment, you know that it hasn't been there longer than a certain date," says EPA's Daughton. "And likewise, some com-

pounds are removed from the market, so you have a date when it couldn't have been introduced to the environment," he adds.

Future steps

Although most of these emerging organic contaminants have low affinity for sediments, based on their physical and chemical properties (e.g., solubility and octanol-water partition coefficient), the USGS researchers believe some compounds will be underestimated by monitoring only aquatic environments. "Antibiotics, in particular, the tetracyclines and fluoroquinolones, are used very heavily, but we didn't find them all that much in water," says Kolpin. "We need to follow up not only with more parent compounds and degradates in water, but also [with] these same sets of compounds in the sediment phase," he says.

Many believe that of all the emerging contaminants, antibiotics are the biggest concern, because of the potential for antibiotic resistance. "There is no control on the fate of antibiotics or the resistance gene," said Stuart Levy of Tufts University School of Medicine in Boston, at a Forum on Emerging Infections at the National Academy of Sciences in early February. "We need to examine what happens to the drugs post-therapy, in soils and streams," said Levy. He posed the question: Could there be such a thing as a self-destructive antibiotic in the future—a drug that does its work and self-destructs?

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