

7. Bibliography of Literature on Pharmaceuticals and the Environment

The following pages highlight articles related to unwanted medicines and other pharmaceuticals in the environment from scientific journals, newspapers, magazines, and radio. These articles describe the current state of knowledge about where unwanted medicine chemicals have been detected in the environment and the observed effects of pharmaceuticals on living organisms.

The list printed in this resource kit was last updated December 2009. Please consult www.iisgcp.org/unwantedmeds for subsequent updates.

A bibliography of additional literature on pharmaceuticals in the environment is available online at www.epa.gov/ppcp/lit.html.

Scientific Journal Publications/Research

The list printed in this resource kit was last updated December 2009. Please consult www.iisgcp.org/unwantedmeds for subsequent updates.

Bound, Jonathan P., and Nikolaos Voulvoulis. 2005. "Household Disposal of Pharmaceuticals as a Pathway for Aquatic Contamination in the United Kingdom." Environmental Health Perspectives 113(12):1705-1711.

<http://www.ehponline.org/docs/2005/8315/abstract.html>

Abstract: Pharmaceuticals are produced and used in increasingly large volumes every year. With this growth comes concern about the fate and effects of these compounds in the environment. The discovery of pharmaceuticals in the aquatic environment has stimulated research in the last decade. A wide range of pharmaceuticals has been found in fresh and marine waters, and it has recently been shown that even in small quantities, some of these compounds have the potential to cause harm to aquatic life. The primary pathway into the environment is the use and disposal of medicines; although much of the research in the area currently focuses on the removal of pharmaceuticals during sewage treatment processes, disposal via household waste might be a significant pathway requiring further research. To investigate the household disposal of unused and expired pharmaceuticals as a source of pharmaceutical compounds in the environment, we carried out a survey and interviewed members of 400 households, predominantly from southeastern England. We used the information on when and how they disposed of unfinished pharmaceuticals to construct a conceptual model to assess the pathways of human pharmaceuticals into the environment. The model demonstrated that **disposal of unused pharmaceuticals, either by household waste or via the sink or toilet, may be a prominent route that requires greater attention.**

Boxall, Alistair B. 2004. "The Environmental Side Effects of Medication." European Molecular Biology Organization Reports 5(12):1110-1116.

<http://www.nature.com/embor/journal/v5/n12/full/7400307.html>

Abstract: Medicines have an important role in the treatment and prevention of disease in both humans and animals. But it is because of the very nature of medicines that they may also have unintended effects on animals and microorganisms in the environment. Although the side effects on human and animal health are usually investigated in thorough safety and toxicology studies, **the potential environmental impacts of the manufacture and use of medicines are less well understood and have only recently become a topic of research interest.** Some of the effects of various compounds—most notably anthelmintics from veterinary medicine and antibacterial therapeutics—are already known (Daughton & Ternes, 1999; Boxall *et al.*, 2003a, 2004a; Floate *et al.*, 2005), but there are many other substances that can affect organisms in the environment. This is further complicated by the fact that some pharmaceuticals can cast effects on bacteria and animals well below the concentrations that are usually used in safety and efficacy tests. In addition, breakdown products and the combination of different biologically active compounds may have unanticipated effects on the environment. Although it may be safe to assume that these

substances do not substantially harm humans, we have only recently begun to research whether and how they affect a wide range of organisms in the environment and what this means for environmental health.

Daughton, C.G. 2003. "Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health."
"I. Rationale for and Avenues toward a Green Pharmacy." Environ. Health Perspect., 111:757-774. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1241487>

and

Daughton, C.G. 2003. "II. Drug Disposal, Waste Reduction, and Future Direction." Environ. Health Perspect., 111:775-785.
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1241488>

Abstract: Since the 1980s, the occurrence of pharmaceuticals and personal care products (PPCPs) as trace environmental pollutants, originating primarily from consumer use and actions rather than manufacturer effluents, continues to become more firmly established. Although PPCPs typically have been identified in surface and ground waters, some are also undoubtedly associated with solid phases such as suspended particulates, sediments, and sewage sludges, despite their relatively high affinity for water. Often amenable to degradation, their continual introduction to waste-receiving waters results from their widespread, continuous, combined use by individuals and domestic animals, giving PPCPs a "pseudo-persistence" in the environment. Little is known about the environmental or human health hazards that might be posed by chronic, subtherapeutic levels of these bioactive substances or their transformation products. The continually growing, worldwide importance of freshwater resources, however, underscores the need for ensuring that any aggregate or cumulative impacts on (or from) water supplies are minimized. Despite the paucity of effects data from longterm, simultaneous exposure at low doses to multiple xenobiotics (particularly non-target-organism exposure to PPCPs), a wide range of proactive actions could be implemented to reduce or minimize the introduction of PPCPs to the environment. Most of these actions fall under what could be envisioned as a holistic stewardship program—overseen by the health care industry and consumers alike. Significantly, such a stewardship program would benefit not just the environment; additional, collateral benefits could automatically accrue, including reducing consumers' medication expenses and improving patient health and consumer safety. In this article, the first of a two-part mini-monograph describing the "green pharmacy," **I focus initially on the background behind the imperative for an ecologically oriented stewardship program for PPCPs. I then present a broad spectrum of possible source control/reduction actions, controlled largely by the health care industry, that could minimize the disposition of PPCPs to the environment.**

In the second of two parts describing the "green pharmacy" **I focus on those actions and activities tied more closely to the end user (e.g., the patient) and issues associated with drug disposal/recycling that could prove useful in minimizing the environmental disposition of PPCPs. I also outline some recommendations and suggestions for further research and pose some considerations regarding the future.**

This two-part mini-monograph attempts to capture cohesively for the first time the wide spectrum of actions available for minimizing the release of PPCPs to the environment. A major objective is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful approach to life-cycle stewardship of PPCPs.

Daughton, Christian G. and Thomas A. Ternes. 1999. "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?" Environmental Health Perspectives 107(6):907-938.

<http://www.ehponline.org/members/1999/suppl-6/907-938daughton/daughton-full.html>

Abstract: During the last three decades, the impact of chemical pollution has focused almost exclusively on the conventional "priority" pollutants, especially those acutely toxic/carcinogenic pesticides and industrial intermediates displaying persistence in the environment. This spectrum of chemicals, however, is only one piece of the larger puzzle in "holistic" risk assessment. Another diverse group of bioactive chemicals receiving comparatively little attention as potential environmental pollutants includes the pharmaceuticals and active ingredients in personal care products (in this review collectively termed PPCPs), both human and veterinary, including not just prescription drugs and biologics, but also diagnostic agents, "nutraceuticals," fragrances, sun-screen agents, and numerous others. These compounds and their bioactive metabolites can be continually introduced to the aquatic environment as complex mixtures via a number of routes but primarily by both untreated and treated sewage. Aquatic pollution is particularly troublesome because aquatic organisms are captive to continual life-cycle, multigenerational exposure. **The possibility for continual but undetectable or unnoticed effects on aquatic organisms is particularly worrisome** because effects could accumulate so slowly that major change goes undetected until the cumulative level of these effects finally cascades to irreversible change--change that would otherwise be attributed to natural adaptation or ecologic succession. **As opposed to the conventional, persistent priority pollutants, PPCPs need not be persistent if they are continually introduced to surface waters**, even at low parts-per-trillion to parts-per-billion concentrations (ng to µg/L). Even though some PPCPs are extremely persistent and introduced to the environment in very high quantities and perhaps have already gained ubiquity worldwide, others could act as if they were persistent, simply because their continual infusion into the aquatic environment serves to sustain perpetual life-cycle exposures for aquatic organisms. This review attempts to synthesize the literature on environmental origin, distribution/occurrence, and effects and to catalyze a more focused discussion in the environmental science community.

Glassmeyer, S.T., E. K. Hinchey, S. E. Boehme, C. G. Daughton, I. S. Ruhoy, O. Conerly, R. L. Daniels, L. Lauer, M. McCarthy, T. G. Nettesheim, K. Sykes, V. G. Thompson. 2009. "Disposal practices for unwanted residential medicines in the U.S." Environment International 35:566-572.

Abstract: The occurrence of trace levels of prescription and over-the-counter pharmaceuticals in the environment began to receive concerted attention nearly two decades ago. The public's growing awareness and concern over the presence of these chemicals, especially in drinking water, has served to catalyze considerable discussion and debate regarding the best practices for

disposal of unused or unwanted medications. In the United States, the first federal guidance for consumers was issued in 2007. It recommends discarding unused pharmaceuticals to household trash, after taking precautions to mix the pharmaceuticals with an inert substance and conceal the contents from view. Providing the consumer with additional options for conscientious disposal are various community, city, and state collection events, ongoing programs, and government-funded pilot projects. These strategies include the opportunity to mail or bring unused medications to various collection points, such as pharmacies, for eventual destruction. All of these approaches to medication disposal play roles in reducing the introduction of pharmaceuticals to the environment.

Hemminger, Pat. 2005. "Damming the Flow of Drugs Into Drinking Water." Environmental Health Perspectives 113(10):678-681.
<http://www.ehponline.org/members/2005/113-10/spheres.html>

Discusses the European Medicines Agency's guidance on ecotoxicity testing and environmental risk assessment for new drugs.

Abstract: Roughly 100 pharmaceuticals have now been identified in rivers, lakes, and coastal waters throughout Europe and the United States in concentrations of parts per billion to parts per trillion. The first major European studies on this topic--in journals such as volume 67, issue 1-4 (1997) of the *International Journal of Environmental Analytical Chemistry* and the November 1998 issue of *Water Research*-- examined German ground and surface waters, and found occurrences of drugs including cholesterol regulators, analgesics, and antiseizure medications. Since that time, numerous other studies have documented the presence of pharmaceuticals, including potential endocrine disruptors, in other locales as well.

Kolpin, Dana W., Edward T. Furlong, Michael T. Meyer, E. M. Thurman, Steven D. Zaugg, Larry B. Barber, and Herbert T. Buxton. 2002. "Pharmaceuticals: Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: a National Reconnaissance." Environmental Science & Technology 36(6):1202-1211.
<http://pubs.acs.org/cgi-bin/article.cgi/esthag/2002/36/i06/pdf/es011055j.pdf>

Abstract: To provide the first nationwide reconnaissance of the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants (OWCs) in water resources, the U.S. Geological Survey used five newly developed analytical methods to measure concentrations of 95 OWCs in water samples from a network of 139 streams across 30 states during 1999 and 2000. The selection of sampling sites was biased toward streams susceptible to contamination (i.e. downstream of intense urbanization and livestock production). **OWCs were prevalent during this study, being found in 80% of the streams sampled.** The compounds detected represent a wide range of residential, industrial, and agricultural origins and uses with 82 of the 95 OWCs being found during this study. The most frequently detected compounds were coprostanol (fecal steroid), cholesterol (plant and animal steroid), *N,N*-diethyltoluamide (insect repellent), caffeine (stimulant), triclosan (antimicrobial disinfectant), tri(2-chloroethyl)phosphate (fire retardant), and 4-nonylphenol (nonionic detergent metabolite). Measured concentrations for this study were generally low and rarely exceeded drinking-water guidelines, drinking-water

health advisories, or aquatic-life criteria. Many compounds, however, do not have such guidelines established. The detection of multiple OWCs was common for this study, with a median of seven and as many as 38 OWCs being found in a given water sample. Little is known about the potential interactive effects (such as synergistic or antagonistic toxicity) that may occur from complex mixtures of OWCs in the environment. In addition, results of this study demonstrate the importance of obtaining data on metabolites to fully understand not only the fate and transport of OWCs in the hydrologic system but also their ultimate overall effect on human health and the environment.

Nash, Jon P., David E. Kime, Leo T. Van Der Ven, Piet W. Wester, Francois Brion, Gerd Maack, Petra Stahlschmidt-Allner, and Charles R. Tyler. 2004. "Long-Term Exposure to Environmental Concentrations of the Pharmaceutical Ethynylestradiol Causes Reproductive Failure in Fish." *Environmental Health Perspectives* 112(17):1725-1733. <http://www.ehponline.org/members/2004/7209/7209.html>

Abstract: Heightened concern over endocrine-disrupting chemicals is driven by the hypothesis that they could reduce reproductive success and affect wildlife populations, but there is little evidence for this expectation. The pharmaceutical ethynylestradiol (EE₂) is a potent endocrine modulator and is present in the aquatic environment at biologically active concentrations. To investigate impacts on reproductive success and mechanisms of disruption, we exposed breeding populations ($n = 12$) of zebrafish (*Danio rerio*) over multiple generations to environmentally relevant concentrations of EE₂. **Life-long exposure to 5 ng/L EE₂ in the F₁ generation caused a 56% reduction in fecundity and complete population failure with no fertilization.** Conversely, the same level of exposure for up to 40 days in mature adults in the parental F₀ generation had no impact on reproductive success. Infertility in the F₁ generation after life-long exposure to 5 ng/L EE₂ was due to disturbed sexual differentiation, with males having no functional testes and either undifferentiated or intersex gonads. These F₁ males also showed a reduced vitellogenic response when compared with F₀ males, indicating an acclimation to EE₂ exposure. Depuration studies found only a partial recovery in reproductive capacity after 5 months. Significantly, even though the F₁ males lacked functional testes, they showed male-pattern reproductive behavior, inducing the spawning act and competing with healthy males to disrupt fertilization. Endocrine disruption is therefore likely to affect breeding dynamics and reproductive success in group-spawning fish. Our findings raise major concerns about the population-level impacts for wildlife of long-term exposure to low concentrations of estrogenic endocrine disruptors.

Potera, Carol. 2000. "Drugged Drinking Water." *Environ. Health Perspectives* 108(10):446.

Abstract: Drugs and personal care products that are excreted from or washed off the body naturally end up in the sewage that flows into sewer systems and septic tanks, but where do they go from there? Scientists are beginning to monitor the extent of pharmaceutical and personal care products (PPCPs) in the aquatic environment and their consequences. What they're finding is that, **through leaching from septic tanks and escaping intact through sewage treatment processes, some of these substances are ending up back in the drinking water.**

Velagaleti, Ranga, Philip K. Burns, Michael Gill, and James Prothro. 2002. "Impact of Current Good Manufacturing Practices and Emission Regulations and Guidances on the Discharge of Pharmaceutical Chemicals Into the Environment From Manufacturing, Use, and Disposal." Environmental Health Perspectives 110(3): 213-220.
<http://www.ehponline.org/members/2004/7209/7209.html>

Abstract: The current Good Manufacturing Practice (cGMP) and effluent emission (use and disposal) regulations of the U.S. Food and Drug Administration (FDA) and manufacturing effluent discharge and emission regulations of the U.S. Environmental Protection Agency (U.S. EPA) require contained manufacture, use, and disposal of pharmaceuticals with the goal of minimizing the release of pharmaceutical chemicals into the environment. However, debate has recently arisen in several scientific forums over whether these regulations adequately protect human and environmental health from the new pharmaceutical drugs introduced each year into the marketplace and the multitude of existing products, each with many distinct biochemical modes of actions. To address this issue, it is important to understand the relevance of current cGMP regulations and emission regulations that have a direct bearing on the releases of pharmaceutical chemicals into the environment during the manufacture, use, and disposal of active pharmaceutical ingredients (drug substances) and drug products. This knowledge may help us assess the quantity of residues that may be released into the environment. Additionally, the information on physical, chemical, and degradation and sorption properties of the pharmaceutical chemicals may help determine the net residue levels that could persist in the environment to evaluate if such residues have any bearing on human and environmental health. **The scientific and regulatory aspects of issues related to the manufacture, use, and disposal of pharmaceutical chemicals are discussed in this article, with special emphasis on potential environmental exposure pathways during the life cycle of an active pharmaceutical ingredient or drug product.** The mechanisms of degradation (transformation or depletion) and dilution of pharmaceutical residues that may be released into aquatic or terrestrial environmental compartments are described. Such degradation and dilution of pharmaceutical chemicals in the environment may significantly reduce the residues. It is important to evaluate whether such residue levels have any measurable impact on human and/or environmental health.

News Reports

The news reports have been updated in 2009. Please consult www.iisgcp.org/unwantedmeds for subsequent updates.

Effects of Pharmaceuticals in the Environment

Associated Press Enterprise: Feds mull regulating drugs in water (By National Writer Jeff Donn)
“Feds mull regulating drugs in water” Dec. 2009.

http://news.yahoo.com/s/ap/20091222/ap_on_he_me/us_pharmawater_drinking

Associated Press Investigation: Pharmaceuticals found in drinking water. (by By Jeff Donn, Martha Mendoza and Justin Pritchard, Associated Press Writers) “Pharmaceuticals found in drinking water, affecting wildlife and maybe humans”

http://hosted.ap.org/specials/interactives/pharmawater_site/

Brodie, Christopher. “Persistently Clean? Antimicrobials accumulate in the municipal sludge used to fertilize crops.” American Scientist. Jan./Feb. 2007.

<http://www.americanscientist.org/template/AssetDetail/assetid/54434>

Cornwall, Warren, and Keith Ervin. “Hormonal chemicals may be imperiling fish.” The Seattle Times. April 1, 2007. <http://archives.seattletimes.nwsourc.com/cgi-bin/texis.cgi/web/vortex/display?slug=hormone01m&date=20070401>

Dean, Cornelia. “Drugs Are in the Water. Does It Matter?” The New York Times. April 3, 2007.

http://www.nytimes.com/2007/04/03/science/earth/03water.html?_r=1&oref=slogin

Dickinson, Boonsri and Todd Neff. “Effluent changes gender of fish.” Scripps Howard News Service. December 12, 2006.

<http://www.trib.com/articles/2006/12/12/news/regional/87a0a21fccb3d8a587257241006d1666.txt>

Eilperin, Juliet. “More Flushed Pharmaceuticals Turning Up in Our Waterways.” The Seattle Times. July 1, 2005. <http://archives.seattletimes.nwsourc.com/cgi-bin/texis.cgi/web/vortex/display?slug=pollute01&date=20050701>

Frank, Patricia. “The Next Drug Problem.” American City and County. June 1, 2007.

http://americancityandcounty.com/water/government_next_drug_problem/

Kidd, Karen. “Hormones and Hormone Mimics in the Aquatic Environment.” Eco-Journal. Published by Manitoba Eco-Network, Jan/Feb 2003.

[http://www.mbeconetwork.org/archives/Eco-Journal13\(1\).pdf](http://www.mbeconetwork.org/archives/Eco-Journal13(1).pdf)

Mittelstaedt, Martin. “Estrogen threatens minnow manhood.” The Globe and Mail. May 22, 2007. (archived; requires subscription or pay-per-view).

www.theglobeandmail.com/servlet/story/LAC.20070522.FISH22/TPStory/TPNational/Ontario/

“Potomac ‘intersex’ fish worry scientists.” Associated Press. Sept. 6, 2006.

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http://sciencenews.org/pages/sn_arc98/3_21_98/bob1.htm
- Raloff, Janet. "Excreted Drugs: Something Looks Fishy." Science News Online. Vol. 157, No. 25 (June 2000). <http://sciencenews.org/articles/20000617/fob1.asp>
- Raloff, Janet. "More Waters Test Positive for Drugs." Science News Online. Vol. 157, No.14 (April 2000). <http://sciencenews.org/articles/20000401/fob1.asp>
- Royte, Elizabeth. "Drugging the Waters." OnEarth magazine. Published by National Resources Defense Council, Fall 2006. pp. 26-31. www.nrdc.org/onearth/06fal/waters1.asp
- Spanne, Autumn. "Human hormones hurt lobsters." The Standard-Times. Jan. 14, 2007.
<http://www.southcoasttoday.com/daily/01-07/01-14-07/01perspective.htm>
- Spinner, Kate. "From estrogen to Prozac, drugs we flush may end up in shark's bloodstreams." Sarasota Herald-Tribune. June 2, 2007.
- Tode, Laura. "Teens examine effect of estrogen in water." Billings Gazette. April 6, 2007.
<http://www.billingsgazette.net/articles/2007/04/06/news/local/20-estrogen.txt>
- Underwood, Anne. "Rivers of Doubt." Newsweek. June 4, 2007.
- Wollheim, Peter. "A Fish Problem This Big." Boise Weekly. Jan. 17, 2007.
<http://www.boiseweekly.com/gyrobase/Content?oid=oid%3A215775>

Collection/Safe Disposal Initiatives

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- Gentile, Jennifer. "Novel program to curb pollution from drugs." The Reporter (Vacaville, CA). Jan. 7, 2007. www.thereporter.com (archived; log-in and fee required to view article. Describes Vacaville's collection system for households' unwanted medicines.)
- Gressitt, Stevan. "Getting Rid of Unusual Drugs a Step to Safety." Bangor Daily News. June 16, 2006. www.bangordailynews.com (archived; log-in and fee required to view article.) Introduces Maine's medicine take-back system.
- "Pharmaceuticals Eyed By EPA for Inclusion on Water Contaminant List." Inside Washington Publishers. April 5, 2006.
- Quirnbach, Chuck. "Flushed Pills Hurt Fish." Wisconsin Public Radio. Sept. 19, 2006. Listen online at <http://www.wpr.org/news/archives/0609.cfm>
- Rastogi, Nina Shen. "Should You Flush Your Drugs Down the Toilet?: The greenest way to get rid of old prescription meds." Slate Magazine. Dec. 1, 2009.
<http://www.slate.com/id/2236431/>
- Seely, Ron. "Flushed drugs pollute water." Wisconsin State Journal. Dec. 10, 2006. (freelance author's work not available through online archives).
- "Wildlife Service, Pharmacists Eye Program to Limit Drug Disposal." Inside Washington Publishers. Sept. 25, 2006.