Pharmaceuticals and Endocrine Active Chemicals
In Minnesota’s Lakes and Rivers

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The unparalleled passage of environmental legislation in the 1970s and 80s was due in large part to the emerging analytical ability to detect and quantify contaminants at parts per million. For the first time, we became aware of the unintended contamination of surface water, drinking water, and ground water with petroleum products, chlorinated solvents, and pesticides. The resulting concern over this contamination resulted in the rapid enactment of the Clean Water Act, the Clean Air Act, Resource Conservation and Recovery Acts, and Superfund laws.

The astonishing advances in analytical technology since then has allowed us to peer with even greater resolution into our environment, so that detection limits for many contaminants are now well below a part per trillion, the equivalent of one drop in 20 Olympic-sized swimming pools. The finding that sewage effluent exerted estrogenic effects on male trout (Purdom et al. 1994) was followed by a flurry of studies to identify endocrine active chemicals, pharmaceuticals, and other organic compounds in wastewater and effluent-impacted surface water.

The USGS national reconnaissance of pharmaceuticals, hormones, and other contaminants in surface water (Kolpin et al. 2002) together with many other studies (Daughton and Ternes 1999; Focazio et al. 2008), revealed that our nation's waterways are typically contaminated by an unsettling number of pharmaceuticals, personal care products, and chemicals suspected of disrupting the normal functioning of the endocrine system. These included alkylphenols, such as nonyl- or octylphenol that are degradation products of the widely used alkylphenol ethoxylate surfactants; bisphenol A, the monomer used in the manufacture of polycarbonate plastics; carbamazepine, an anticonvulsant medication; sulfa drugs and trimethoprim; hormones, including synthetic steroid contraceptives; and a wide array of medicines that routinely pass through our waste water treatment plant facilities. A recent investigation by the Associated Press revealed that many of these compounds find their way into the drinking water of at least 41 million Americans (http://www.usnews.com/science/articles/2009/04/19/tons-of-released-drugs-taint-us-water?page=2).

In Minnesota, this inquiry was expanded to include a limited analysis of ground water in the proximity of landfills as well as a focus on rivers and streams affected by wastewater treatment plant effluent (Lee et al. 2004). Subsequent studies on the Mississippi River (Lee et al. 2008b), and tributaries to the Mississippi River (Lee et al. 2008a) broadened
our understanding of the degree to which waterways contain these chemicals. Table 1 lists the pharmaceutical chemicals that have been detected in Minnesota’s surface water to date.

A study of 25 wastewater treatment plants across Minnesota (Lee et al. 2011) demonstrated that not only were pharmaceuticals, personal care products, and hormones appearing in surface water downstream of treatment plants, they were also accumulating in bed sediment and at locations upstream of several treatment plant outfalls (Figures 1, 2). Thus, while municipal sewage treatment plant effluent was clearly an important and perhaps the primary source of pharmaceuticals and personal care products (PPCPs) to the aquatic environment, it was clear that unidentified upstream sources were contributing alkylphenols and other contaminants to surface water.

| 17-alpha-Estradiol | Diltiazem | Oxycodeone |
| 4-Androstene-3,17-dione | Diphenhydramine | Progesterone |
| Allyl trenbolone | Epitestosterone | Prometon |
| Alprazolam | Equilenin | Ranitidine |
| Amitriptyline | Equilin | Sertraline |
| Androstenedione | Estriol | Simvastatin |
| Androsterone | Estrone | Sulfadiazine |
| Benztrapine | Fluoxetine | Sulfadimethoxine |
| Bupropion | Fluvoxamine | Sulfamerazine |
| Caffeine | Formononetin | Sulfamethazine |
| Carbadox | Gemfibrozil | Sulfamethizole |
| Carbamazepine | Hydroxybupropion | Sulfamethoxazole |
| Cholesterol | Iopamidol | Sulfanilamide |
| Ciprofloxacin | Meprobamate | Sulfathiazole |
| cis-Androsterone | Mestranol | Testosterone |
| Citalopram | Metronidazole | Theophylline |
| Codeine | Norsertraline | Triclosan |
| Colchicine | Norverapamil | Trimethoprim |
| Coprostanol | Ofloxacin | Tylosin |
| Dehydronifedipine | Oxazepam | Valsartan |
| | | Venlafaxine |

Table 1: Pharmaceuticals detected in Minnesota's surface water.
These studies followed the logical inclination to focus sampling efforts on locations most prone to contamination: the surface water downstream of wastewater treatment plants. However, a survey of 11 Minnesota lakes in 2008 (Writer et al. 2010) revealed that not only did lake water contain a similar profile of PPCPs to that of river water downstream of
wastewater treatment plants, but that many of the lakes in very rural settings also harbored many of these contaminants of emerging concern. While lakeside residential septic systems undoubtedly contributed to the presence of these chemicals, the detection of pharmaceuticals in remote lakes lacking any shoreline development was perplexing.

In 2012, fifty lakes were randomly selected for analysis across Minnesota as part of a National Lake Assessment Program study (Ferrey 2012). Surface water was analyzed for 125 pharmaceuticals, representing the largest, statistically significant investigation yet of ambient lake water. The results show that pharmaceuticals and other commercially available chemicals are surprisingly widespread in lakes lacking sources of wastewater or shoreline development. The tricyclic antidepressant amitriptyline and the swine antibiotic carbadox were detected in roughly a third of the fifty lakes, while bisphenol A was present in 42% of the lakes. The illicit drug cocaine and its metabolite benzoylecgonine were found in 32% and 28% of the samples, respectively (Figure 3). Fluoroquinoline and sulfonamide antibiotics were also detected.

![Figure 3. Detection frequency of the chemicals found in ambient surface water of 50 lakes sampled in the 2012 National Lake Assessment Study.](image)

Together, these studies reveal a widespread presence of antibiotics, hormones, lipid regulators, antidepressants, anticonvulsants, and other medically important compounds in surface water at low concentrations. Moreover, they are detected at remarkably consistent frequencies and concentrations, regardless of geographical location. While earlier studies drew attention to the contribution of contaminants to surface water by wastewater treatment plants, the detection
of these contaminants on such a widespread level forces us to consider additional sources to lakes. These include runoff from agricultural row cropping, animal feedlots, residential septic systems, and the atmospheric transport of extremely fine dust particles (PM$_{2.5}$) to which these pharmaceuticals may be adsorbed.

The presence of these pharmaceuticals and other chemicals in our surface water at parts per trillion might be passed off as trivial if it were not for the recent studies that show that these biologically active compounds can have a dramatic effect on fish and wildlife, even at these vanishingly small concentrations. *In vitro* studies of pharmaceuticals at environmentally relevant concentration show that they have adverse physiologic and cytotoxic effects on fish cells (Pomati et al. 2007) and human embryonic cells (Pomati et al. 2006). Other researchers demonstrated that exposure to diclofenac, gemfibrozil, and carbamazepine in the low part per billion range reduced freshwater mussel cell viability *in vitro* (Parolini et al. 2011).

On the organism level, exposure to part per billion concentrations of nonylphenol alters the reproductive fitness of fathead minnows by reducing their ability to defend nest sites (Schoenfuss et al. 2008), and exposure to the antidepressants fluoxetine, venlafaxine, bupropion, and sertraline (selective serotonin reuptake inhibitors, or SSRIs) at concentrations commonly found in surface water increases the time for fathead minnows to respond to external stimuli, suggesting that exposure to these compounds in their natural habitat could reduce their ability to successfully avoid predation (Painter et al. 2009).

Several of these contaminants are endocrine active chemicals, adversely affecting the growth, development, or reproduction of organisms. Because these compounds trigger physiologic responses via the endocrine system, they exert adverse effect at extremely low concentration by mimicking naturally occurring hormones. Known or suspected endocrine active chemicals include nonylphenol, bisphenol A, polybrominated biphenyl ethers (flame retardants), a number of pesticides, and, of course, hormones and contraceptives - all detected in our aquatic environment (Streets et al. 2008).

Several of the monitoring campaigns in Minnesota have included analysis of endocrine disruption in fish at locations selected for water sampling. Vitellogenin, a protein associated with the development of eggs, is naturally produced only in female fish. The expression of this protein in male fish indicates that they have been exposed to estrogenic chemicals in their environment. Male fathead minnows that were caged for 21 days in lakes or streams (Writer et al. 2010) or in proximity to WWTPs (Lee et al. 2011) frequently expressed considerable amounts of this protein, in some instances at concentrations several fold greater than that of the females. Intersex in male fish – the formation of eggs in
the testes of males—also indicates an exposure to estrogenic chemicals in their environment, and has been observed at numerous locations (Hinck et al. 2009; Jobling et al. 1998).

In addition to studies on individual organisms, other researchers have demonstrated dramatic effects of endocrine disrupting chemicals at the population level. The addition of the synthetic contraceptive ethinylestradiol (EE2) to an experimental lake at five parts per trillion caused the resident fathead minnow population to collapse within two years (Kidd et al. 2007). This population eventually rebounded once the addition of EE2 was halted. Freshwater mussels that were exposed briefly to 30 parts per trillion of the SSRI fluvoxamine induced an immediate spawning in those organisms (Fong 1998).

Finally, the presence and impact of antibiotics in the soil and aquatic environment has been extensively studied and reviewed (Boxall et al. 2003; Sukul and Spiteller 2007; Sukul et al. 2006). The possibility that bacteria are developing antibiotic resistance when exposed to antibiotics in water near livestock or fish farming facilities is a serious concern. An extensive literature on this subject includes reports of chlortetracycline, monensin, and tylosin leaching from manure (Dolliver and Gupta 2008; Dolliver and Gupta 2008), the appearance of monensin in ground water beneath a dairy operation (Watanabe et al. 2008), and the detection of lincomycin to surface water and ground water from manure amended cropland (Kuchta et al. 2009). Several studies have demonstrated that antibiotics are taken up in plants (Kumar et al. 2005) and may affect plant growth (Jjemba 2002). Antibiotic resistance genes have been detected in dairy lagoons and irrigation ditch water (Pruden et al. 2006). Some studies indicate that the practice of administering subtherapeutic doses of antibiotics to livestock to promote weight gain and to prevent disease can result in antibiotic resistant Campylobacter infections (Smith et al. 1999), and that antibiotic resistant bacteria may be transferred to humans (Rhodes et al. 2000). Antibiotic resistance in bacteria has been observed to increase in soils treated with pig manure (Sengelov et al. 2003) and in the waters associated with fish farming (Schmidt et al. 2000).

References


