Drugging the Environment

Humans have spiked ecosystems with a flood of active pharmaceuticals. The drugs are feminizing male fish, confusing birds, and worrying scientists.

By Megan Scudellari | August 1, 2015

In the fall of 2012, PhD student Hendrik Wolschke leaned over the side of a boat on the Elbe River in Northern Germany and lifted a stainless steel bucket from the water’s depths. Pulling it aboard, he set the sloshing bucket next to a pile of empty plastic bottles.
Once he’d filled them with the river water, Wolschke packed the bottles into coolers for transport southeast to the chemistry laboratory of his doctoral advisor, Klaus Kümmerer, at Leuphana University of Lüneburg. There, the bottles joined water samples collected from all around Germany: the North Sea, drainage streams from wastewater treatment plants, even drinking water straight from municipal taps.

Each sample was tested for the most widely prescribed antidiabetic drug in the world—metformin, which treats high blood sugar by suppressing glucose production in the liver. Humans do not metabolize the drug, so within 24 hours of being swallowed, metformin is excreted from the body essentially unchanged.

Because of its high prescription rate—the U.S. alone dispensed 76.9 million metformin prescriptions in 2014—it’s not surprising that the drug is abundant in the environment. Metformin was present in every water sample Kümmerer’s team tested, including tap water, at concentrations exceeding environmental safety levels proposed by an international Rhine River Basin agency by 50 percent. When publishing the results in 2014, Kümmerer and his coauthors concluded that the drug is likely “distributed over a large fraction of the world’s potable water sources and oceans.”

That sounds melodramatic, but he may be right, and the problem is not limited to metformin. Rebecca Klaper and colleagues at the University of Wisconsin–Milwaukee recently measured concentrations of pharmaceuticals in Lake Michigan, where researchers had speculated that any drugs that were present would be highly dilute and not detectable. On the contrary, Klaper’s team found evidence of 32 pharmaceuticals and personal care products in the water and 30 in the lake’s sediment. Fourteen of these were measured at concentrations considered to be of medium or high risk to the ecosystem, based on data from the US Environmental Protection Agency (EPA) and other researchers.

Metformin topped the list, at concentrations of concern even 3 kilometers off the shores of Milwaukee.

Ecologists have long recognized that pharmaceuticals, both unmetabolized drugs like metformin and others that break down into various metabolites, are polluting the environment, but researchers have traditionally focused on just two classes: antibiotics and endocrine-disrupting compounds such as the birth control hormone estradiol. Antibiotics in the environment promote antibiotic resistance in a range of bacterial species, and endocrine disruptors are known to affect development and reproduction in animals.

Metformin was not thought to have either of those effects on animals. But in lab experiments conducted earlier this year, Klaper’s team discovered that male minnows exposed to metformin at concentrations comparable to those of wastewater treatment plants produce proteins typically found only in female fish, develop feminized gonads, weigh less, and have fewer offspring. The antidiabetic is now one of a growing list of drugs that researchers are realizing pose major ecological problems.

“All [pharmaceuticals], by design, are meant to elicit a biological response. We need to know what the environmental consequences are.”

—Dana Kolpin, US Geological Survey

What lies beneath

Pharmaceuticals are ubiquitous in wastewater, deposited primarily from human urine and feces. The active ingredients from leftover pills thrown in patients’ trash or even hospital waste also find their way to waterways, but the contribution of those sources pales in comparison to the share “from all of us,” says Kümmerer.
Currently, the Environmental Protection Agency does not regulate even a single human pharmaceutical in drinking water.

Sewage treatment plants remove some pharmaceuticals from water during basic filtering processes, says Klaper, but many pass through unhindered. Metformin, for example, is stable against common water treatments such as UV light irradiation. And at this point, it is prohibitively expensive to add technologies that can filter out these chemicals.

From sewage plants and landfills, drugs make their way into streams, rivers, lakes, seawater, and even into drinking water. Currently, however, the EPA does not regulate even a single human pharmaceutical in drinking water. An EPA list of pollutants that may make water unsafe, but are not regulated, includes eight hormones and one antibiotic. Metformin is not on the list. “Legislation is not protecting ecosystems at the moment,” says Kathryn Arnold, an ecologist at the University of York in the U.K., where there are also no regulations for pharmaceuticals in water.

Many ecologists believe that should change. Pharmaceutical use in the general population is growing, with sales expected to increase five percent annually for the next five years, so more and more drugs are likely to be entering the environment. Like so-called “legacy” pollutants that have been banned in many countries, including polychlorinated biphenyls (PCBs) and DDT, pharmaceuticals can persist for years, even decades. Pharmaceuticals are designed to maintain their strength and quality on the long route from manufacturer to pharmacy to medicine cabinet, and even sometimes inside the human body. That same stability, unfortunately, prevents many pharmaceuticals from degrading in the environment.

Researchers at Umeå University in Sweden measured concentrations of the widely marketed antianxiety drug oxazepam in sediment cores from the same lake bed deposited over three decades. Based on the sediment samples, they were able to identify the specific year that oxazepam first came on the market, and the amount of drug deposited in newer layers over the years correlated tightly with the numbers of prescriptions. Then, when the researchers measured concentrations in core samples extracted 30 years ago, they found that the older cores and more-recent samples had the same drug levels at the same time depths. Oxazepam hadn’t degraded at all over time, says study author Tomas Brodin, an ecologist at Umeå.

To make matters worse, pharmaceuticals are hard to detect and measure in the environment. Detection methods are improving, however. Early methods used by the US Geological Survey required one liter of water and could identify 15 to 20 compounds, while the latest method measures more than 100 drugs in just a 20-milliliter sample. But scouring for individual agents isn’t enough. Our modern environment contains a swirling mixture of pharmaceuticals, pesticides, industrial by-products, and a plethora of other chemicals. “What’s happening in reality is an exceedingly complex cocktail of compounds,” says Kolpin.

And within that chemical concoction, drugs interact with one another, with bacteria, and with basic environmental elements such as water. Chemical and biological reactions can result in a host of transformation products—new chemicals with new properties. Some bacteria break down metformin, for example, yielding a metabolite called guanylurea, which is also bioactive and stable in the environment. Similarly, the antidepressant enlafaxine (trade name Effexor) degrades into desvenlafaxine (Pristiq), another antidepressant. Such metabolites can sometimes be more toxic than their parent compounds.

“Degradation expands that universe of potential chemicals exponentially,” says Kolpin.

Knock-on effects
At high enough levels, pharmaceutical compounds can be lethal to wildlife. More often, however, drugs have subtle but significant effects on the behavior and development of organisms.

Of the drugs that scientists test for in the environment, an emerging class of interest is selective serotonin re-uptake inhibitors (SSRIs), commonly prescribed for depression and anxiety disorders. “These chemicals are psychotropic. In humans they affect cognition, mood, and behavior,” says Melanie Hedgespeth, a graduate student at Lund University in Sweden. “So if they’re out there, they have potential to also affect behavior in aquatic organisms.”

Last year, Hedgespeth analyzed the effects of a popular SSRI, sertraline (trade name Zoloft), which had previously been detected in water samples and fish tissue in the U.S., Canada, and elsewhere. She spiked tanks full of juvenile perch with three concentrations of sertraline: 120 nanograms per liter (a level detected in wastewater), 89 micrograms per liter, and 300 micrograms per liter. After just eight days of exposure, the fish started eating less, even at high prey densities and at the lowest environmental drug concentration, though the effect at that level was “marginal.”

Hedgespeth hypothesizes that the behavioral change is due to loss of appetite, a recorded side effect of the drug in humans. If such a decline in feeding occurs in the wild, it could impact the reproduction and life span of entire populations of fish, says Hedgespeth. “People tend to focus on mortality, but this could potentially impact fish in the longer term.”

Other research has shown how widespread the ecological effects of pharmaceutical pollutants can be. Every summer from 2001 to 2003, researchers in Canada poured a small amount of 17α-ethynylestradiol, the synthetic estrogen used in many birth control pills, into an experimental lake in northwestern Ontario. They then measured the effects of the hormone on a diversity of aquatic wildlife, including algae, microbes, zooplankton, minnows, trout, and other fish. Over the course of the experiment—the researchers collected data through 2005—the fathead minnow population in the lake nearly crashed due to reproductive failure. The lake trout and white suckers that relied on the minnows for food also suffered, declining in abundance due to lack of food. The minnow’s prey—zooplankton and insects—subsequently flourished.

“Not only were there direct effects on one species, there were direct and indirect effects on multiple species at different trophic levels within the lake,” says Arnold, who edited the special issue of Philosophical Transactions of the Royal Society B in 2014 on pharmaceuticals in the environment that included the study. “It’s clear there are lots of knock-on effects that are difficult to predict with standard ecological risk assessments.”

Pharmaceuticals can also accumulate as they work their way up the food chain, exposing predators to higher levels than those found in the environment. Brodin and colleagues at Umeå found that while oxazepam had no effect on damselfly behavior, it did accumulate in the insects. And when perch ate oxazepam-riddled damselfly nymphs, the fish retained an average of 46 percent of the drug from the insects. The more damselflies they ate, the more the drug accumulated in the fish. In a separate
experiment, the normally shy perch that hunt in schools became considerably bolder after exposure to oxazepam, eating more quickly and leaving their schools more often. “It was a drastic behavioral modification,” says Brodin.

It may be that the drug reduced the perch’s tendency to seek safety in numbers from predation, Brodin speculates. “Perhaps they perceived their environment as less risky.” Interestingly, when no predators were around, the effect was positive for the fish, making them more efficient hunters. But testing such effects in the wild is a difficult thing to do, Brodin notes. While it is easy to measure whether a chemical is deadly to a species, there is rarely an easy way to tell if it is promoting survival, which can also cause significant changes in an ecosystem.

Doped carrion

While most studies on the effects of environmental pharmaceuticals have focused on aquatic species, terrestrial organisms such as birds, worms, and insects can also be exposed to the drugs when they feed on sewage, on fields fertilized with human or animal waste, or on the flesh of livestock treated with drugs. In the late 1990s, for example, tens of millions of vultures began dropping dead around India and Pakistan. First, scientists assumed it was an infectious agent, then an environmental toxin. It was neither. In 2004, they pinpointed the cause: an anti-inflammatory drug named diclofenac. The birds had suffered acute kidney failure after ingesting diclofenac from the carcasses of livestock that had been given the drug to treat lameness and fever. “Vultures in that region were exceedingly sensitive to diclofenac,” says Kolpin. “That’s a classic example of unintended consequences.”

India, Nepal, and Pakistan banned veterinary use of diclofenac, but in 2013, Spain, home to 95 percent of Europe’s vultures, authorized the sale of the drug for use in animals. Wildlife groups immediately called for a full veterinary ban on the drug, and the European Commission asked the European Medicines Agency (EMA) to conduct a review of the risk of the drug. In December 2014, the EMA concluded that vultures and other carrion-eating birds were at risk from diclofenac, but the European Commission has not yet made a final decision on whether it will outlaw the drug. Meanwhile, many more terrestrial species are at risk from countless other pharmaceuticals polluting the environment. Some 10 to 30 percent of the antidepressant fluoxetine (trade name Prozac) is excreted unchanged by humans, and, like many other pharmaceuticals, fluoxetine is environmentally stable. The University of York’s Arnold estimated the concentration that would accumulate in earthworms living in sewage, and then how much of the drug would make it into a bird’s system if half its diet consisted of such worms. Adjusting for body mass, the total amount was equivalent to roughly 5 percent of a human dose of fluoxetine.

Knowing that fluoxetine can cause reduced libido and decreased appetite in human patients, Arnold feared birds might suffer similar effects. “That could have big implications on survival,” she notes. Daily for four months, she and her team fed wild-caught starlings wax worms injected with low doses of fluoxetine. Sure enough, the birds that ingested the drug ate less and at all the wrong times: they snacked throughout the day rather than consuming large meals at sunrise and sunset, the optimal mealtimes for wintering birds. “If you have a harsh winter, [and] you have an animal not feeding heavily at the start and end of the day,
they’re likely to starve,” says Arnold.

With more and more examples of the effects of pharmaceuticals on wildlife, researchers are growing increasingly worried about potential effects of such pollutants on humans. “Human health is the million-dollar question,” says Kolpin. “All our environmental research, while maybe not a direct link to human health, certainly suggests that, as we start seeing things that affect aquatic and terrestrial organisms, we should be concerned about human health as well.”

“Benign by design”

Papers on the ecological impact of drugs have examined only a handful of the estimated 4,000 pharmaceuticals used around the globe in medicine and agriculture. Some scientists argue that we should spend less time identifying individual drugs in the environment and more time trying to prevent them from reaching it in the first place. “We have to think about preventative measures, not wait until the negative effects play out,” says Kümmerer.

One option is to outfit wastewater treatment plants with equipment to remove pharmaceuticals. In Sweden, for example, Brodin and colleagues are rebuilding an entire wastewater plant to incorporate ozonation, a process that can remove some pharmaceuticals from water by bubbling ozone gas through it. The team of researchers will then monitor local streams to see how the plant upgrades affect organisms in the surrounding ecosystem.

Technologies such as ozonation and nanofiltration are expensive, however, and no one method has been shown to remove all bioactive agents. Therefore, some researchers advocate measures to prevent pharmaceuticals from ever entering the water system, namely by designing drugs that quickly degrade in the environment—“benign by design,” as Kümmerer calls it. After giving a talk at a German cancer research center, Kümmerer was approached by scientists who had made a derivative of the anticancer drug ifosfamide. In the hopes of increasing absorption of the drug in the gut and reducing side effects in patients, the chemists replaced the part of the molecule known to keep the drug stable with a sugar. The chemists realized that the replacement might also make the drug more biodegradable in the environment, and they asked Kümmerer to test it.

He found that the derivative, glufosfamide, was biodegradable and still as potent an anticancer agent as the original. Glufosfamide is currently in a Phase 3 clinical trial for metastatic pancreatic cancer.

Pharmaceutical companies can and should use such “green” chemical techniques to design drugs that biodegrade quickly in the environment, says Paul Anastas, director of the Center for Green Chemistry and Green Engineering at Yale University. “For not just pharmaceutical chemists, but for all chemists, whenever we know things are going into the environment, we have an obligation to make sure they are as least toxic as possible.”

There is nothing inherently difficult about doing so, Anastas adds. “It’s all about just controlling properties to get the function you want. That is simply another design challenge.” And it shouldn’t be hard to convince companies to manufacture drugs to be greener, he says. “Nobody purposely designs a substance to be toxic in humans or the environment. There is just a lack of awareness of what’s possible.”

But until drugs are truly environmentally friendly, research into their distribution and effects carries on, says Kolpin. “Over the next five years, we’re going to have a much better understanding of the bad actors out there.”

Megan Scudellari is a freelance science writer in Boston, Massachusetts.

References

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