7. Bibliography of Literature on Pharmaceuticals and the Environment

In the coming years, the use of pharmaceutical products is expected to increase due to an expanding and aging population. New medications and therapies are available every year. Consequently, tons of unwanted pharmaceuticals are generated annually in the United States alone. Part of that amount is either disposed of down the sink/toilet or sent to landfills.

Scientists are just beginning to reach a fuller understanding of this issue. Estrogen-related compounds used in birth control pills have been observed to cause feminization of male fish: depending on the concentration, researchers have seen laboratory fish population sex ratios shift up to 100% female.[1] Increased bacterial resistance to antibiotics is also a concern, though this may not be caused by antibiotics reaching the environment, but by drug-resistant pathogens from treated human and animal patients entering sewage and reproducing there.[2]

The following pages highlight articles related to pharmaceutical waste from scientific journals and newspapers, magazines, and radio. They will inform you of the current state of knowledge of the extent to which pharmaceutical chemicals appear in the environment and the observed effects of pharmaceuticals on living organisms.

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

[1] Joanne Parrott. "Anthropogenic Chemicals: Pharmaceuticals and Personal Care Products." Plenary presentation at State of the Lakes Ecosystem Conference, Milwaukee, WI, November 2, 2006.
[2] Daughton, Christian. Personal communication, Nov. 27, 2006.

Scientific Journal Publications/Research

Autier, Philippe; Ramesh Govindaraj; Robin Gray; Rama Lakshminarayanan; Homira G. Nassery and Gerard Schmets. "Drug Donations in Post-Emergency Situations." The International Bank for Reconstruction and Development / The World Bank. (2002).
http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/Nassery-DrugDonation-whole.pdf

Abstract: The objectives of this project were to conduct situation analyses on drug donations in East Timor (post-conflict country), El Salvador and Gujarat State in India (both affected by earthquakes), and Mozambique (floods), applying criteria derived from the Interagency Guidelines for Drug Donations; to determine how and whether the implementation of the Guidelines has affected the processes and outcomes of drug donations; and to build evidence to facilitate wider acceptance of the Guidelines. The study teams undertook to identify the organizations responsible for inappropriate donations, a step not often taken in earlier investigations. This information can now be used to facilitate educational initiatives aimed at preventing similar problems in the future.

Bound, Jonathan P., and Nikolaos Voulvoulis. "Household Disposal of Pharmaceuticals as a Pathway for Aquatic Contamination in the United Kingdom." Environmental Health Perspectives 113.12 (2005): 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. "The Environmental Side Effects of Medication." European Molecular Biology Organization Reports 5.12 (2004): 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. "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 (2003) 757-774.
http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1241487

and "II. Drug Disposal, Waste Reduction, and Future Direction." Environ. Health Perspect., 111 (2003) 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. "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?" Environmental Health Perspectives 107.6 (1999): 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.

Hemminger, Pat. "Damming the Flow of Drugs Into Drinking Water." Environmental Health Perspectives 113.10 (2005): 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. "Pharmaceuticals: Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: a National Reconnaissance." Environmental Science & Technology 36.6 (2002): 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 repellant), 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. "Long-Term Exposure to Environmental Concentrations of the Pharmaceutical Ethynylestradiol Causes Reproductive Failure in Fish." Environmental Health Perspectives 112.17 (2004): 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 (EE_2) 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 EE_2. **Life-long exposure to 5 ng/L EE_2 in the F_1 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 F_0 generation had no impact on reproductive success. Infertility in the F_1 generation after life-long exposure to 5 ng/L EE_2 was due to disturbed sexual differentiation, with males having no functional testes and either undifferentiated or intersex gonads. These F_1 males also showed a reduced vitellogenic response when compared with F_0 males, indicating an acclimation to EE_2 exposure. Depuration studies found only a partial recovery in reproductive capacity after 5 months. Significantly, even though the F_1 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.

Palace, V.P., K.G. Wautier, R.E. Evans; P.J. Blanchfield; K.H. Mills, S.M. Chalanchuk, D. Godard, M.E. McMaster, G.R. Tetreault, L.E. Peters, L. Vandenbyllaardt, and K.A. Kidd. "Biochemical and Histopathological effects in pearl dace (*Margariscus margarita*) chronically exposed to a synthetic estrogen in a whole lake experiment." Environ. Tox. Chem. 2006. 25(4): 1114-1125.
http://journalclub.tox.ncsu.edu/linked_files/fall06/Palace2006.pdf

Abstract: Potential effects of exposure to the synthetic estrogen 17alpha-ethynylestradiol (EE2) were examined in several species of fish from a lake experimentally treated with environmentally relevant concentrations of the contaminant. Ethynylestradiol was added to Lake 260, a small Precambrian shield lake at the Experimental Lakes Area in northwestern Ontario, Canada, from May to October of 2001, 2002, and 2003. Mean concentrations of EE2 in epilimnetic waters ranged between 4.5 and 8.1 ng/L during the three years, with overall means of 6.1 (+/- 2.8), 5.0 (+/- 1.8), and 4.8 (+/- 1.0) ng/L for the three years, respectively. **Male and female pearl dace (Margariscus margarita) captured after EE2 additions began contained up to 4,000-fold higher concentrations of the egg yolk precursor vitellogenin than fish captured from the same lake before the EE2 additions or when compared to fish from reference lakes. Edema in the ovaries, inhibited development of testicular tissue, intersex, and histopathological kidney lesions were all evident in fish exposed to EE2.** Some indications that EE2 exposure affected in vitro steroidogenic capacity of the ovaries and the testes existed, although results were not always consistent between years. Pearl dace abundance was similar in the lake treated with EE2 and the reference lake. A trend exists toward a reduced overall population of pearl dace from the treated and reference lakes, as do indications that young-of-the-year size classes are less abundant in the EE2-treated lake. Biochemical and histopathological impacts observed in fish exposed to EE2 in this study have not yet been linked to clear population level impacts in pearl dace. Monitoring of these populations is ongoing.

Palace, Vince P., Robert E. Evans, Kerry Wautier, Christopher Baron, Lenore Vandenbyllardt, Wendy Vandersteen and Karen Kidd. "Induction of Vitellogenin and Histological Effects in Wild Fathead Minnows from a Lake Experimentally Treated with the Synthetic Estrogen, Ethynylestradiol." Water Qual. Res. J. Canada. 2002. v.37, n.3, 637-650.
http://www.mindfully.org/Water/Fathead-Estrogen-LakesJul02.htm

Abstract: Potential effects of exposure to contaminants with estrogenic activity are currently being examined in fish from a lake experimentally treated with the synthetic estrogen, ethynylestradiol (EE2). EE2 was added to Lake 260, a small Precambrian shield lake in the Experimental Lakes Area (ELA) of northwestern Ontario, from late May to October 2001. Concentrations of EE2 in epilimnetic waters ranged between 4.0 and 8.1 ng/L, with a mean (±SD) of 6.0±2.8 ng/L. **Male fathead minnows (*Pimephales promelas*) captured from Lake 260 after EE2 additions began contained 9000-fold higher concentrations of the egg yolk precursor vitellogenin (VTG), than were detected in fish captured from the same lake prior to the EE2 additions, or when compared to fatheads from reference lakes during the same sample period.** VTG in females was induced 8- to 80-fold and was sustained beyond the normal window of vitellogenesis in Lake 260. Histological examination of tissues from EE2-exposed male fatheads in Lake 260 showed widespread fibrosis and inhibition of testicular development.

Enlargement of liver cells, edema in the interstitium between kidney tubules, and eosinophilic deposits in the kidney tubule lumen were also evident in male fatheads from Lake 260. Further studies will examine the relationships between biochemical and histological alterations and population level effects.

Potera, Carol. "Drugged Drinking Water." Environ. Health Perspectives 108.10 (2000): 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. "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 (2002): 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.

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Effects of Pharmaceuticals on the Environment

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