Environmental Stewardship of Pharmaceuticals: The *Green Pharmacy*

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ABSTRACT

The occurrence of pharmaceuticals and personal care products (PPCPs) as environmental pollutants is a multifaceted issue whose scope continues to become better delineated since the escalation of concerted attention beginning in the 1980s. PPCPs typically occur as trace environmental pollutants (primarily in surface but also in ground waters) as a result of their widespread, continuous, combined usage in a broad range of human and veterinary therapeutic activities and practices. With respect to the risk-assessment paradigm, the growing body of published work has focused primarily on the origin and occurrence of these substances. Comparatively less is known about human and ecological exposure, and even less about the documented or potential hazards associated with trace exposure to these anthropogenic substances, many of which are highly bioactive and perpetually present in many aquatic locales.

The continually growing, worldwide importance of freshwater resources underscores the need for ensuring that any aggregate or cumulative impacts on water supplies and resultant potential for human or ecological exposure be minimized. This has prompted the more recent investigations of waste treatment processes for one of the major sources of environmental disposition, namely sewage.

Despite the paucity of health effects data for long-term, simultaneous exposure to multiple xenobiotics (particularly PPCPs) at low doses, a wide range of proactive actions could be implemented in the near-term (and research initiated for the longer term) for reducing or minimizing the introduction of PPCPs to the environment. These actions and activities fall in the category of pollution prevention (or source reduction, minimization, or elimination), a particular aspect of the risk paradigm that has received very little attention — risk management of PPCPs.

Many of the actions that can be foreseen for pollution prevention fall under what could be envisioned as a holistic stewardship program — overseen by the healthcare industry and consumers alike. Significantly, such a stewardship program would benefit not just the environment — additional, seemingly unrelated benefits could automatically accrue, including lessening medication expense for the consumer and improving overall patient health and consumer safety. Such wide-ranging benefits are a characteristic of the so-called "cradle-to-cradle" approach to stewardship.

This paper briefly summarizes the imperative for an ecologically oriented stewardship program for PPCPs — the "Green Pharmacy" — a holistic approach that accounts for the many facets of the overall, complex issue. It then attempts to give a flavor for the broad spectrum of possible actions that could be implemented or researched to minimize the environmental disposition of PPCPs in general. The wide spectrum of actions available for minimizing the release of PPCPs to the environment has been formulated for the first time in a single (2-part) document to be published in *Environmental Health Perspectives*: "Toward a Green Pharmacy – Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition while Promoting Human Health" (Daughton 2003a,b; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/greenpharmacy.htm).

It is important to recognize that guidance affecting the responsible environmental disposition of PPCPs need not originate from regulators. A cohesive, scientifically sound set of guiding principles could be formulated and adopted by the industries involved with the design, manufacturing, packaging, distribution, and purveyance of PPCPs — principles that would also serve to influence or guide consumer actions.

One of the major objectives of this work is to generate an active dialog or debate across the many disciplines that must become actively involved to design and implement a successful voluntary compliance approach to life-cycle stewardship of PPCPs — a "cradle-to-cradle" approach that not only minimizes their potential to impact the environment, but one that could also improve medical healthcare outcomes for consumers and reduce healthcare costs. By focusing on developing an industry consensus and cultural mind set toward holistic environmental responsibility, rather than compliance to regulations, all aspects of society can play integral, productive, and sustainable roles.

Biographical Sketch

Christian Daughton (daughton.christian@epa.gov; 702-798-2207; fax 702-798-2142) has served as the Chief of the Environmental Chemistry Branch at the U.S. Environmental Protection Agency's National Exposure Research Laboratory in Las Vegas since 1991. His prior experience was supervisory research faculty at U.C. Berkeley and Lawrence Berkeley Laboratory (1979 to 1990) after earning a B.A. in Biology from University of California, San Diego-Revelle College (1971), a Ph.D. in Ecology from U.C. Davis (Department of Environmental Toxicology, 1976), and research as an NIH Postdoctoral Fellow at Cornell University with Prof. Martin Alexander.

Background - Drugs as Pollutants

Pharmaceuticals and personal care products comprise an extraordinarily large and diverse galaxy of chemicals. As environmental pollutants, they are collectively referred to as "PPCPs". Although waste streams from the manufacturing of PPCPs are regulated by the U.S. EPA, once the commercial end product leaves the manufacturing facility, federal regulations or guidance only govern the environmental disposition of but a select few of these chemicals. Among this galaxy of thousands of distinct chemical entities possessing numerous mechanisms of biological action are those that can elicit subtle responses from non-target organisms as well acute effects. Adverse effects can result from interactions across different therapeutic classes and also from cumulative exposure to multiple stressors that happen to share the same mechanism of action.

While their individual contributions might be minuscule, the combined actions, activities, and behaviors of consumers and other end users (such as confined animal feeding operations) of PPCPs contribute to a significant overall environmental input as well as to the total environmental load of anthropogenic chemical stressors. These chemicals find their way into the environment after purposeful disposal by consumers (especially to sewage) and primarily by their continual inadvertent release (via excretion or washing). The complexity of the releases is magnified by the concomitant excretion of sometimes numerous bioactive metabolites from any single parent PPCP, and also by abiotic transformation processes in sewage treatment plants or the environment, which can create yet more products from the original parent PPCP or metabolite (chlorination and ozonation oxidative steps can yield numerous, partially oxidized products). The continual release of PPCPs via treated sewage gives them a "pseudo-persistent" presence (regardless of structural stability) in any aquatic environment that receives sewage input (from either humans or domestic animals). Municipal sewage treatment facilities were not designed to remove exotic anthropogenic chemicals, and the documented presence of PPCPs in treated sewage effluent reflects this limitation.

That PPCPs (among a galaxy of other consumer-use chemicals) should gain ready access to the environment is obvious today only as a result of several decades of research by environmental analytical chemists, who succeeded in shepherding this issue to the fore of the larger environmental science community, as well as

making it visible to the public, the media, and regulatory agencies. The vast majority of work published on PPCPs has been driven by analytical chemistry — with the objectives of establishing the magnitude and extent of their environmental distribution, structural transformation, and fate. In stark contrast, however, much less is known regarding ecological and especially human exposure (such as from water re-use), and nearly nothing is known regarding the potential for adverse ecological effects (with exceptions such as for antimicrobials and certain steroids). Advancement in this area will require the concerted efforts of toxicologists and biologists, among others.

The continually growing, worldwide importance of freshwater resources (highlighted by critically needed water re-use projects) underscores the need for ensuring that any aggregate or cumulative impacts on water supplies and resultant potential for human or ecological exposure be minimized. This has prompted a recent escalation of investigations for improved waste treatment processes for what is perhaps the major source of environmental PPCP disposition, namely sewage (e.g., see: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Wastewater).

Leaving aside the numerous unknowns and uncertainties surrounding the many controversies involved with the toxicological significance of simultaneous low-level exposure to multiple stressors (especially drugs), surprisingly little discussion has been devoted to actions that could be taken in the near-term and longer-term to reduce or eliminate the introduction of PPCPs to the environment. After all, pollution prevention (or source reduction, minimization, or elimination) embodies many advantages compared with waste treatment or environmental remediation.

Background - Pollution Prevention for PPCPs

An historical disconnect continues to persist between discussions of human health and "ecological heath". This disconnect is a topic of active discussion and is central to the concept of cradle-to-cradle stewardship of PPCPs (e.g., see discussions at: Daughton 2003a; Di Giulio and Benson 2002; National Academy of Sciences' Institute of Medicine (IOM) "Roundtable on Environmental Health Sciences, Research, and Medicine": http://www.iom.edu/iom/iomhome.nsf/pages/environmental+health+roundtable). In addition to the imperative of merging these two camps, it is also important to transition away from a reductionist approach for study of complex systems and toward a holistic systems-level understanding — one that encompasses a larger degree of complexity and interplay. Many benefits could accrue to the consumer, to the environment, and to manufacturers alike by designing an integrated systems-wide approach for eliminating or continually reducing the introduction of PPCPs to the environment. This is a key feature of "cradle-to-cradle" design and stewardship programs, an approach that embodies the concepts put forth in numerous other efforts for pollution prevention, captured under a host of monikers, such as: design for the environment (DfE), industrial ecology, life cycle planning/design/assessment (LCA), product-stewardship, extended product responsibility (EPR) (including not just the producer, but rather the entire use-chain, including consumer), product "take-back" programs (where unused/unneeded product travels back up through the distribution chain — "reverse distribution"), zero waste, zero emissions, green chemistry, eco-effectiveness, ecological intelligence, waste to wealth, and many others. A cradle-to-cradle approach places the emphasis on managing the life-cycle flow of materials always with the objective of seizing new opportunities to lessen environmental impact while at the same time improving conditions for people and industry — managing all materials as perpetual resources rather than as wastes.

The portion of the overall risk puzzle contributed by PPCPs as pollutants is unknown. But even in the absence of further data on the extent, magnitude, and human and ecological toxicological significance of PPCP contamination of surface and ground waters (as well as terrestrial environments receiving sewage and manure sludges, such as "biosolids"; e.g., see NRC 2001), a wide array of actions could nonetheless be taken to reduce or minimize the introduction of these chemicals to the environment. Unfortunately, no nationwide standards or guidance currently exist for minimizing the release of PPCPs to the environment. In fact, the purposeful

introduction of drugs to the environment is even encouraged by some states that require the disposal of unused drugs to municipal sewage systems (such as at long-term care facilities), as well as by certain poison prevention centers (a result of human safety concerns).

The ecologically sound disposal of PPCPs is but one part of the larger issue. Numerous other tactics could be employed to minimize the release of PPCPs to the environment. A cohesive, scientifically sound set of guiding principles could be voluntarily formulated and adopted by the industries and service sectors involved with the entire life-cycle of a drug — from design, manufacturing, packaging, and distribution, to purveyance, use, and disposal or recycling. These principles could in turn serve to influence or guide parallel consumer actions.

The wherewithal for designing such an "environmental stewardship" program for PPCPs already exists. The knowledge base has already been largely developed. But unfortunately, the numerous disparate pieces for such a program are spread across a wide and disconnected literature that spans many disciplines that traditionally never communicate with one another.

A Stewardship Solution - The *Green Pharmacy*

To facilitate and partially coordinate international research on the many issues involved with PPCPs as trace environmental pollutants, the U.S. EPA maintains a web site devoted to the overall topic: http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm. This web site is a compilation not just of international publications and activities but also serves as a central repository for EPA's Office of Research and Development (ORD) in-house work on PPCPs conducted at its National Exposure Research Laboratory (NERL) in Las Vegas, Nevada. NERL's work has involved the development of new chemical analysis approaches for PPCPs as well as the production of several seminal publications covering the many facets of the larger topic (e.g., see: http://www.epa.gov/nerlesd1/chemistry/pharma/overview.htm).

NERL is attempting to bring to the fore the topic of environmental stewardship for drugs — applied beyond the traditional considerations limited to the many aspects of product manufacturing ("industrial ecology"). For a discussion of the industrial ecology aspects of drugs, see Velagaleti and Burns (2002). Note that many pharmaceutical companies have promulgated their own "environmental stewardship" values or perspectives (e.g., see: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Perspective), but these fall short of a holistic approach, largely because guidance from the national (and international) government levels is lacking.

It is important to foster cross-communication and forge collaborations between environmental scientists and the medical community to leverage and synergize existing knowledge. The existing literature regarding the environmental aspects of PPCPs is almost exclusively a result of efforts from environmental scientists (primarily analytical chemists). Much could be contributed from the many fields of medical science and practice. Partly in an attempt to catalyze inter-disciplinary efforts and dialog between the pharmaceutical, health-care, and environmental arenas, the British medical journal *The Lancet* published a commentary that represented the first attempt to involve the medical community (Daughton 2002).

The *Lancet* article, in turn served as the introduction to a 2-part article (referred to as the "*Green Pharmacy*"), scheduled for publication in *Environmental Health Perspectives* (Daughton 2003a,b). This paper in part outlines a broad spectrum of possible actions that could be implemented or researched to minimize the environmental disposition of PPCPs. A coordinated array of activities and pollution prevention actions could be envisioned for a holistic PPCPs stewardship program — overseen by the healthcare industry and consumers alike. The wide spectrum of actions available for minimizing the release of PPCPs to the environment has been formulated for the first time in this single resource. The unedited, on-line pre-publication versions are available at: http://www.epa.gov/nerlesd1/chemistry/ppcp/greenpharmacy.htm; the final published versions will also be available at this same URL. Significantly, such a stewardship program would benefit not just the environment.

Additional, seemingly unrelated benefits could automatically accrue, including lessening medication expense for the consumer and improving overall patient health and consumer safety.

Objectives & Outcomes

The 2-part *Green Pharmacy* article has multiple objectives, including: (1) facilitating a broad and open dialog and exchange of ideas regarding innovative approaches to pollution prevention for PPCPs, (2) encouraging communication and collaboration amongst the traditionally separate and insular disciplines that comprise environmental and medical sciences (much can be gained by an exchange of knowledge amongst these disparate disciplines), (3) catalyzing ongoing advancements in reducing the environmental impact of the health care industry, (4) focusing attention on the need for uniform, nationwide regulations, guidance, or voluntary stewardship programs designed specifically for PPCPs, and (5) fostering the development of stewardship approaches that benefit not just the environment, but also improve medical healthcare outcomes for consumers and reduce healthcare costs.

A number of significant collateral outcomes could also be expected to accrue from the integration of environmental stewardship into the worldwide health care community. Among these is raising public consciousness regarding the general principles of environmental science and thereby also possibly improving the communication of risk — an extremely problematic topic of growing importance, especially with regard to wastewater re-use for human consumption; "toilet-to-tap" water re-use programs in particular need vastly improved approaches for communicating risk. Another is increased security of our water supplies as a result of focusing more attention on un-regulated trace pollutants (most potential water sabotage agents are not regulated pollutants subject to routine monitoring).

The major routes for achieving any desired environmental and public health outcomes could include:

- Changing consumer behavior and values (via outreach programs and education, including a re-designed use of direct-to-consumer [DTC] advertising); raising public awareness of the environmental consequences of their consumption decisions
- More effective communication of risk (the cognitive sciences should play a key role, one that to date has been largely unfulfilled; social scientists and psychologists, for example, should play more substantive roles)
- Voluntary stewardship programs (currently non-existent for PPCPs, but outlined in the *Green Pharmacy* article)
- Aiming for consensus on what role (if any) the Precautionary Principle should play in guiding environmental stewardship programs for drugs (see: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#The Precautionary Principle)
- Formal rules, decisions, guidance (especially regarding disposal and re-use; implementation of take-back programs to consumer level).

An Emphasis on Proactive Voluntary Actions

The issue of "pollution prevention" in regard to PPCPs as environmental pollutants has always prompted considerable inquiry from the public and the media. Publication of the *Green Pharmacy* paper represents the first time than the topic has been expansively delineated in the literature and the first time that a comprehensive series of suggestions and recommendations has been proposed for minimizing the introduction of PPCPs to the environment. The philosophy and approach adopted by the *Green Pharmacy* paper favors the development of proactive, voluntary stewardship programs and community involvement. While the paper was developed independently of EPA's *Innovation Strategy* (http://www.epa.gov/opei/strategy), as well as with U.S. EPA's Science Advisory Board's interest in industrial ecology (SAB 2002), it happens to comport with this now preferred approach to effecting change. While the paper sets forth a wide spectrum of possible approaches for minimizing the introduction of PPCPs to the environment (spanning the spectrum from drug and package design

to the reclamation of drugs from wastes), the pollution prevention strategies that are highlighted are primarily non-conventional — few involve any waste treatment engineered solution.

Some Simple Examples

The means for attaining a *Green Pharmacy* are limited only by the imaginations of those scientists, engineers, and others involved in the countless aspects of PPCP discovery, design, formulation, dosage delivery, manufacturing, advertising, distribution, sales, and use, and eventual disposal or recycling of these diverse products. A number of pertinent activities are already underway at pharmaceutical companies (not necessarily with environmental stewardship in mind, but rather with the objective of improved drug efficacy), and many other avenues are possible (overview presented in the *Green Pharmacy* article, Daughton 2003a,b). The following are a few examples related to marketing, product substitution, product alternatives, advertising/education.

Marketing (Drug Nomenclature): An aspect of the drug industry that suffers from some peculiarities of the nature of organic chemistry nomenclature is its bewildering and oftentimes confusing array of chemical synonyms, contractions, generic names, trade names, and others. One of countless examples is: N-(4-Hydroxyphenyl)acetamide: aka 4'-hydroxyacetanilide; p-hydroxyacetanilide; p-acetamidophenol; p-acetaminophenol; p-acetylaminophenol; N-acetyl-p-aminophenol. The name"N-acetyl-p-aminophenol" led to three major common names:

U.S.: N-acetyl-*p*-aminophenol => acetaminophen
U.S.: N-acetyl-*p*-aminophenol => Tylenol™
Europe: (para) N-Acetyl-aminophenol => paracetamol

This is but one example of vastly different names used for the same widely used drug. The other end of the spectrum includes drugs from completely different therapeutic categories with similar-looking names (Celebrex vs. Celexa vs. Cerebyx), similar-sounding names (e.g., Sarafem [fluoxetine hydrochloride for premenstrual dysphoric disorder, PMDD] and Serophene [clomiphene citrate for treatment of ovulatory failure]), similar-looking pills, and similar-looking packaging; many examples at: http://www.usp.org/reporting/prnews/dsw_085.htm. This contributes to confusion and errors for the consumer as well as for health-care practitioners (from physicians to pharmacists; similar names accounted for 15% of all USP-reported medication errors from 1996-2000). There are more than 15,000 formulary names in the U.S.

This cacophony of jargon leads to several questions that could have direct bearing on the possible over-consumption of drugs and their unnecessary release to the environment. Does the presence of the same drug entity in different OTC formulations intended for different purposes (e.g., acetaminophen in antihistamines, cough and cold preparations, flu medication, and analgesics) lead to consumer intake unintentionally higher than recommended? The analogous problem can exist when a patient with multiple doctors receives prescriptions with the same drug entity as the major or auxiliary ingredient for different disorders (different brand names for the same drug for unrelated therapeutic purposes; e.g., Sarafem and Prozac [both fluoxetine hydrochloride] for PMDD and depression); a closely related problem is the prescribing of multiple medications (by multiple specialists) that all share the same common side-effect mechanism (e.g., anticholinergic effects in geriatric patients). Clearly, progress towards international standardization of naming conventions could reduce medication errors, reduce over-dosing, and consequently lead to reduced purchase and consumption.

Substitutes for Antimicrobials: As one of many possible examples of "product substitution," consider the multifaceted concerns surrounding the use (and inappropriate use) of antimicrobials (see references at: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Imprudent Use of Antibiotics). Minimization of antibiotic usage can be attained by any number of means, including: use of non-drug alternatives or use of synergists [probiotics (for humans) or competitive exclusion products (domestic animals), live phage therapy

(pioneered by the Soviets in the 1920s), enzyme therapy, vaccines, efflux pump inhibitors]; holistic improvement in conventional animal husbandry and hygiene (especially for CAFOs); minimization of OTC sales; continuing education for veterinary and health-care professionals (emphasizing appropriate use as well as environmental stewardship); and education of the patient (to instill realistic expectations for treatment, e.g., as for viral infections).

Nutritional Measures: Another area that highlights one of many possible examples of "natural" alternatives to medication includes the possibly unnecessary use of certain medications for treating symptoms that can be frequently controlled simply by proven nutritional measures. One example is the growing medication of young children and teens for the symptoms of depression and obsessive compulsive disorder. The historic off-label pediatric use of drugs such as methylphenidate and fluoxetine (among others), coupled now with FDA's approval for pediatric use of such drugs as fluoxetine (3 January 2003: http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html) continually escalates the use of these drugs for conditions that can frequently be treated by well-documented nutritional measures. Countless controlled studies, for example, continue to show the profound antidepressant effect of omega-3 food oils, while being devoid of the many side effects associated with these medications. This is accomplished simply by increased consumption of the omega-3 essential fatty acid (linolenic acid) coupled with intake of a much lower ratio of omega-6 (linoleic) to omega-3 oils (e.g., via flax or hemp oils) and augmented intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [linolenic anabolic products, available in concentrated form from cold-water fish oil].

Naturally Occurring Personal Care Product Substitutes: Other examples include the use of naturally occurring chemicals as alternatives to widely used PPCPs. One example is the USDA's *SoyScreen* (feruloylated acylglycerols made from ferulic acid and soybean oil), which has broad UV-absorption characteristics (over the A, B, & C bands) and is a possible replacement for all four current sunscreen agents (octylmethoxy cinnamate, padimate-O, oxybenzone, and dioxybenzone). A second example is a chemical isolated from tomatoes (recently revealed to be 2-undecanone) that has powerful insect repellent properties, especially for mosquitoes (to be marketed under the trade name *SkeeterShield*), and which could reduce the environmental introduction of the widely used and ubiquitous DEET (N,N-diethyl-m-toluamide). For more information, see: "Illustrative Examples of Alternative 'Green' Active Agents" (at: http://www.epa.gov/nerlesd1/chemistry/ppcp/greenpharmacy.htm).

Underappreciated Emerging Issues: While antibiotics supply many obvious opportunities for cradle-to-cradle environmental design, at the same time it is important to not lose sight of other PPCP domains that could prove critical with respect to environmental impact but which are receiving little attention. One such area is that of "molecular farming," sometimes referred to as "biopharming" — the production of PPCPs by transgenic organisms. The use of genetically modified human food crops to produce "plant-made pharmaceuticals" (PMPs) has created a host of controversies that have received remarkably little attention from those other than the specialists in this area (see discussions at: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#MolecularFarming). While one of the major concerns of PMPs is the potential for increased allergenicity or intestinal irritation, one particular aspect of PMPs that has received little attention is their environmental disposition (and effects on foraging wildlife or detritus feeders) during crop growth and harvesting.

Role of Advertising/Education: As a final example, an area that probably plays a key role in the escalating increase in drug use, and therefore in the introduction of drugs to the environment, is DTC advertising. DTC is extraordinarily controversial in all sectors of the medical community and perhaps promotes an unknown portion of inappropriate or unnecessary drug usage. While DTC ads are reviewed by the FDA (http://www.fda.gov/cder/ddmac/lawsregs.htm), these reviews are performed while and after the ad campaigns are underway. DTC is extraordinarily controversial, reflected by the fact that it is banned in almost all countries (a couple of exceptions being the U.S. and New Zealand). DTC advertising is intended to educate the consumer.

But it has prompted a long series of furiously debated questions, such as "Does DTC...": Interfere with the physician-patient relationship (e.g., encouraging "doctor shopping"). Create unrealistic patient expectations? Mislead or provide incomplete information for the consumer? Lead to escalation of medication pricing? Increase prescribing for previously unrecognized (invented) conditions? Lead to inappropriate or unneeded use/treatment? Encourage prescription drug use over otherwise suitable OTC medication or nutritional measures? Encourage prescribing of substantially more expensive new drugs that are only marginally more effective than prior generations? Improve healthcare outcomes (via consumer education) or lead to unnecessary increase in drug consumption? Lead to consumers not understanding the purported outcome of treatment with a particular drug (e.g., the difference between treating symptoms versus obtaining an actual cure)?

DTC advertising in the U.S. has grown as a result of FDA changes in 1997 to advertising regulation (as a result of the need now for only brief mention of side effects). As of 2002, DTC spending was roughly $3B, while consumers spent about $500B on medication. The relevance of DTC to stewardship is wide-ranging. An improved and expanded consumer-education component could theoretically improve consumer health and reduce drug costs while at the same time serve to protect the environment simply by way of providing sound guidance on the recycling/disposal of unused mediation and by reducing inappropriate drug use. A recent overview of the multi-faceted topic of DTC advertising was published by *Consumer Reports* (2003). For an historical perspective on the commercialization of medicine via advertising, see "Medicine and Madison Avenue" (Duke University; http://scriptorium.lib.duke.edu/mma/); historical examples of OTC products once widely advertised to consumers include heroin, cocaine, and oral antibiotics of high toxicity (e.g., bacitracin)

Limitations of Regulation

EPA's involvement with the overall issue of PPCPs as environmental pollutants from all non-manufacturing sources would traditionally be driven by four regulatory mandates (as supported by available science and monitoring data), only three of which could have substantive impact on the environmental disposition of these chemicals. Historically, these regulatory routes have been used to reduce the introduction of various defined chemical constituents (and sometimes their colligative properties) and effect desired environmental and public health outcomes.

Regulatory mandates potentially relevant to PPCPs (for a more general presentation of EPA regulatory mandates, see: http://www.epa.gov/epahome/laws.htm):

Safe Drinking Water Act (SDWA, 1974 & 1996) [in part, requires EPA to establish a list of contaminants (Office of Water's Drinking Water's "Contaminant Candidate List" [CCL]: http://www.epa.gov/safewater/ccl/cclfs.html) to aid in priority-setting for the Agency's drinking water program, under the EPA's "Unregulated Contaminant Monitoring Rule" [UCMR]: http://www.epa.gov/safewater/ucmr.html); also see the 2001 NRC publication "Classifying Drinking Water Contaminants for Regulatory Consideration," available at: http://www.nap.edu/catalog/10080.html]

Clean Water Act (CWA, 1972) [relevant to PPCP occurrence in, and removal from, sewage treatment works - STWs; e.g., see: U.S. EPA "Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Industry": http://www.epa.gov/ost/guide/pharm.html]

Resource Conservation and Recovery Act (RCRA, 1976) [relevant to disposal of certain PPCPs; e.g., "reverse distributors," see: Smith 2002]

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 1948) [e.g., orchard antibiotics, broad-spectrum biocides, emergency exemptions such as for caffeine and acetaminophen, used for controlling the *coqui* frog and the Brown Tree snake, respectively, see "Other Uses" at: http://www.epa.gov/nerlesd1/chemistry/pharma/tracers.htm]

To fully appreciate the continued viability of these entrenched approaches to controlling chemical pollutants — ones necessarily based on narrow, pre-defined chemical lists amenable to target-based chemical analysis — one

must consider its limitations in the context of the larger universe of chemical pollutants (see: http://www.epa.gov/nerlesd1/chemistry/pharma/critical.htm).

Using as an analogy the "Expanding Organic Chemical Pie" — which is bounded by the *Universe* of organic chemicals (including both those naturally occurring and anthropogenically derived) — the limitations of a target-based approach become apparent. Within this universe of chemicals, if our planet of present concern simply comprises those current numbers of listed and regulated pollutants (worldwide), then this is but several percent the size of the solar system containing those organic chemicals that are commercially available (and therefore capable of entering the environment). This continually expanding slice of the universe (driven by continual advances in technology, which for drugs includes the "omics" revolution) is smaller than the galaxy of known organic chemicals (both anthropogenic and naturally occurring) and dwarfed by the galaxy clusters of those chemicals that currently exist (but many of which, especially the myriads of toxicologically significant naturally occurring toxicants, *have yet to be identified*). These clusters of existing galaxies are, in turn, dwarfed by the universe of potential structures, which essentially exceeds a theoretical number with no known bounds (see following).

The expanding organic chemical universe
(for supporting references, see: http://www.epa.gov/nerlesd1/chemistry/pharma/critical.htm)

$\approx 0.25 \times 10^6$ – **Planet** of *Listed/Regulated* chemicals (and properties) worldwide)
$\approx 6 \times 10^6$ – **Solar System** of *Commercially Available* organic chemicals
$< 24 \times 10^6$ – **Galaxy** of *Known* organic chemicals (those that have been identified, both anthropogenic and naturally occurring)
$>> 0.025 \times 10^9$ – **Galaxy Clusters** of *Existing* organic structures (known plus those not yet identified [unknowns])
$>> 10^{60}$ – **Universe** of *Existing plus Potential/Theoretical* structures (those that *could* be synthesized)

As of January 2003, more than 140,000 bioactive compounds were in various phases of drug research and development (Prous Scientific Ensemble: http://www.prous.com/databases/ensemweb/ensemweb.html). The rapid evolution of the "omics" revolution (from study of the genome, proteome, glycome, metabonome, etc.; see glossary at: http://www.genomicglossaries.com/) will undoubtedly feed an expansion of new drug entities that has already been underway.

A growing and ever-changing topography of chemicals with potential ecological or human health significance as trace environmental pollutants is a concern posed by drugs in particular – because many will have mechanisms of action never before encountered by biological systems. New entities are introduced commercially on a regular basis while others are withdrawn from market. This would create a moving target for regulation. Other major obstacles to regulating on a chemical-by-chemical basis include:

(i) Lack of an ability to know to what degree type II errors are being avoided — that is, how many health-critical chemicals are being overlooked.

(ii) Certain chemicals (e.g., regulators/modulators of efflux pumps, microsomal oxidases, cellular stress response, etc.) pose no inherent health risk on their own and would be overlooked by using solitary, single-chemical risk-evaluation approaches) but could greatly potentiate the toxicity of other chemicals. Such stressors whose solitary effects do not manifest themselves in adverse endpoints, when present with other stressors either make possible or potentiate adverse outcomes. This points to the importance of accommodating for the "4Ts" of exposure in risk assessment: "Toxicant Totality Tolerance Trajectory" (see: http://www.epa.gov/nerlesd1/chemistry/ppcp/stressors.htm).

The current approach to regulating chemicals in the environment essentially carves imperceptibly ever-widening concentric circles from the chemical universe pie (the center being the "planet" of currently listed/regulated

chemicals). This approach manages to serve successive slices of regulated chemical pie that are only infinitesimally larger and can never have assurance of capturing any particular portion of toxicants comprising overall hazard. An alternative, but hypothetical, approach would slice the pie into comprehensive portions comprising radial sections of the entire pie; the majority of chemical constituents in each slice might include chemicals that have not yet been identified. One way to do this would be to set trigger values for the modulation (inhibition/induction, up-regulation/down-regulation) of key evolutionarily conserved biochemical/cellular processes (implemented as toxicogenomic arrays); this would place the emphasis more on effects (and potential outcomes) rather than exposure. Such a biological/biochemical-process approach would automatically integrate all those chemicals sharing a like-mechanism of action (i.e., the cumulative exposure aspect of the "risk cup"; see Fig. 1: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/pollution1.pdf/). By using a conserved biological-processes approach (which maximizes the relevancy for as many genera as possible), it's conceivable that indicators of the presence of chemical stressors (PPCPs would be only one of many possible "toxicant galaxies") could be detected whereas the actual chemical(s) itself may not yet be amenable to ready chemical detection.

Clearly, especially in light of the precautionary principle, measures for the comprehensive control of PPCPs in the environment on a chemical-by-chemical approach could be easily overwhelmed. Stewardship programs could prove especially important given the difficulties that could be faced in any attempt to regulate the occurrence of pharmaceuticals in the environment on a chemical-by-chemical basis. The pharmaceutical galaxy has demonstrated its ability to continually expand — and this expansion will probably accelerate as a result of the "omics" revolution (http://www.genomicglossaries.com/). New drug entities, many with mechanisms of action never before encountered by humans or any other organism, can be expected to enjoy continued introduction to commerce — while others are retired or withdrawn from market. This could create a continually moving target for regulatory action, a problem compounded by the limitations of risk assessment (particularly in regard to simultaneous exposure to trace levels of multitudes of stressors) — especially where risk is traditionally assessed on the basis of solitary chemicals, isolated from any interactions with the myriads of other stressors (see: http://www.epa.gov/nerlesd1/chemistry/pharma/critical.htm) to which organisms can be exposed at any point in time (see: http://www.epa.gov/nerlesd1/chemistry/ppcp/stressors.htm). This latter point is extremely important with regard to those many drugs that pose no inherent hazard of their own (for example, regulators/modulators of efflux pumps, cellular stress response, or microsomal oxidases) but which can profoundly potentiate the toxicity of other drugs and chemical stressors.

Possible Next Steps

The U.S. EPA's Science Advisory Board has expressed its broad interest in expanding the concept and implementation of pollution prevention and environmental stewardship (under the concept of Industrial Ecology; SAB 2002). A number of EPA programs have historically played active roles in various facets of environmental stewardship. These existing programs have the ability to shepherd the evolution of a *Green Pharmacy*. As examples, the EPA's Office of Solid Waste could collaborate with the U.S. FDA and the DEA to develop a nationwide consumer-level take-back program for unused/unwanted drugs; this would partially entail a reworking of RCRA (e.g., see: http://www.epa.gov/epaoswer/osw/vision.pdf); such an effort aligns with OSW's existing work with pollution prevention (e.g., see: http://www.epa.gov/epaoswer/osw/polprev.htm). These same organizations could work with the states to replace the patchwork of often conflicting state regulations that govern the disposal of unused drugs (e.g., from long-term care facilities) with a consistent nationwide policy protective of both environmental health and public safety. The long-standing work on life-cycle assessment (LCA) by the EPA's ORD (http://www.epa.gov/ORD/NRMRL/lcaccess/) could play a lead role in developing cradle-to-cradle design concepts for PPCPs. Collaboration with industry [e.g., via industry trade associations such as Pharmaceutical Research and Manufacturers of America (PhRMA) and Cosmetic, Toiletry, and Fragrance Association (CTFA)] would be important. The EPA's STAR grants program (http://www.epa.gov/nerlesd1/chemistry/pharma/star.htm) could be used to develop innovative, cutting-edge approaches. These are just some of the many possibilities for a federally led initiative for a *Green Pharmacy*.

Using the *Green Pharmacy* article as a foundation and framework, the EPA, together with the FDA and other federal agencies, could play a lead role in developing a national, integrated environmental stewardship program for PPCPs. The overall objective of such a *Green Pharmacy* program would be to reduce the potential for adverse environmental consequences of PPCPs while simultaneously yielding improved public health and safety and improved industry efficiency and effectiveness in providing healthcare.

Perhaps the ultimate question that should be asked is whether an overarching stewardship program (encompassing all aspects of the healthcare industry) aimed at overall reduction in drug usage, recycling, and disposal could yield a larger reduction in potential human and ecological exposure for far less investment in R&D and end-of-pipe control technologies, and at the same time yield collateral benefits for consumer/public health.

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