

Pharmaceuticals in the environment

JEFFREY T. SHERER

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Pharmaceuticals are the major method of treating human disease in Western medicine, with hundreds of tons being produced, dispensed, and consumed annually. Use of pharmaceuticals in veterinary medicine is also common. After administration, or if they are discarded by patients or health care professionals, many drugs and their metabolites make their way into the environment through a variety of mechanisms. The past few decades have brought increasing concern about the presence of these pharmaceutical compounds in the environment and their potential effects on human and environmental health.

In August 2004, the British Broadcasting Corporation reported on the presence of fluoxetine in drinking water in the United Kingdom.¹ The story was subsequently commented on by major media outlets in the United States and created a minor stir among the public.² While the presence of prescription drugs in the environment may be initially startling, little reason to panic exists. The effects of certain key classes of drugs, such as hormones, antidepressants, and antibiotics, on nonhuman species are concerning and should be further investigated, but no direct harm to humans has been reported or is likely. Pharmacists and other health professionals should reassure the public that only minute concentrations of pharmaceuticals are detectable in the environment and should help to minimize the presence of drugs in the environment by

encouraging the appropriate disposal of unwanted medications.

Many reasons for the increasing awareness of pharmaceuticals in the environment exist. The burgeoning human population, coupled with growing demands on existing freshwater supplies due to increased agricultural use, is requiring that larger amounts of wastewater be treated and reused. This is particularly true in Europe, where a high population density necessitates greater use of treated water.³ Because existing wastewater-treatment methods are inefficient at removing many pharmaceuticals, more consumers are being exposed to drugs that remain in treated water. Additionally, the rise in per capita medication use in the United States and western Europe has resulted in more pharmaceuticals being excreted into the environment.

In the United States, the Office of Research and Development (ORD) of the Environmental Protection Agency (EPA) has taken the lead in monitoring this issue and since April 2000 has maintained a Web site containing a large amount of useful information.⁴ The ORD term "pharmaceuticals and personal care products" includes prescription drugs, nonprescription medications, drugs used in veterinary care, neutraceuticals, sunscreens, perfumes, and other similar products.

This commentary focuses primarily on prescription and nonprescription drugs used in humans, although, because many medications are used in both humans and animals, determining their origin is generally not possible when drugs are detected in the environment. Excipients and propellants contained in pharmaceutical preparations are also not discussed, as virtually no data exist regarding their presence in the environment or their potential health ramifications.

Pharmacokinetics. The absorption, metabolism, and elimination characteristics of drugs in general are relevant when considering the introduction of drugs into the environment. The majority of drugs used in humans and animals are administered orally for convenience. To be absorbed from the gastrointestinal tract, drugs must be at least somewhat water soluble, although a certain amount of lipid solubility is needed for penetration of lipid membranes. While drugs may be eliminated from the body by a variety of routes, most are excreted in the feces or urine.

Drugs are most frequently metabolized before they are excreted. Metabolism has two main effects. First, it generally makes the compound less physiologically active. However, many drugs have active metabolites, some of which are more potent than the original or parent drug. Second, metabolism makes lipid-soluble drugs more water soluble and hence more easily eliminated by the kidneys.

Drugs usually go through two metabolism phases. Phase I reactions

JEFFREY T. SHERER, PHARM.D., BCPS, CGP, is Clinical Assistant Professor, College of Pharmacy, University of Houston, 1441 Moursund Street, Houston, TX 77030.

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are oxidation-reduction reactions in which the chemical structure of the molecule is altered. These are generally followed by phase II reactions in which the drug or metabolite is conjugated to a water-soluble molecule, such as through glucuronidation or sulfation. In addition to increasing water solubility, phase II reactions typically make the substance pharmacologically inert. These two factors, high water solubility and existence of conjugated metabolites, have important ramifications when comparing drugs with other common environmental contaminants.

Differences between drugs and other wastes. Pharmaceuticals in the United States, unlike virtually all other new chemicals, are specifically tested for safety in humans before reaching the market because of the requirement of the Food and Drug Administration (FDA) that they be proven "safe and effective" before they are approved for marketing. While this provides some assurance of safety, it does not preclude the possibility of problems. Studies performed to gain FDA approval are performed with doses resulting in predictable effects over relatively short periods of time and in highly selected populations. The results of exposing a much broader population, including people who may be at particular risk of adverse effects, to the drug at low doses and for prolonged periods are not known at the time of marketing. Also, safety is tested only in a small number of mammalian species; effects on other mammals or nonmammalian organisms are generally not determined.

FDA also requires drug manufacturers to conduct an environmental assessment to be submitted as part of a new drug application and in certain other circumstances if the expected introduction concentration of the drug into the aquatic environment is at least one part per billion.⁵ In practical terms, the amount of active drug expected to be produced over the

next five years determines whether this threshold is reached.

Unlike most other environmental pollutants, drugs are specifically designed to be biologically active. Typically, very small amounts—often a few milligrams or less—may exert an overt effect in a typical patient. Because of this potency, the risk of adverse effects in humans and other species may be higher than with substances that are not designed to interact with specific receptors.

Also, most drugs and their metabolites are water soluble and are not stored to a large extent in fat. Because of this, the phenomenon of biomagnification, in which lipid-soluble substances are passed up the food chain in increasing amounts at each step, is not typically an issue with pharmaceuticals. Biomagnification is a major reason why substances that are present in the environment in minute quantities, such as DDT or certain industrial chemicals like the polychlorinated biphenyls, may be found in much larger concentrations in living organisms than in the surrounding environment.

Pharmaceuticals in the environment. Most pharmaceuticals present in the environment are believed to arrive there by discharge into municipal sewage systems after excretion of drugs and metabolites via the renal and fecal routes. However, medications that are not consumed are often disposed of by flushing them into the sewage system. This bypasses the body's metabolic pathways that generally make drug molecules less physiologically active and more polar.

In less urbanized settings, sewage may be released into the environment with no treatment or after passing through a septic system. Other routes of drug entry into the environment include animal manure and urine, runoff from landfills, and industrial waste.

Several studies have investigated the presence of pharmaceuticals in the environment in Europe. In the

most highly publicized of these, researchers sampled drinking water, river water, and river sediments at nine locations in Italy and tested for the presence of 16 drugs or metabolites at each site.⁶ Thirteen of the 16 drugs were detectable in river water from at least one location, while 7 were detectable in river sediment and only 3 in drinking water. Among the substances present in measurable concentrations were diazepam, atenolol, erythromycin, lincomycin, oleandomycin, ibuprofen, and cyclophosphamide. When detectable at all, they were present in nanogram-per-liter concentrations, which are far below those necessary to exert their known effects in humans.

The most comprehensive information about pharmaceuticals in the environment in America comes from a group at the U.S. Geological Survey.⁷ Over a two-year period, the researchers tested for 95 organic compounds, including several drugs and metabolites, at 139 stream sampling sites. Commonly discovered drugs included an erythromycin metabolite (found in 22% of samples), lincomycin (19%), sulfamethoxazole (19%), trimethoprim (27%), caffeine (71%), and acetaminophen (24%). Various forms of estrogen and corticosteroids similar to cortisol were also identified at several sites. Overall, 80% of the streams tested positive for at least one drug, and a median of seven substances were found at each site. Similar to what was observed in Italy, most drugs were present in concentrations of nanograms per liter, or at least two orders of magnitude less than the concentration necessary to produce overt effects in humans.

Effects of pharmaceuticals on the environment and human health. At present, the greatest concern about pharmaceuticals in the environment is their potential effects on small aquatic organisms. This is mainly because short generation times mean multiple generations are easily exposed. Furthermore, when water is

prepared for human consumption, it is treated, removing additional traces of pharmaceuticals and thus further limiting human exposure. Concentrations in drinking water are almost invariably lower than those in the environment.⁶

Research on the environmental hazards of pharmaceuticals has largely focused on antibiotics and hormones. The release of antibiotics into the environment exposes massive numbers of microorganisms to sublethal concentrations, allowing for the development of resistance. Also, because the digestive tracts of humans and other animals contain huge amounts of bacteria that were not killed by exposure to administered antibiotics, discharging this waste into the sewage system releases these resistant organisms directly into the environment.

The effects of hormones, particularly estrogens, have been studied in a variety of species. Evidence exists that high concentrations of estrogens in aquatic environments can cause feminization of male fish and may cause behavioral changes in both sexes.⁸ What is less clear is whether these hormones are present as the result of excretion of pharmaceuticals into the environment or are present naturally, since endogenous hormones and metabolites are typically eliminated via the urine.

In terms of other specific drugs or drug classes, several researchers have investigated the effects of very low levels of pharmaceuticals on various nonhuman species. For example, verapamil impairs the efflux pumps by which certain aquatic microorganisms move toxic substances outside the cell.⁹ This could potentially increase the toxicity of otherwise innocuous substances that the organisms could easily handle when the drug is not present. In addition to their antibacterial effects, certain antibiotics may kill algae.¹⁰ Fluoxetine affects spawning behavior in both male and female mussels at very low

concentrations.¹¹ Fluvoxamine is one of the most potent bivalve spawning inhibitors ever discovered. Even a drug as commonplace as acetaminophen may have detrimental effects. Very low concentrations of acetaminophen cause immobilization of *Daphnia* species (water fleas), which are an important source of food for freshwater fish. Diazepam has similar effects.¹²

Pharmaceuticals identified in the environment are generally present in concentrations two or more orders of magnitude below those required to exert their known effects in humans. This makes direct toxicities unlikely but does not rule out the possibility of more subtle, longer-term changes that are harder to detect. Exposure to multiple agents over decades may have previously unseen effects, particularly on tissues other than those on which the drugs were designed to act. Currently, no definitive evidence exists linking the presence of drugs in the environment to human health risks. However, much work remains to be done in this area.

One particular area of concern is substances that have been termed endocrine disrupters, such as compounds acting as agonists or antagonists at estrogen, progesterone, or androgen receptors. Colborn et al.^{13,14} argue that dozens of compounds present in the environment alter fetal development. Among the substances mentioned are the prescription drugs ketoconazole and lindane. Clearly the relationship between endocrine disrupters that are pharmaceuticals or their metabolites and the effects on fetal development requires further study.

Fate of pharmaceuticals in the environment. Existing sewage treatment plants do a relatively poor job of removing pharmaceuticals, and none are specifically designed with this goal in mind. The best available data come from Germany, where the removal of 14 drugs by a sewage

treatment plant was quantified.¹⁵ For most of the drugs tested, the facility removed about half of the original concentration, but this ranged from only 7% for carbamazepine to 96% for propranolol.

While this information is useful, it should be interpreted cautiously. First, sewage treatment plants are not uniform in design or operation, so it should not be expected that similar results would be found at other plants. Second, only the concentrations of parent drugs were measured. Pharmacologically active metabolites, or inactive metabolites that could be converted back to active drugs by microorganisms inside and outside the treatment plant, were not measured. Finally, conditions such as the amount of rainfall or changes in water demand could affect drug removal by altering the rate at which water enters or leaves the facility. One thing is clear, however: Sewage treatment plants do not purify treated water with respect to pharmaceuticals. By law, sewage treatment plants are required to test for and remove only a small number of substances; no drugs are included in these regulations.

Even though almost all drugs are eventually broken down by light, microbial, or other processes, a continual release of additional amounts into the environment leads to what is known as pseudo-persistence. One interesting phenomenon that has been observed is the reactivation of drug metabolites by microorganisms. As mentioned previously, many drugs are conjugated by the body to make them more water soluble and less pharmacologically active. Some bacteria in sewage treatment plants have been shown to cleave the portion of the metabolite that was added during conjugation, thus converting it back to active drug.

An additional interesting area of research on the fate of drugs in the environment involves pharmaceuticals that become trapped in the

sludge layer at sewage treatment plants. This sludge is often used as fertilizer, and it is possible that drugs are eventually taken up by the plants the sludge is used to fertilize. Fortunately, the lack of lipid solubility of most drugs and metabolites generally prevents biomagnification.

Minimizing pharmaceuticals in the environment. The release of pharmaceuticals into the environment after they are eliminated from human or animal bodies is inevitable. In the United States, both EPA and FDA regulate waste pharmaceuticals and other byproducts that result from drug manufacture, so only limited quantities reach the ecosystem by this method. One area in which consumers and health care professionals need to be educated is in the appropriate disposal of unwanted medications.

Many individuals flush expired or unneeded medications down the toilet. While this method has some advantages, such as keeping the drugs away from rummaging children and pets, it is no longer preferred because of the inability of sewage treatment plants to efficiently remove pharmaceuticals. The best method of disposal is taking unwanted drugs to household hazardous waste collection sites or destroying them in medical waste incinerators.^{16,17} Many households do not have access to the latter, however, and drugs that are controlled substances cannot be legally transferred to anyone other than the person for whom the prescription was written. In some cases, obtaining the assistance of law enforcement officials in disposing of controlled substances may be appropriate. If disposal by one of these methods is not possible, making the drugs unpalatable by mixing them with cat litter or a similar substance and putting them in a sealed container in the trash is acceptable.^{18,19}

Discussion. Although the direct threat to human health is probably small, publicizing the presence of

even tiny amounts of prescription medications—particularly psychoactive agents, hormones, and cytotoxic agents—could elicit an exaggerated response from the public.^{1,2} The ability to understand risks, particularly those due to environmental issues, is often poor among even otherwise well-educated citizens.

The limited data on this topic are published primarily in the environmental rather than health science literature. While it appears to be an environmental rather than a human health concern at this point, more information published in the mainstream medical literature would be beneficial, as it would draw attention to the possibility of the problem worsening in the future. Also, health professionals should be aware of relevant issues related to drug disposal so that they may get rid of unwanted drugs safely and advise their patients to do the same.

Pharmacists should take particular notice of how drugs are being disposed of. State and local regulations vary, but clearly it is desirable to carefully consider how waste and expired pharmaceuticals are handled. Pharmacists who work in health systems should collaborate with those responsible for waste management at their facilities to devise a policy to determine which medications and parenteral solutions may be drain-wasted and which require more environmentally friendly disposal.

In summary, while many pharmaceuticals are present in the aquatic and soil environments in measurable concentrations, the amounts present are too low to exert overt effects on humans. Whether long-term, low-level exposure to drugs results in long-term adverse effects is unknown, and the multitude of drugs present in the environment makes finding cause-and-effect relationships nearly impossible. The primary threat of drugs in the environment currently appears to be to aquatic organisms. Still, it is refreshing that this

issue is being investigated before large environmental or health effects are seen. Concentrations of pharmaceuticals in the environment can be monitored over time, and, with luck, any adverse effects on the health of humans and other species can be recognized sooner rather than later. At present, far more questions than answers exist.

Conclusion. Pharmaceuticals are introduced into the environment by various routes but currently appear to pose little risk to humans.

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