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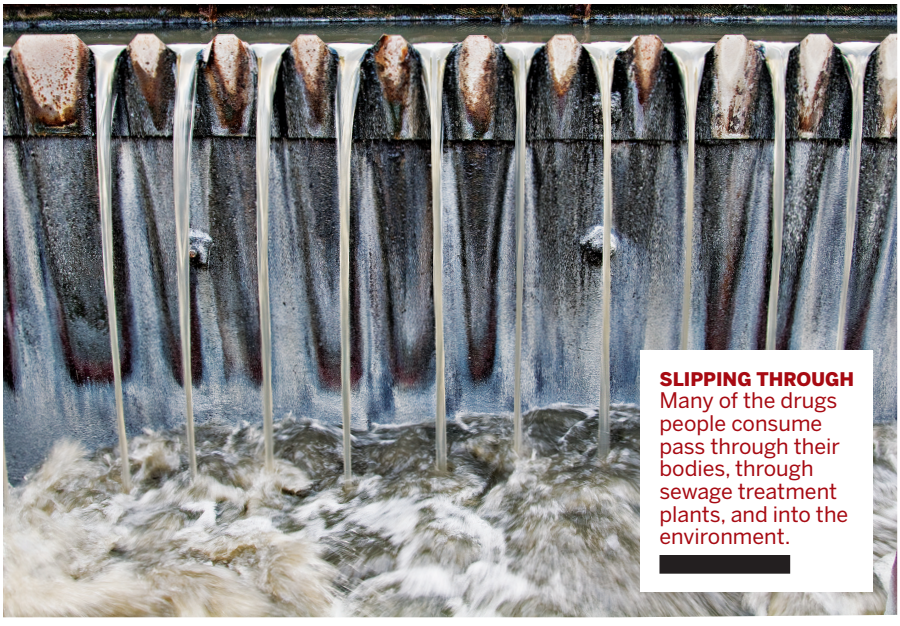


SLIPPING THROUGH Many of the drugs people consume pass through their bodies, through sewage treatment plants, and into the environment.

DRUGS IN THE ENVIRONMENT

Stakeholders consider ways to reduce the **IMPACT OF DRUGS** that get past sewage treatment plants and into nature

SARAH EVERTS, C&EN BERLIN

WHEN YOU SWALLOW A PILL, chances are you're anticipating the drug's effects on your body, not thinking about its final destiny. Yet the pharmaceuticals we consume, as well as their metabolites, percolate through our bodies, get flushed down the toilet, and end up in the environment.

Since the late 1990s, a steady trickle of ecological toxicity data about the fate of drugs in the environment has raised alarms among some scientists and, more recently, members of the general public. The concern is that some of the nearly 10,000 drugs currently on the market are not passive, benign travelers in the environment but instead are bioaccumulative, persistent, and toxic to wildlife—and possibly humans.

Although hormones such as synthetic estrogens and progesterones have been found to accumulate in fish at levels that disrupt reproduction, a vast majority of other drugs remain unmonitored and their long-term impacts to sensitive organisms untested (C&EN, Feb. 25, 2008, page 13).

All sorts of pharmaceuticals have been detected in the environment, from ibuprofen to Zoloft, "but we don't have a lot of information that connects their presence in the environment to effects in animals," says Duane B. Huggett, an environmental researcher at the University of North Texas. "With currently available data, the weight of evidence is that hormonally active compounds are an issue. But we need a coordinated effort to get data on a wide range of pharmaceutical classes before we know if there is a wider problem."

Until more data come in, some scientists say, it is presumptuous to take action on a problem that might not be widespread. Yet among those who advocate taking a precautionary approach, there is a growing dialogue about what might be done to minimize the impact of pharmaceutical drugs in the environment.

One of the easiest ways to reduce the impact of drugs in the environment would be to take a so-called benign-by-design approach, in which a drug lead's architecture would be examined for persistence, toxicity, or bioaccumulation before it went into optimization, says Klaus Kümmerer, a chemist at the University of Freiburg Medical Center, in Germany, who is developing criteria for this early consideration. "You've got to start thinking about the environment at the very beginning. It makes no sense to do the assessment after you've spent millions of dollars in development," he notes.

The question is whether medicinal chemists—who are already pruning their leads on the basis of considerations such as solubility, bioavailability, genotoxicity, pharmacokinetics, and carcinogenicity—are willing to add even more variables to their no-go list. "When I speak to our medicinal chemists about considering a benign-by-design approach, they say there's just no way they are going to further triage any leads," says a sustainability officer at a major pharmaceutical company, who requested anonymity.

David Taylor, a consultant for the pharmaceutical industry who recently retired from AstraZeneca, says that with upper management of drug companies fixated on dwindling pipelines, "there is precious little driving force" for benign-by-design drug discovery.

Getting the industry to design more environmentally friendly drugs is "going to take a combination of a carrot and regulations," adds Berkeley W. (Buzz) Cue Jr., a pharmaceutical company consultant who established Pfizer's green chemistry initiatives over a decade ago.

In the U.S., the Food & Drug Administration currently requires that new drugs be tested for their ability to harm or kill aquatic animals. These are short-term survival tests that use high concentrations of the drug. Many researchers concerned with the environmental impact of drugs believe the predictive abilities of such tests are limited because harmful effects on wildlife would likely not be short-term but would instead occur over long periods, even generations, of low-dose drug exposure.

THE EUROPEAN Medicines Agency (EMEA), which has a role similar to FDA's, has already taken a few regulatory steps to encourage production of drugs with improved end-of-life environmental profiles. For example, in December 2006, the agency expanded environmental testing requirements for new drug approvals. EMEA now requires pharma companies to submit low-dose drug exposure data on the ability of invertebrates to reproduce, on the impact on fish growth and develop-

& MORE ONLINE Read more about benign-by-design drug development by clicking on this article at *C&EN Online,* www.cen-online.org.

ment, and on the growth rate of algae.

"EMEA is on the right track," North Texas' Huggett says, although he adds that there is room for improvement. One way to make things better, says Joakim Larsson, an environmental scientist at the University of Gothenburg, in Sweden, is to require evaluations of the ability of fish to reproduce when exposed to drugs. "The standard tests required today would not have been able to identify the true potency of the hormones ethinylestradiol and levonorgestrel," he says. "We know how potent these pharmaceuticals are because of independent research, not because of the regulatory tests performed."

Although EMEA expects more ecotoxicity data from firms when they are applying for a new drug's approval than before, the data cannot be used to deny a human drug's approval—although it can be used to deny approval of veterinary medicines.

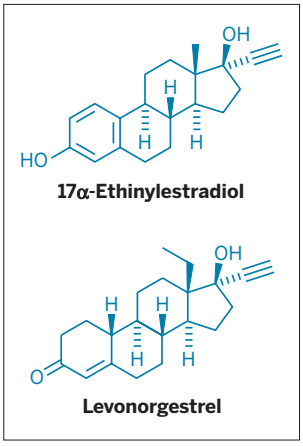
"The real question is, 'What about the 10,000 drugs already approved?' which are by far the most abundant drugs in the environment," Taylor says. Even if governmental regulations become more stringent, there is little incentive for drug companies to go back and tweak drug structures to ameliorate environmental effects. The altered drugs would have to go through costly clinical trials and the regulatory approval process all over again.

To address the challenge of getting pharma companies to speed up their assessment of a drug's eventual role in the environment, the delegates at the 2nd International Conference on Sustainable Pharmacy in Osnabrück, Germany, held in February, broke into groups to brainstorm possible regulatory incentives. The conference was attended by representatives from the pharmaceutical, academic, nongovernmental, and governmental sectors.

One suggested regulatory change was to offer patent prolongation for newly approved drugs with better environmental profiles. Delegates also suggested that FDA's priority review vouchers—which are given to companies that develop drugs for orphan diseases (conditions that affect fewer than 200,000 people in the U.S.)—might also be given to companies developing environmentally safe drugs. The fast-track vouchers could be used for any drug under development by the company—an incentive that might translate into millions of dollars in revenue for a company by bringing a blockbuster drug to market months earlier than would otherwise have been possible.

Incentives and regulations that mandate benign-by-design approaches are normally directed toward drug companies. However, Sweden has initiated a national program that provides doctors with some power to reduce the environmental footprint of drugs they prescribe. The Swedish Association of the Pharmaceutical Industry (LIF) established a database for the ecotoxicity data that companies submit when they seek approval for a drug.

CURRENTLY, the database has entries for more than 1,000 drugs, each of which is rated for potential impacts in the environment on the basis of toxicity, bioaccumulation, and persistence. When prescribing a medication, Swedish doctors can offer their patients information about the potential environmental impact of the prescription options. For treatments for which there are many options—cholesterol-lowering drugs or birth control pills, for example—patients and doctors can choose medications that don't have harmful consequences for the environment.



Another way the general public can help the environment is to responsibly dispose of drugs—which means not pouring them down the drain or flushing them down the toilet. A recent study by Gerard Vollmer of the European Union's Joint Research Centre, in Ispra, Italy, found that some 3% of pharmaceutically active ingredients go down the drain unnecessarily in Germany, amounting to "364 tons per year of avoidable environmental burdens," he says. Germany is a country with a national unused-pharmaceutical take-back program. In the U.S., take-back programs and other policies to help reduce drugs in the environment are only just being established; Texas and Maine are pioneering such programs.

Researchers interested in mitigating the problem of pharmaceuticals in the environment also point to the possibility of dealing with the problem in sewage treatment plants—for example, by adding catalysts that break down wastewater contaminated with excreted drugs. But looking to the sewage treatment stage as a solution to environmentally persistent pharmaceuticals might not be ideal. "You can't count on the fact that sewage treatment facilities will be uniform—or exist—around the world," Freiberg's Kümmerer says.

As discussions continue about how to reduce the environmental footprint of drugs, researchers continue to publish data about the impact of drugs that slip past waste treatment facilities. Earlier this year, selective serotonin reuptake inhibitors in waste treatment effluent were found to accumulate in the brains of fish. In March, researchers discovered that levonorgestrel, a synthetic progesterone found in effluent from waste treatment facilities, could, in some cases, accumulate at four times the human therapeutic dose in fish blood plasma—levels that can impede egg development.

And in preliminary experiments that evaluate the impact of antibiotics in the environment, Larsson has found that downstream of treated effluent from pharmaceutical production facilities in India, where antibiotics are released, there is an increase in antibiotic resistance genes among bacteria in the waterbed sediment.

Whether the concerning effects of hormones, selective serotonin reuptake inhibitors, and antibiotics are shared by other drugs cannot be determined until better monitoring of such effects becomes feasible, Larsson says. "The question is, 'Who should do the monitoring, and who should pay for that monitoring?' There's a lot of mistrust among the different players about pharmaceuticals in the environment," he says. If pharma companies were to acquire the data, then nongovernmental organizations might not believe it. Likewise, if NGOs obtain the data, pharma might not believe it, he says. Academics and regulators don't generally have sufficient funding to do grand-scale monitoring, Larsson adds.

"Any monitoring effort has to be a multistakeholder effort," Huggett says. "Right now there are a lot of people doing different things. There's no coordinated effort. Everybody needs to come to the table and work together." Perhaps professional nonprofit societies such as the Society of Environmental Toxicology & Chemistry and the American Chemical Society could act as matchmakers, he suggests. "The future," he adds, "is dependent on how well we can all collaborate as a group." ■