Pharmaceuticals in the Environment - - Why Should We Care?

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"Take only pictures. Leave only footprints." Perhaps the ultimate expression for the concepts of sustainability and the "ecological footprint," this credo of the hiker and spelunker reflects the collective importance of the seemingly innocuous, minuscule impacts that can accrue from each individual's isolated actions. In reality, however, this credo is simply not possible to uphold, as humans unavoidably leave behind indelible trails of telltale fingerprints. Wherever we live or travel, we impart unique chemical signatures on the environment in the form of minute residues of pharmaceuticals and personal care products that we excrete, wash from our bodies, or discard to sewerage or trash. Even the literal fingerprints we leave behind can contain residues of drug ingredients secreted through our sweat. While the residues originating from each individual may be insignificant by themselves, the combined contributions from all individuals, as well as from medicated animals, can reach measurable levels in surface and ground waters and on land receiving treated sewage residuals.

Yet another acronym for one of the many menageries of chemicals that without invitation take up residency in the environment is PiE - - *Pharmaceuticals in the Environment*. With continually escalating attention devoted by the technical literature and popular press, pharmaceuticals as pollutants in the environment comprise a large, diverse class of thousands of active pharmaceutical ingredients (APIs). These chemicals serve as a widely recognized archetype for the much larger galaxy of so-called "emerging contaminants" (ECs). The ECs aren't necessarily new to the environment - - rather it's the attention we have begun to devote to their ubiquitous presence - - where they occur as interlopers at best, or troublemakers at worst.

Why do (or should) we devote such attention to the PiE issue, especially if we stop to consider that APIs reside in the ambient environment at concentrations that not long ago were considered infinitesimally low - - from parts-per-billion to sub-parts-per-trillion (sub-nanograms per liter, or picomolar) and lower? Roughly a decade ago, these levels were extraordinarily difficult for chemists to routinely detect for any chemical in an environmental matrix and were also far below any levels of known toxicological concern. At the least, however, exposure to PiE incrementally contributes to the overall burden of chemical stressors with which each organism must maintain its homeostasis.

The mere fact that APIs gain unintended, unexpected, and usually unwelcomed entry to the environment has probably served to better engage the public with a graphic realization of the intimate, immediate, and inseparable connection that every individual has with the environment - - PiE makes us acutely aware of the chemical sea that surrounds us, composed of the universe of chemicals that we create as well as those naturally formed in the biosphere. Perhaps more so than for any other class of environmental contaminants, PiE has also made us focus on the much larger world of unregulated contaminants, where quite a variety of linguistic shortcuts have evolved to describe these chemicals with which we coexist. Some of the many terms and acronyms used in the literature are shown in Table 1; these chemicals include not just anthropogenic chemicals but also naturally occurring xenobiotics. The coining of each term or acronym has generally resulted from a need to categorize chemical stressors in different ways to suit different purposes.

While the published literature on unregulated and emerging contaminants is enormous, the literature devoted to PiE alone is exponentially expanding. Are we doing a sufficient job at mining these new data and synthesizing them into a meaningful knowledge base? If not, we risk wasteful duplications of effort and gross inefficiencies in targeting limited research resources (see: http://dx.doi.org/10.1897/09-138.1). Even worse, we risk not realizing that the answers to certain questions may already exist. How do we best define what outcomes are desired from further research, especially outcomes that benefit as many stakeholders and beneficiaries as possible?

Moreover, without a firm idea as to whether PiE is an important issue, why should we continue to invest resources? The answer to this question is partly provided by some of the very questions that PiE has provoked. What are the ramifications as chemists continue to improve their analytical armamentarium for detecting and identifying ever-lower concentrations of pollutants? How will society respond to the expanding knowledge of increasing numbers of xenobiotics occurring in our waters and foods simply because the already minuscule concentrations that are detectable are driven ever lower? Can risk be understood or effectively communicated in the face of chemical mixtures at such low concentrations that the statistical power and abilities of toxicology today are exceeded? How will the new paradigm of confronting the possibility of subtle environmental effects be effectively communicated to the public so that it is perceived in a meaningful manner and that trust in drinking water supplies can be maintained? Can any risk possibly contributed by PiE be placed in a meaningful context of overall risk posed by the galaxies of other anthropogenic and naturally occurring xenobiotics to which humans and the environment are continually exposed? Perhaps the major question is how do we ensure the sustainability (and minimize the exposure hazards) of a chemical-based, chemical-centric society in the most cost-effective manner?

Even though there seem to be very few definitive answers to what might appear to be too many questions, these questions alone can justify continued examination of the PiE issue. But there are a number of other reasons that PiE should hold our attention as scientists and as consumers. PiE makes obvious the connection that should ordinarily exist between the practice of medicine and the study and protection of the condition of the environment. The two are intimately tied but little recognized as such. The two share many commonalities and connections. Just consider the processes of data collection, epidemiology, diagnosis, mitigation/treatment, prognosis, determination of vulnerability, and pollution/disease prevention. Each of these plays a critical role in both health care and environmental protection - - in the ecology of health and in the health of ecology. Of key significance in determining how to allocate limited resources to ever-growing numbers of priorities, improvements in one can often leverage unintended, collateral improvements in the other. By implementing any number of the myriad ways to minimize PiE, significant improvements in the quality and cost of healthcare can possibly be achieved.

For the aquatic environment, major unknowns include the consequences of chronic (sometimes mutigenerational) exposure to very low levels of multiple pharmaceutical residues. This exposure sometimes involves receptors that differ from those in humans, and mechanisms of action can change as the exposure levels are reduced. The potential for effects can increase with exposure to multiple like-acting drugs, as a result of concentration (or dose) addition. Unpredictable and perhaps surprising adverse effects can result, as witnessed by the decimation of certain vulture populations from scavenging carcasses from domestic animals that had been treated with diclofenac, or demonstrated in the collapse of fish populations by exposure to low parts-per-trillion of 17α-ethynylestradiol.

Exposure for humans to environmental API residues, compared with aquatic exposure, is probably lower because feral residues occur in drinking water at greatly reduced levels; but foods grown on sewage- or manure-amended acreage may contain substantially higher concentrations - - a consequence of the preferential sorption of certain APIs to sewage sludge. The occurrence of even minute residues of APIs in drinking waters, especially waters created for immediate reuse, poses special problems with regard to risk perception as they constitute unexpected, unintentional, unwelcome exposure that traces directly back to a water's origin from sewage.

In contrast to aquatic exposure, additional unknowns arise regarding human exposure. How do we assess the significance of unintended exposure due to:

- chronic exposures to APIs designed for short-term therapeutic use;
- exposure routes that differ from the intended clinical routes of administration (e.g., oral ingestion of APIs intended exclusively for dermal use);

- simultaneous exposure to low-levels of multiple APIs, especially those that are contraindicated (this could be particularly problematic for APIs present below purported no-effects levels but which share common modes of action, making the effective dose the sum of the individual doses);
- unintended, unexpected exposure of certain sub-populations to APIs that they should actively avoid (e.g., drugs contraindicated during pregnancy). With regard to the last item, exposure during critical times of developmental vulnerability can yield subtle but lasting functional defects; this concern was codified in the "Faroes Statement" on "Human Health Effects of Developmental Exposure to Chemicals in Our Environment" (http://dx.doi.org/10.1111/j.1742-7843.2007.00114.x), which emphasizes that beyond the traditional view of toxicity - - where the "dose makes the poison" - - exists a second dimension where the "timing amplifies the poison".

An important aside is the way in which risk communication has often been formulated in attempts to convey the extremely low risk currently assessed for the trace levels of APIs in drinking water. Attempts to place trace concentrations into context by using analogies (such as a part-per-trillion roughly equating to but a single drop in an Olympic-size pool) may only inject further confusion - - or at worst serve to misdirect. The concept of concentrations not only can add confusion to risk communication, it can also serve to distract from pertinent facts or even pose a degree of self-contradiction. For example, statements are often made that concentrations in the part-per-trillion (ng/L) range are vanishingly low. But at the same time, it is common knowledge in the water and beverage industries that certain ubiquitous organic chemicals interact with biological receptors and result in obvious biological responses at levels below the lowest currently measurable levels for APIs in water. For example, objectionable taste or odor can be imparted to water at concentrations down into the tens of picograms per liter (nearing a part per quadrillion, pg/L). Examples of chemicals that can elicit such taste or odor effects at sub-ppt levels include: geosmin, guaiacol, 2,4,6-trichloro- and 2,4,6-tribromo-anisole, and 2-isobutyl- and 2-isopropyl-3-methoxypyrazine. This incongruity in attempting to convey a lack of significance in low concentrations of APIs can only lead to confusion.

Finally, even if concentrations might currently be considered extremely low, continued reductions in water supply (from extended drought) and increasing incidence of effluent-dominated receiving waters, punctuated with raw sewage overflow events, could inevitably lead to higher concentrations of all trace contaminants (because of less dilution). The problem of diminished stream flows is further exacerbated when sewage escapes untreated such as in locales where straight-piping (direct discharge without treatment) of raw sewage is still practiced.

If we acknowledge that it may not be possible to sustain a chemical-by-chemical approach to regulating or even for monitoring environmental contaminants, then we need

to examine if there are simple ways in which to at least make continual progress in lessening, and preferably minimizing, exposures. Even in the absence of understanding the extent and magnitude of the actual chemical-exposure universe, certain actions aimed at reducing exposure to APIs could have unrelated collateral benefits, greatly increasing their cost-effectiveness.

Most of the pollution prevention measures that could be implemented to reduce the introduction of ingredients from pharmaceuticals to the environment stand a good chance of also reducing the introduction of other substances, some of which we may not even be currently aware. A reachable goal would be to educate the public to the fact that ALL of their actions, activities, and behaviors can impact our shared environment. This major learning point can be reinforced by providing guidance on the environmentally sound and safe disposal of all consumer items. The immediate outcome sought is to redirect consumer wastes down the avenues with the smallest ecological footprints. The ultimate outcome is to continually reduce unneeded, imprudent consumption.

Likewise, all treatment technologies (none of which was ever specifically designed for removing APIs from wastewater, sewage sludge, or drinking water) act by broad mechanisms that span many chemical classes. By controlling one class, control of others will also occur. Money spent in removing one class of pollutants is highly leveraged because it can also facilitate the collateral removal of other contaminants - - some of which, including certain APIs, undoubtedly continue to elude the detection prowess of analytical chemists.

Examining the life cycle of a medication perhaps reveals the most important aspect of why we should care about trace levels of APIs in the environment. PiE actually serves to dramatize wasted healthcare resources and lost opportunities to achieve therapeutic objectives. Our focus to date has tended to dwell on discrete aspects of the life cycle of APIs - - limited primarily to establishing environmental occurrence and studying source control (waste and drinking water treatment) and the potential for aquatic effects. The actual origin of the problem and possible solutions, however, have garnered significantly less attention, with the one exception being the design of approaches for dealing with unwanted, leftover medications; in the U.S., the first federal guidance for consumer disposal of unused drugs was issued in February of 2007 by the White House Office of National Drug Control Policy and subsequently elaborated upon by the US FDA (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/default.htm). Important to note, however, is that the magnitude of the contribution of APIs to the environment via disposal (versus excretion) is unknown and probably varies dramatically across APIs (as a function of the pharmacokinetics, delivery routes, and compliance rates for the respective medications). While the proper disposal of unwanted drugs might be important for reducing the unnecessary entry of at least certain drugs to the environment, it may never achieve

dramatic reductions in the overall magnitude of PiE. Prudent disposal is perhaps more important for minimizing the very real problem of human morbidity and mortality due to diversion of drugs from accumulated stockpiles of medications and those medications imprudently discarded to trash, and the consequent poisonings of humans and pets.

Beyond the proper disposal of unwanted drugs, the ultimate focus with regard to pollution prevention is perhaps better placed on the way in which drugs are marketed, prescribed, and dispensed. Healthcare systems could be re-designed so that only the optimal medications are prescribed (for correct and therapeutically justified purposes) in minimal doses individualized for each patient, and dispensed in quantities and for durations to facilitate their full consumption; the potential for environmental impact can also be considered in selecting medications. The ideal outcome would be a profound reduction in the types and quantities of leftover drugs requiring disposal; see http://dx.doi.org/10.2165/0002018-200831120-00004. Little recognized is that redesign of prescribing and dispensing practices could also lessen the quantities of APIs that gain entry to the environment as a result of their intended use - - e.g., simply by reducing excretion as a result of lower doses or shorter courses. Many additional factors beyond the prescribing and dispensing chains play roles, such as patient compliance and direct-to-consumer advertising (in the US and Australia).

The end result of a greener healthcare system could be not just a cleaner environment, but also more efficient usage of healthcare resources, reduced healthcare costs, improved therapeutic outcomes, and reduced incidence of purposeful abuse and accidental poisonings from diversion of stockpiled or improperly disposed drugs. The health of humans is indeed intertwined with that of the environment. Perhaps the healthcare community should develop a credo analogous to the spelunker's - - something akin to "Prescribe and dispense only what's needed – no more. Leave no medication behind."

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Table 1. Terminology of Chemical Pollutant Classifications

Class or Grouping	*Grouped According to:*
EDC / **EAC** (Endocrine Disrupting [or Active] Chemical) **CMR** (Carcinogenic, Mutagenic, toxic to Reproduction	toxicological mode of action or endpoint
PBT (Persistent, Bioaccumulative Toxic) **vPvB** (very Persistent, very Bioaccumulative) **POP** (Persistent Organic Pollutant)	environmental properties
micro-pollutants; **micro-constituents** **trace pollutants** / **residues** **TOrC** (Trace Organic Compounds	frequency/level of occurrence
OWCs [a] (Organic Wastewater Contaminants)	location of occurrence
PPCPs [b] (also PhACs, PACs, and PiE; these each comprise a subset of PPCPs, which includes personal care products)	type of intended usage
priority pollutants	regulation
unregulated pollutants	absence of regulation
"**chemical weeds**" [c]	public perception ("out of place chemicals")
emerging contaminants/pollutants [d] **ECCs** (emerging chemicals of concern) **EPOCs** (emerging pollutants of concern) **ESOCs** (emerging substances of concern) **COCs** (chemicals of concern) [e] **COPCs** (chemicals of potential concern) **CECs** (chemicals of emerging concern)	novelty, fad, timeliness, or new concern
xenobiotics, exotics **xenobiotic organic compounds (XOCs)**	foreign versus endogenous
toxicants, toxins, toxics, perturbogens (agonists, antagonists, activators, repressors, inhibitors, regulators, modulators)	overall toxicity (note: "toxins" comprise a special subset of toxicants – namely, those that are naturally synthesized, primarily proteins; "toxics" is jargon for "toxicants")
HPV [f] (high production volume) chemicals	quantity (manufactured/imported in US > 1 million pounds/year)
PDPs or **HDPs** (population- or human-derived pollutants/constituents) **POHO** (pollutants of human origin)	source or origin

Footnotes:

[a] **OWCs**: coined by Kolpin et al., *Environmental Science & Technology*, 2002, *36*(6):1202-1211.

[b] **PPCPs**: "pharmaceuticals and personal care products" (coined by Daughton and Ternes, *Environmental Health Perspectives*, 1999, *107*[suppl. 6]:907-938); PhACs: "pharmaceutically active compounds" (coined by Sedlak, Gray, and Pinkston, *Environmental Science & Technology*, 2000, *34*:508A-515A); PiE: “pharmaceuticals in the environment” [came into use around 2001, when PhRMA (Pharmaceutical Research and Manufacturers of America) created its internal *PIE Task Force*].

[c] **Chemical Weeds**: coined by Daughton, *Renewable Resources Journal*, 2005, *23*(4):6-23.

[d] **Emerging Contaminants**: term first used prominently by the National Research Council ("Identifying Future Drinking Water Contaminants: based on the 1998 Workshop on Emerging Drinking Water Contaminants," National Academy Press, Washington, DC, 1999).

[e] **COCs/COPCs**: came into use in early 1990s.

[f] **HPV**: see the U.S. EPA's The High Production Volume Information System (HPVIS): http://www.epa.gov/hpvis/index.html