Pharmaceuticals in the environment: Overview of significance, concerns, and solutions

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Introduction

Pharmaceuticals and personal care products (PPCPs) comprise large, diverse arrays of chemicals that can occur in the environment as unregulated pollutants. They originate largely from the combined activities and actions of multitudes of individuals as well as from veterinary and agricultural use; the wide spectrum of sources and origins of PPCPs is illustrated here: http://epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf.

Concerted research that began in Europe about two decades ago, and in the U.S. in the late 1990s, has been rapidly expanding in the last few years, as reflected by an escalation in publications. Investigations that were originally limited to studying the sources, origins, and occurrence of PPCPs (mainly in waters) were led primarily by analytical chemists. The scope of this research has expanded, now accommodating more dimensions of the risk assessment paradigm (see illustrations at: http://epa.gov/nerlesd1/chemistry/ppcp/stressors.htm). The scope has widened to encompass not just occurrence over a wider spectrum of environmental matrices but also to address the complexities involved with assessing the range of unanticipated and subtle effects that might occur from chronic, low-dose exposure of non-target organisms (Daughton 2003a; Daughton and Ternes 1999). Risk management options designed around the principles of pollution prevention and environmental stewardship are also under discussion in the many sectors of the healthcare community and by various state and local legislatures (http://epa.gov/nerlesd1/chemistry/pharma/faq.htm#disposal).

Purpose

The PPCP activities begun in the late 1990s by the U.S. Environmental Protection Agency's Office of Research and Development (ORD) in Las Vegas have focused on: (i) Performing and promoting anticipatory research, (ii) catalyzing and fostering interdisciplinary research networks across government, academe, and private sectors, (iii) fostering communication and collaboration between those involved in the historically disconnected fields of environmental science and human medicine and healthcare, and (iv) ensuring that any possible future regulatory decisions are based on comprehensive science. One of the ways by which ORD has fostered research on PPCPs is via its STAR grants program (http://epa.gov/nerlesd1/chemistry/pharma/grants.htm); note that other organizations have also funded research on PPCPs.

Overview

ORD's PPCPs web site (http://epa.gov/nerlesd1/chemistry/pharma/) captures much of the work and supporting ideas that have been developed to date by a growing number of scientists worldwide. Most of the peer-reviewed publications covering the many aspects of this topic are captured here: http://epa.gov/nerlesd1/chemistry/ppcp/reference.htm; a wide array of associated,

relevant materials available from the Internet can be accessed here: http://epa.gov/nerlesd1/chemistry/ppcp/relevant.htm. It is important to recognize that the overall topic extends beyond the many aspects of PPCPs as pollutants *per se* to involve other topics such as: (i) capitalizing on the occurrence of PPCPs as pollutants for their use of as "tools" to probe, trace, and study other environmental processes (http://epa.gov/nerlesd1/chemistry/pharma/tracers.htm), (ii) the complexities involved with the perception and communication of risk associated with water reuse/recycling as exacerbated by the mere presence of trace levels of PPCPs (Daughton 2004a), and (iii) development and implementation of strategies for minimizing pollution and enhancing environmental stewardship (Daughton 2003a-c).

Those chemical pollutants that are regulated under various international, federal, and state programs represent but a very small fraction of the universe of chemicals that can and do occur in the environment as a result of both natural processes and human influence. Although this galaxy of targeted chemicals might be minuscule compared with the universe of both known and yet-to-be identified chemicals (an unknown portion of which can act as chemical stressors if organisms sustain sufficient exposure), an implicit historical assumption is that these limited, selective lists of regulated chemicals are responsible for the most significant share of risk with respect to environmental or economic impairment or to human health. Perhaps overlooked is the significance of the universe of so-called "emerging" pollutants, of which PPCPs comprise a number of galaxies. Many of the issues surrounding emerging pollutants have been discussed by Daughton (2004b).

Although the concentration of any individual PPCP rarely ever exceeds the sub-ppm level (if present in drinking water, concentrations of individual PPCPs are generally less than the ppt-ppb level, ng-µg/L; see: http://epa.gov/nerlesd1/chemistry/pharma/drinking_water.htm), evidence continues to emerge that these trace-level pollutants are ubiquitous, they can have a continuous presence (e.g., where domestic wastewaters enter the environment) and can therefore be considered as pseudo-persistent, regardless of their actual environmental half-lives, and the numbers of distinct and varied chemical entities could be extremely large (given that thousands of active ingredients are used in tens of thousands of commercial formulations).

The trace concentrations of individual PPCPs are invariably many orders of magnitude below the levels required to elicit their intended therapeutic effects in humans and domestic animals. The range of biochemical mechanisms whereby these chemicals elicit their intended effects is very broad, extending beyond the receptors required for therapeutic effects. Less appreciated, however, is that many also possess promiscuous potential for interacting with a wide range of as-yet unidentified receptors. A number of little-discussed toxicological factors further complicates a realistic assessment of hazard (Daughton 2004b).

The presence of PPCPs in the environment highlights perhaps better than for any other group of pollutants some of the major challenges facing environmental toxicology. These consumer chemicals epitomize the importance of: assessing cumulative exposure (all chemicals sharing the same mode of action) and aggregate exposure (multiple exposure routes for the same chemical); better understanding of low-dose effects (nM-pM and lower) and complex mixture interactions (e.g., synergism and antagonism); the potential significance of hormesis (e.g., paradoxical low-dose response); identifying sensitive sub-populations (e.g., unexpected effects resulting from polymorphisms); and developing more effective ways to communicate risk (critical with respect to the recycling of wastewater for drinking). The complexities in hypothetically evaluating risk in a holistic manner, accommodating for "Toxicant Totality Tolerance Trajectory" (the *4Ts*) are

summarized here: http://epa.gov/nerlesd1/chemistry/ppcp/stressors.htm. The numerous factors involved with the 4Ts pose many challenges for assessing human and ecological risk. Many of the less-appreciated factors involved with emerging pollutants are discussed by Daughton (2004b).

Regardless of whether any toxicological concerns from low-levels of PPCPs in the environment ever become evident, there are several factors that merit further examination: (i) Concentrations of PPCPs have the potential to reach transiently high concentrations in sewage truck lines during the disposal of unwanted drugs to sewage; this has ramifications in particular for the exposure of bacterial biofilms to concentrations of antibiotics potentially sufficiently high to select for resistance (http://epa.gov/nerlesd1/chemistry/pharma/images/nas-iom.pdf). (ii) Transient temporal and spatial excursions into higher concentrations during disposal events could render the monitoring data obtained from discrete grab samples less representative than data from sampling approaches that integrate over time (e.g., see: http://epa.gov/nerlesd1/chemistry/ppcp/trends.htm). (iii) The occurrence of even minute traces of drugs in point-of-use drinking water (or even in source waters) has the potential to eventually cause problems with public acceptance of the growing need to recycle water. Minute quantities of drugs (those designed solely for internal use) in drinking waters hold the potential to evoke intense emotional responses from consumers because of the strong mental image readily formed of the direct connection between the excretion of drugs in human waste and their eventual cycling into drinking water. This topic, which is intimately related to the importance of truly understanding "what water is" (and what the water cycle really is) are discussed by Daughton (2004a).

Although the major focus on the potential for adverse effects has been on aquatic exposures to low concentrations of PPCPs, it is important to recognize that exposures to high, acutely toxic doses theoretically can also occur from little-recognized routes, including: (i) wildlife scavenging of carcasses from medicated domestic animals (e.g., raptors feeding on euthanized pets or dead cattle; see: http://epa.gov/nerlesd1/chemistry/pharma/images/double-drugs.pdf), (ii) scavengers of drugs improperly disposed to domestic trash, (iii) medicated feed residuals from aquaculture, and (iv) exposure of bacterial biofilms in sewage trunk lines to transiently high levels of unwanted antibiotics discarded via toilets (http://epa.gov/nerlesd1/chemistry/pharma/images/nas-iom.pdf).

Finally, regardless of whether PPCPs in the environment are shown to pose adverse concerns, a large number of potential actions could be taken to reduce the introduction of PPCPs to the environment. Pollution prevention and environmental stewardship of PPCPs defines a new field called the "Green Pharmacy," a topic covered in depth by Daughton (2003a-c). Pollution prevention could also prove critical with respect to securing and maintaining public trust in municipal water supplies - - a critical factor for securing the future viability of reusing domestic wastewater for drinking (Daughton 2004a).

Future Needs

Even though continued research is needed on the occurrence and fate and transport of PPCPs in aquatic environments, more focus is needed across a broad spectrum of other areas, including: (i) a greatly improved analytical repertoire (amenable to routine use) to accommodate a larger spectrum of PPCPs at lower concentrations (below ng/L), (ii) extent of occurrence in groundwater and point-of-use drinking water (iii) the occurrence of PPCPs and bioactive metabolites in non-aqueous matrices such as sewage biosolids, (iv) low-dose, multi-stressor toxicology of PPCPs in non-target organisms, (v) cost-effective improvements in sewage treatment and recycling of

water, and (vi) design and implementation of pollution prevention and environmental stewardship programs to minimize the introduction of PPCPs to the environment. A wide spectrum of research needs arrayed across the risk paradigm are outlined in Daughton (2004c).

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Prepared for: 228th National Conference of the American Chemical Society, Philadelphia, PA (22-26 August 2004). Available: http://epa.gov/nerlesd1/chemistry/ppcp/images/daughton-acs-extabstract-25aug04.pdf