

Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health.

I. Rationale for and Avenues toward a Green Pharmacy

Christian G. Daughton

Environmental Chemistry Branch, Environmental Sciences Division/National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Las Vegas, Nevada, USA

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 long-term, 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. 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. *Key words:* cradle-to-cradle stewardship, drugs, environmental pollution, green pharmacy, pollution prevention. *Environ Health Perspect* 111:757–774 (2003). doi:10.1289/ehp.5947 available via <http://dx.doi.org/> [Online 12 December 2002]

The occurrence of pharmaceuticals and personal care products (PPCPs) in the environment has received growing attention since the 1980s. The major issues associated with the origins and occurrence of these chemicals in surface, subsurface, and drinking waters (as well as what little is known about the potential effects on nontarget species) have been captured in a number of reviews, books, and proceedings, examples of some recent ones of which include Daughton (2001a), Daughton and Jones-Lepp (2001), Daughton and Ternes (1999), Heberer (2002); see also Kümmerer (2001), Servos *et al.* (2002), and the entire special issue of *Toxicology Letters* (2002). The most comprehensive target-monitoring study ever performed was completed by the U.S. Geological Survey (USGS) (Kolpin *et al.* 2002). Many of these materials (and more) are accessible from the U.S. Environmental Protection Agency (U.S. EPA) website devoted to the topic of PPCPs in the environment (Daughton/U.S. EPA 2002a).

This article is the first of a two-part examination of the many facets of a little-discussed but very important aspect of the overall issue of PPCPs as environmental pollutants: pollution prevention. In light of the fact that trace residues from this large, diverse galaxy of sometimes highly bioactive chemicals gain entry to the environment simply through their use and disposal, and regardless of what little is known regarding the consequences for ecologic or human health (Daughton 2001a; Daughton and Ternes 1999), a wide spectrum of actions could be taken to minimize or eliminate the continued environmental disposition of PPCPs. Significantly, these actions toward pollution prevention (e.g., source reduction/control) hold the potential at the same time for beneficial human health consequences unrelated to the occurrence of PPCPs as pollutants. In this article I focus on those aspects of source control/reduction that reside under the control of the health care industry (further up the chain of events

involved with a drug’s cradle-to-grave disposition). In part II (Daughton 2003), I address those activities tied more closely to the end user (e.g., the patient) and issues associated with drug disposal/recycling. In this article I also present some of the background and context for why pollution prevention is a topic worth considering for PPCPs; in part II, I make specific suggestions and recommendations centering more on end use, present recommendations for further research, and pose some considerations regarding the future.

With a focus on pollution prevention (e.g., source elimination or minimization) via voluntary actions as an alternative to conventional pollution control via prescribed standards, this mini-monograph is intended as a companion piece to the review published in *Environmental Health Perspectives* (Daughton and Ternes 1999) that focused primarily on the origins and environmental occurrence of PPCPs together with an introduction to what little was known at that time about the potential for adverse ecologic effects.

One of my major objectives in this monograph 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—an approach that not only minimizes their potential to affect the environment but

This article is part of the mini-monograph “Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health.”

Address correspondence to C.G. Daughton, Chief, Environmental Chemistry Branch, ESD/NERL, Office of Research and Development, U.S. EPA, 944 East Harmon, Las Vegas, NV 89119 USA. Telephone: (702) 798-2207. Fax: (702) 798-2142. E-mail: daughton.christian@epa.gov

I thank the following for their valuable time in providing helpful review of both technical and policy aspects of the manuscript: O. Conerly (U.S. EPA, Office of Water) and *EHP*’s anonymous reviewers, all of whom contributed to improving the quality of the manuscript.

The U.S. EPA, through its Office of Research and Development, funded and performed the research described. This article has been subjected to the U.S. EPA’s peer and administrative review and has been approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation by the U.S. EPA for use.

The author declares he has no conflict of interest.

Received 20 August 2002; accepted 10 December 2002.

also could collaterally improve medical health care outcomes for consumers and reduce health care costs. Although the onus for environmental stewardship rests primarily with the larger health care community (including the consumer), almost no discussion of the overall issue has taken root in the medical literature (Daughton 2002a). A cohesive, scientifically sound set of guiding principles could be adopted by the industries involved with manufacturing, packaging, distribution, and purveyance of PPCPs—principles that would also influence or guide consumer actions. By focusing on developing an industry consensus and cultural mindset toward holistic environmental responsibility rather than relying on compliance to regulations, all sectors of society could play integral, productive roles in striving for a sustainable environment.

Opportunity for Caution: Toxicity Out of Context

Although PPCPs are often considered “emerging” pollutants, it is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. Their occurrence has become more widely evident since the 1990s only because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. There is no reason to believe that any given PPCP has not had the potential to find its way into the environment since the date of its introduction to commerce—or even from the date it was first used for experiments or clinical trials.

Most current approaches to pollutant tracking center on the small subset of anthropogenic (and some naturally occurring) toxicants in the environment. Significantly, these “conventional” pollutants do not necessarily serve as surrogates representing the extremely wide spectrum of modalities by which toxicants can adversely affect organisms. That regulated pollutants account for such a small fraction of potential chemical stressors begs a question that can be formulated from a notion often attributed to Einstein, paraphrased as “Not everything that can be counted counts, and not everything that counts can be counted.” A corollary can be derived from this for environmental monitoring: “Not everything that can be measured is worth measuring, and not everything worth measuring is measurable.” The spectrum of pollutants typically identified in an environmental sample typically represents an unknown portion of those actually present (possibly very small), and they are of unknown overall risk significance (Figure 1).

Because of the extraordinary complexity of both exposure and outcome, toxicologists usually are forced to look at cause–effect issues “out of context”: The historic ramification has been

to consider exposure solely as a function of a single toxicant or a very limited set of chemical stressors. The overall picture, however, is complicated not just by the large universe of potential toxicants to which an organism can normally be exposed at any point (or period) of time but also by the host of other variables such as exposure level, exposure route (e.g., dermal, enteral, pulmonary), exposure timing (windows of vulnerability, e.g., developmental stage), prior exposure history, prior exposure duration (e.g., acute—short-term, sequential, intermittent, episodic—or chronic), nutrition, age, sex, genetics, and nonchemical costressors (temperature, physical/metabolic stress, noise, electromagnetic radiation, pathogens). All these factors determine an organism’s historic “exposure trajectory,” which in turn determines its current health status and sets the stage for the outcome of current exposure (vulnerability vs. resistance to homeostasis perturbation). With science’s limited understanding of this complex,

dynamic interplay of multiple factors, risk assessment is necessarily restricted to assessing the ramifications of potential adverse toxic events without the larger holistic perspective.

A convenient shorthand term that captures the complete context of an organism’s cumulative exposure to chemical stressors does not exist. One possibility offered here is “toxicant–totality–tolerance–trajectory” (the “4Ts”; see Daughton/U.S. EPA 2003a), which accounts for an organism’s complete exposure time line (a trajectory described by prior multidimensional exposure history) and the fact that a major objective of all organisms is to maintain homeostasis (in the face of continual perturbation by stressors). Homeostasis can be maintained only within the tolerance bounds for the organism’s biochemical defensive repertoire. So the 4Ts describe the hypothetical overall true risk as reflected by the sum total of exposure to all toxicants (anthropogenic and naturally occurring) throughout

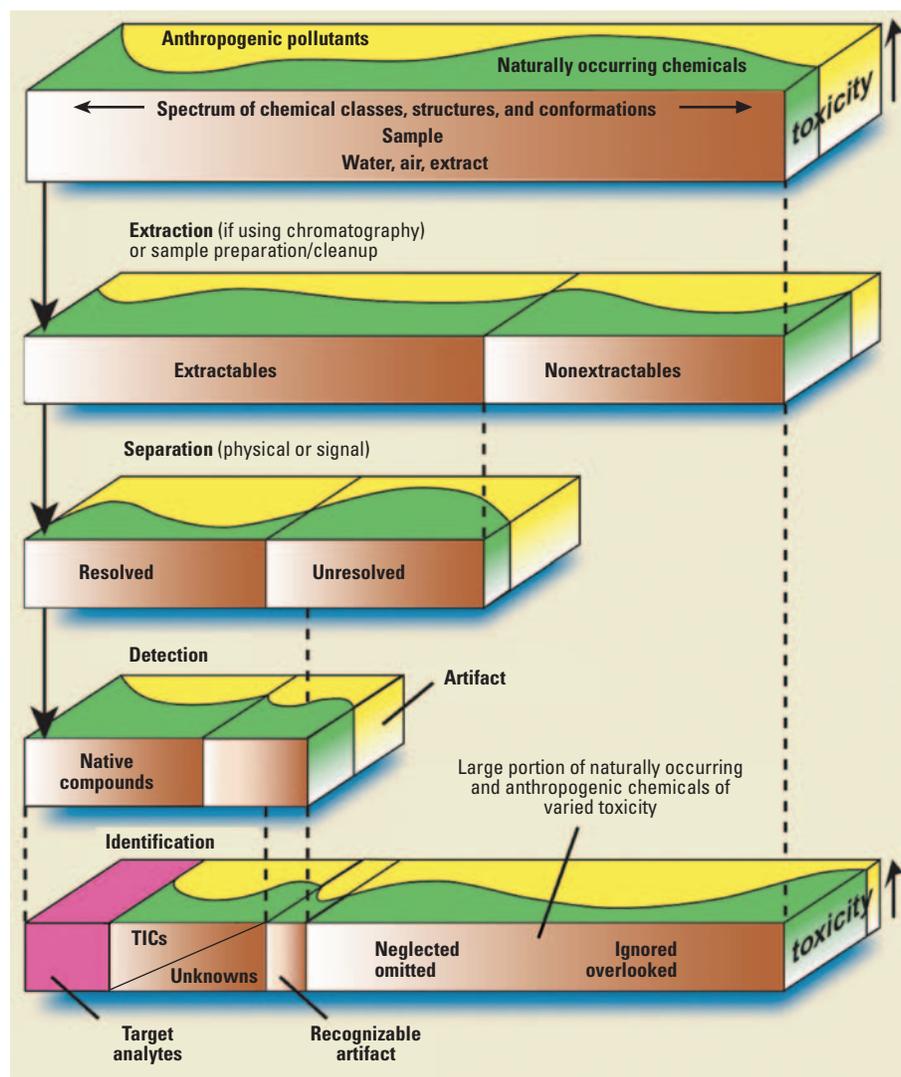


Figure 1. Limitations and complexities of environmental chemical analysis. TIC, tentatively identified compound.

the historical multidimensional space and trajectory of all other exposure variables. A key aspect to this concept is the critical state determined by the 4Ts—the state at which an additional single exposure event can result in an adverse effect.

The documented occurrence of PPCPs in the environment may or may not eventually have any implications regarding either ecologic or human health—primarily because their known concentrations are so low [nanograms per liter (parts per trillion) to micrograms per liter (parts per billion)]. The issues associated with potential ecologic effects in particular cannot be resolved until aquatic and computational toxicologists (for an overview of computational toxicology, see Bradley 2002) begin to evaluate the effects on nontarget organisms by simultaneous, long-term exposure to multiple PPCPs at low doses and to assess the significance of cumulative exposure to PPCPs sharing the same biochemical mechanism of action (MOA). Indeed, therapeutic doses for target organisms (which are often many orders of magnitude higher than dissolved waste concentrations) may not be relevant benchmarks against which to assess risks to nontarget species. Furthermore, environmental monitoring tends to focus on concentrations of PPCPs dissolved in water (because of their water solubility). This emphasis, however, could underestimate environmental loads by unknown magnitude because of sorption to suspended particulates, sediments, or sewage biosolids; this could prove critically significant regarding interface phenomena and lead to higher than projected exposure levels (e.g., exposure of microorganisms to antibiotics).

Given the ever-expanding universe of receptors targeted for drug action, the futility of attempting to assess environmental effects using a chemical-by-chemical approach (indeed, the traditional approach has relied only on lists of preselected, individual chemicals) becomes clearer as advances in drug design continue. Instead, the focus could be directed to understanding the ramifications of entire classes that share a common MOA (or common physiologic or behavioral end point)—because of the probability of cumulative exposure. Delineating the total environmental burden of chemicals sharing a particular MOA could be the objective instead of targeting specific chemicals for regulation. First, however, those MOAs or cellular processes that pose inherent risks would have to be identified and prioritized, including significant effects or perturbations to homeostasis that are *a*) unique to each therapeutic class (e.g., resistance selection for antibiotics) and *b*) mediated via biochemical features and pathways that are evolutionarily conserved across taxa and are elicited by many therapeutic classes (e.g., efflux pumps, cellular

stress protein response, apoptosis, specific signaling pathways). Many of these same toxicologic issues are discussed in a recent overview (WHO 2002a) of endocrine-disrupting compounds (EDCs), a small subset of which are PPCPs; an EDC is an exogenous substance that “alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations” (WHO 2002a). Although the topics of PPCPs and EDCs intersect only partly, they share some controversial issues.

A critical aspect of determining the significance of MOAs must be factored into this process. MOAs that lead directly to adverse effects are not the only consideration—or, paradoxically, not even necessarily the most important. Chemicals that have no inherent toxicity of their own but rather potentiate the toxicity of others might contribute significantly to risk. Examples include inhibitors of efflux pumps and of microsomal oxidases (Daughton 2001a; Daughton and Ternes 1999; Epel and Smital 2001). Finally, arguing against the utility of MOA-directed risk assessments are two factors: Many drugs have multiple MOAs (these are sometimes referred to as “dirty” drugs), large numbers of which yet remain to be identified. Further, gross, within-class endpoint differences are known to exist for certain drugs; for example, some selective serotonin reuptake inhibitors (a class of antidepressants) have extremely potent effects on shellfish reproductive behavior, whereas others have almost no effect (Daughton and Ternes 1999; Fong 2001).

Regardless of the risks that might be posed by the current generations of PPCPs, the fact that many members of this large, diverse universe of bioactive chemicals have the demonstrated potential to enter the environment provides the rare opportunity to investigate proactively whether each of the myriad new drugs under development poses adverse risks to the environment (or humans). This knowledge essentially affords us the luxury of an early warning to direct more attention to potential, unintended ramifications of introducing new PPCPs to commerce. It gives us the advance opportunity to be watchful regarding the future introduction to commerce of drugs designed with completely new mechanisms of action and ever-increasing biochemical potencies.

Nonetheless, many actions can be taken in the shorter term to minimize the introduction of PPCPs to the environment. These recommendations and suggestions are the subject of this mini-monograph. The ideas presented here are based largely on the manner in which medical care (which includes pharmaceutical use) is conducted in the United States and to lesser degrees in Canada,

Western Europe, and Australia. The wide range of issues and suggestions presented here might have no relevance to other parts of the world. Also, the major focus of this mini-monograph is a survey of the many avenues available for reducing the controllable introduction of PPCPs to the environment; I do not address the many issues (especially the potential for adverse effects) associated with the unintended, uncontrollable excretion of PPCPs and their metabolites into the environment (an issue that can be addressed via engineering “end-of-pipe” controls).

Fragmentation of Science

The large number of disciplines of science and other professions that must be integrated to address the many facets of PPCPs as pollutants drives home the importance of cross-communication among disparate disciplines. Unfortunately, the fragmentation of science (driven by specialization) is a problem that continues to grow (Daughton 2001b, 2002b). In this mini-monograph I attempt to weave together many facets involved with preventing environmental pollution by PPCPs. In doing so, I address two objectives. First is an effort to bring together the limited and fragmented literature that exists from the diverse fields and interwoven aspects involved with approaches for reducing the introduction of pharmaceuticals to the environment—in the face of what little is known about possible risks that might be associated with these bioactive substances in the environment. Second is an attempt to delineate some of the major actions that could be taken to minimize the introduction of drugs to the environment—actions that could be implemented with little planning, those that would require major attention by the numerous agencies involved with a patchwork of laws and regulation of drug recycling and disposal, and those that would require further research and development. A major motive for this mini-monograph is to foster an awareness of the many complexities involving this emerging issue—to present a wider perspective for and appreciation of the larger literature. Although recognizing the importance of in-depth, critical reviews (Daughton 2001b, 2002b), I do not attempt to review comprehensively the many pertinent subjects or aspects, but rather to cite some key references so that those interested in particular aspects can gain faster entry to a literature that is often difficult to locate. Most of the literature covered in this mini-monograph has never been synthesized into a unified “message” or understanding. The literature on pharmaceuticals encompasses a number of fields that are infrequently visited by environmental scientists. Likewise, those involved in medical science and health care practice are not fully informed of the environmental issues and consequences

associated with drugs. I aim to bring these two disparate fields together here because much could be gained by their cross-collaboration.

Engaging the Public

The topic of PPCPs as pollutants has captured much attention from the press (Daughton/EPA 2002b), and its visibility in the public is marked by its introduction to educational curricula (from elementary school through college) and to the popular press (e.g., Buhner 2002). The public, educators, and students have expressed much interest in the topic because they can identify easily with its primary origin, which embodies the interconnectedness of humans and the environment—the occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the diffuse actions and activities of individuals and their environment (Daughton 2001a; Daughton/U.S. EPA 2002a). PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative use by multitudes of individuals. Although the public has long understood that individual actions and activities are partly responsible for terrestrial and air pollution (obvious examples being litter and vehicle exhaust), public connection with water pollution usually remains lost in the perception that industry and agriculture are the primary sources, not consumerism and personal activities. This misconception is illustrated by the underappreciated fact that of the petroleum introduced to North American oceans each year, about 85% comes from the seemingly minuscule actions of individuals, not large oil spills and pipeline leaks [National Research Council (NRC) 2002a]. The strong interest expressed by the public in the topic of PPCPs grants scientists, educators, and policy makers a rare opportunity to engage consumers in learning about the environment and the many actions they can take as individuals to improve overall ecologic and human health. Indeed, the critical importance of involving the public in scientific debates and decision making for creating sustainable communities is becoming more widely recognized (NCSE 2001).

Advance Warning

With regard to assessing environmental risk associated with PPCPs as pollutants, the science to date has focused on the issues of environmental sources and occurrence—primarily chemical identities and concentrations in waters and, to a much lesser degree, sewage sludge. Newer occurrence data continue to be published by researchers in Europe, Canada, and the United States. One of the objectives of the first-ever U.S. national reconnaissance of “emerging pollutants” in waters, conducted by the USGS, was to establish baseline occurrence

data (Kolpin et al. 2002; USGS 2002). Some further perspective on the USGS study is important, however. The PPCPs documented to occur in U.S. surface waters probably represent but a fraction of all those that actually occur (because the USGS monitoring study, like all monitoring studies, used a target-based approach, where only a limited number of compounds must be preselected for monitoring). Whether the potential for human health or ecologic effects from this subset of PPCPs is eventually demonstrated is largely irrelevant. More important, these occurrence data demonstrate the potential for any consumer-use chemical to enter the environment. This foresight provides the opportunity to watch for the future introduction to commerce of drugs possessing totally new mechanisms of action and ever-increasing biochemical potencies.

We can expect drug use to continue to expand and increase because of a confluence of drivers: increased per capita consumption, expanding population, expanding potential markets (partly due to mainstream advertising/marketing), patent expirations (shift to less expensive generics), new target age groups, inverting age structure in the general population, and new uses for existing drugs. Old therapeutics are being used not just for additional clinical conditions (those for which they were not originally developed) but also for nondisease states—for example, medical manipulation or alteration of personality traits and satisfaction of certain social needs—referred to as “cosmetic pharmacology.”

Limitations of Guidelines for Environmental Risk Assessments

Our ability to assess any risks that might be posed to ecologic or human health by PPCPs in the environment is hampered greatly by the profound lack of relevant toxicologic information, especially for the aquatic environment, which tends to be the ultimate sink for these predominantly nonvolatile, amphiphilic compounds (although terrestrial exposure can occur when sewage sludge with sorbed or occluded PPCPs is applied to land) (Daughton and Ternes 1999; NRC 2002b). For example, in the United States, environmental assessments for approving new drug applications are required by the U.S. Food and Drug Administration (FDA) only when the concentration of a drug predicted to enter the aquatic environment [expected environmental concentration (EEC) or predicted environmental concentration (PEC), as used in Europe] would be 1 µg/L (1 ppb) or greater (U.S. DHHS 1998). The FDA’s historical toxicity data for standard aquatic tests demonstrate no conventional effects at concentrations lower than 1 ppb (also see regulatory discussions in Velagaleti and Gill 2001 and Velagaleti et al. 2002). In contrast,

the European Agency for the Evaluation of Medicinal Products (EMA 2001) has proposed a trigger value of 0.01 µg/L (10 ppt) (see discussion in Straub 2002). Regardless of the actual value, however, the scientific validity of these trigger approaches has been questioned (e.g., CSTEE 2001), an issue stemming primarily from the dearth of toxicologic information on nontarget species. Regardless of whether trigger values may be used, three major additional factors are not accounted for in any approach that uses “predicted” environmental concentrations (i.e., EEC or PEC); each factor is discussed in turn below.

Ramifications of geographic variability in drug use. Calculation of PECs assumes a uniform geographic usage. In practice, however, environmental occurrence is a function of the local prescribing practices and usage customs and the confluence of hospitals (whose use of drug types differs from that of the general community). Although PPCP production/use figures are largely confidential, recent data from the first study ever published on geographic variation (across the United States) of prescription drug use (Express Scripts 2001) show that at least for some drugs, regional preferences in use can vary by severalfold or more. The types of drugs (and dosages) can vary significantly from municipality to municipality, county to county, region to region, and country to country—largely as a function of age structure of the populations and of prescribing customs. This means that for highly populated metropolitan areas with use of a particular drug exceeding what would be expected by a uniform distribution, the actual environmental concentration (EEC or PEC) could be higher than predicted.

Unaccounted sources. A variety of largely undetectable, alternate sources for PPCPs (other than legal sales through approved market channels) contribute to overall use and are not accounted for in EEC or PEC calculations. Further complicating matters is that prescription numbers and over-the-counter (OTC) sales are only a rough measure of a drug’s use because they account for just a portion of the overall use. Physician samples (drugs that are intended not to be sold but rather to promote the sale of a drug), the resale “diversion market,” black market sales, free trial offers by manufacturers, and the little-publicized “prescription drug patient assistance programs” sponsored by the pharmaceutical industry (e.g., see links at DisabilityResources.org 2002) are other, perhaps substantial, sources that are difficult to account for. As an example, the sales of drugs via the Internet may incur a substantial, unregulated import of unknown quantities of drugs from foreign countries; Internet sales continue to increase and thus pose a concern to the U.S. FDA (2002a) in terms of consumer health. Countries also vary as to whether a

drug is available by prescription only or via OTC; this could be significant for those drugs that have the potential to be transported across geographic boundaries.

Interactions. Exposure to just a single toxicant at a time is most likely an extraordinarily rare event, especially in the aquatic domain. Exposure is more likely a routine multidimensional occurrence involving multiple chemical stressors with dynamic spatial and temporal components and whose outcomes have a strong dependency on prior exposure history (the 4Ts). The current practice of risk assessment considers a single stressor at a time, and if the PEC for the single stressor is below the “no effect concentration” (which is a direct reflection solely of the select few of the countless end points that happen to be selected), further assessment is usually deemed unnecessary. This approach clearly relies on stressors acting in sequence and independently (i.e., no interactions), but aggregate and cumulative exposure may play significant roles (Figure 2).

In the final analysis, maximum PECs should eventually be corroborated through more extensive monitoring of all relevant environmental compartments—the only way to verify whether predicted concentrations agree with reality. One way to collect sufficient data would be through a program such as the U.S. EPA Office of Water’s Drinking Water Contaminant Candidate List, which is administered under the U.S. EPA’s Unregulated Contaminant Monitoring Rule (U.S. EPA Office of Water 2002).

PPCPs in the Environment and Their Control

Sources. From the patterns that have emerged in the published occurrence data, it is now clear that all municipal treated sewage (unless subjected to advanced wastewater treatment technologies, e.g., reverse osmosis and granular activated carbon)—regardless of location—will contain PPCPs. The issue is not unique to any particular municipal area. Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs. Several major sources contribute to the introduction of both licit and illicit drugs to the environment (Daughton/U.S. EPA 2002c). The major three are probably excretion, washing, and purposeful disposal. These three sources most likely feed into municipal waste systems and storm runoff (e.g., sanitary or combined sewers), and to a lesser but significant degree are discharged directly to surface waters via “straight-piping.” Waste discharged to engineered systems is subjected to various levels of treatment-technology sophistication before discharge to receiving waters. PPCPs, however, display a broad range of removal efficiencies by waste and water treatment technologies; some travel through sewage treatment facilities with only minor reductions in concentration (the antiepileptic carbamazepine is but one example) (Daughton and Ternes 1999; Heberer 2002). Also, some minor overall sources could potentially play significantly large local roles. One is cemeteries, which could provide a source of PPCPs to the subsurface (Daughton 2003).

The continual input of PPCPs to the aquatic environment via sewage can impart a persistence-like quality to those compounds that otherwise possess little inherent chemical stability in the environment (Daughton and Ternes 1999) because new molecules replenish those that are being removed; these chemicals can be referred to as “pseudo-persistent” pollutants (Daughton 2002a). The full extent, magnitude, and ramifications of their presence in the aquatic environment, however, are largely unknown. The two largest unknown domains in toxicology, which are centrally germane to PPCPs as environmental pollutants, are the significance of *a*) chronic, multigenerational, low-dose exposure [i.e., nanomolar to picomolar (below parts per billion/parts per trillion), a common concentration range for PPCPs in waters] and *b*) simultaneous exposure to multiple stressors. Both of these are complicated further by each chemical’s perhaps being in a constant state of flux in both absolute and relative abundance. The occurrence differences of PPCPs in raw sewage are a function of *a*) local prescribing and use customs, *b*) confluence of hospitals, *c*) state policies and customs regarding disposal of unused PPCPs, and *d*) local manufacture and use of illicit and abused drugs. For surface and ground waters, the differences are a function of *a*) whether any treatment technologies are employed (straight-piping, malfunctioning septic systems, overflow events), *b*) types of treatment technologies employed (for sewage, potable water, or reinjection waters), and *c*) local/seasonal fluctuations in biophysicochemical transformation potential (e.g., biodegradation, photolysis, sediment/particulate sequestration).

Key importance of water resources: impact of untreated sewage. Regardless of whether the efficiencies of waste or drinking water treatment approaches can be improved, large volumes of untreated wastewater are discharged to surface waters each year. The release of PPCPs into the environment would be maximized by the release of raw sewage. Sources of raw sewage in the United States released to streams, lakes, estuaries, oceans, and groundwater are responsible for high but largely unknown volumes: *a*) combined sewer overflows (CSOs), which contribute more than 4×10^{12} L/year [CSOs handle rainwater runoff, domestic sewage, and industrial wastewater, and are designed to discharge untreated sewage during adverse storm events (U.S. EPA Office of Wastewater Management 2002a)]; *b*) sanitary sewer overflows (severe weather, system malfunction, improper system operation/maintenance); *c*) leakage from sewage transport infrastructure (sewer pipe cracks caused by tree roots and defective/collapsed pipes); *d*) failing septic systems; *e*) unpermitted privies; and *f*) straight-piping.

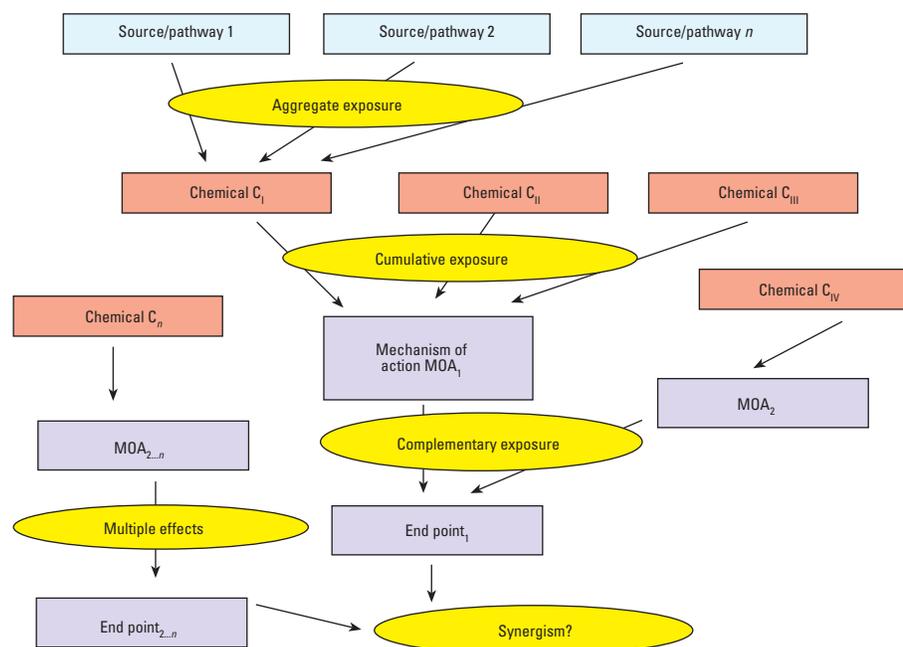


Figure 2. Contributions of different chemicals to the Risk Cup, which shows the differences between the various exposure scenarios. The Risk Cup presents a particular perspective of the first three of the four dimensions of the 4Ts (toxicant, totality, tolerance) but does not capture the fourth (trajectory).

Repair of existing sewage and water handling infrastructure in the United States will require huge resources. The American Society of Civil Engineers' 2001 Report Card for America's Infrastructure (ASCE 2001) assigned nationwide grades of "D" for both drinking water and wastewater infrastructures. More than \$20 billion annually is the estimated need for rectifying the nation's degenerating water/waste infrastructures.

If PPCPs eventually prove to be an environmental concern, it is not known whether sewage treatment facilities could even be cost-effectively modified to reduce emissions—especially given the huge costs associated with reestablishing and maintaining their original performance. Ultimately, source control (pollution prevention) aimed at disposal practices as well as actual therapeutic use may prove more effective. The remainder of this article and all of part II (Daughton 2003) present ideas regarding the broad spectrum of activities that could be encompassed by pollution prevention.

Pollution Prevention

Regardless of the outcome of the toxicologic significance of PPCPs for ecologic systems (including humans), and regardless of the progress that can be made with respect to improving waste or water treatment technologies, a wide variety of actions can be initiated in the near term to minimize the introduction of PPCPs (as well as other consumer-oriented xenobiotics) to the environment and thereby reduce the potential for emerging risks or risks that have yet to be gauged or characterized. These proactive actions span a wide spectrum of disciplines and serve as the focus for this mini-monograph, a focus that is driven by four of the 10 goals that formed the basis of the U.S. EPA's (2000) Strategic Plan—Goal 2 (Clean and Safe Water), Goal 4 (Preventing Pollution and Reducing Risk in Communities, Homes, Workplaces, and Ecosystems), Goal 5 (Better Waste Management, Restoration of Contaminated Waste Sites, and Emergency Response), and Goal 8 (Sound Science—Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems) (U.S. EPA 2000). In addition, one of the primary goals of the U.S. EPA's Office of Research and Development is to identify and foster investigation of previously "hidden" or potential environmental issues/concerns before they become critical ecologic or human health problems—pollution prevention (e.g., source elimination or minimization) being preferable to remediation or restoration (so as to minimize both public cost and human/ecologic exposure).

An important consequence of reducing the introduction of PPCPs to the environment is that a wide range of other benefits

could accrue to both consumers and industry. By addressing the environmental issues associated with PPCPs as environmental contaminants, in most respects substantial collateral improvements to health care could also be achieved. These are highlighted in various sections of both parts I and II of this mini-monograph. Benefits to consumers could include reduced health care costs partly as a result of a more efficient and safe administration of all chemicals used in health care.

Environmental Surprise and the Precautionary Principle

A proactive approach to dealing with issues posing unknown or unpredictable consequence is rooted in the concept of "surprise" in environmental systems. This concept was perhaps originally formalized by ecologist Crawford S. (Buzz) Holling in the early 1970s. "Surprise" occurs when

causes turn out to be sharply different than was conceived, when behaviors are profoundly unexpected, and when action produces a result opposite to that intended—in short, when perceived reality departs *qualitatively* from expectation. (Holling 1986, p. 294)

Environmental surprise occurs when the ultimate hazards differ from those that were anticipated. Further discussion is provided by Schneider and Turner (1994).

In Holling's view, "resilience" may enable an ecosystem to return to a steady state after being subjected to an unusual event (or an ongoing succession of cumulative events) denoted as being a surprise. But the state to which it reverts may be different—in other words, a discontinuous change is effected. The ramifications of subtle perturbations to complex systems such as ecosystems have been discussed in many forums [sometimes called the "butterfly effect," where the flapping of a butterfly's wings in one geographic locale may make the difference sometime in the future between calm and unstable weather in another locale (Gleick 1987)]. Edward Lorenz (an MIT meteorologist who laid the groundwork for what would become known as "sensitive dependence on initial conditions," a prime factor in "deterministic chaos," later known as the butterfly effect) concluded that the sensitivity to initial conditions

implies that two states differing by imperceptible amounts may eventually evolve into two considerably different states. If, then, there is any error whatever in observing the present state—and in any real system such errors seem inevitable—an acceptable prediction of an instantaneous state in the distant future may well be impossible. (Lorenz 1963, p. 133)

Minuscule differences in initial conditions can lead to differences far out of proportion in the system's subsequent behavior. In this sense, minor perturbations can essentially be slowly

amplified to yield major effects. Subtle, cumulative effects, largely undistinguishable from natural change, perhaps eventually culminate in profound change (Daughton 2001a; Daughton and Ternes 1999; Thornton 2000). This concept has parallels with the idea of "the tyranny of small decisions" (a term adapted for ecologic thinking from economist Alfred Kahn by William Odum) or what Odum refers to as "small decision effects"—major unforeseen outcomes resulting from a "multitude of small pin pricks" (Odum 1982). Moreover, it may not be possible to detect subtle changes in systems so complex (e.g., ecosystems) that their intricately interwoven processes are poorly understood to begin with. This paradox is further complicated by our inability to distinguish the "normal" functioning of a complex system from the abnormal. If the basis for comparison is an already affected system (albeit unrecognized as such), then further detection of any change can be impaired or obscured.

Proportionality between cause and effect, although a tenet of single-organism-based toxicology, does not necessarily hold for higher levels of organization such as communities or ecosystems because of the myriad interactions and spatial relationships within the system—some imparting vulnerability to synergistic effects. When perturbations exceed the resilience of a system, irreversible change can occur. Ecologic systems inherit information (cumulative effects) through time (part of the 4Ts); their complex interlinkages affect one another synergistically, and their continually changing complexity makes them vulnerable to irreversible change. These ideas are formalized in the "community conditioning hypothesis" (Landis 2002, p. 197), where the etiology of each ecologic structure evolves from a unique trajectory. This hypothesis holds that any predictions are rife with uncertainty, but that most stressors leave lasting signatures, and stressors can "act from a distance."

Most recently, the philosophy that all systems self-organize in perpetual imbalance (cusps or knife edges of instability, poised at the edge of chaos), as synthesized by Buchanan (2001) around nonequilibrium physics, further consolidates the idea that small events can trigger disproportionately large responses that are not predictable—cause and effect are not linked in certainty, but rather in surprise. Response is more a function of the composite history of the system than of its snapshot status (the concept of "historical physics" vs. equilibrium physics, and as embodied in the 4Ts). Given these ideas, evidence continues to accumulate that although it may never be possible to gauge humanity's contribution to adverse environmental or human health events or outcomes, it might behoove us to eliminate as many extraneous variables (impacts) in ecosystems

as possible—regardless of their perceived immediate importance.

The idea of unexpected change from perturbation of ecologic systems is one of the driving forces behind the precautionary principle. When applied to assessing risks associated with chemicals as pollutants, the principle of precautionary action redistributes the burden of proof because the science required for truly and fully assessing risks lags far behind what is needed. For some comprehensive discussions on the precautionary principle (also known as the principle of “reverse onus”), refer to the links provided at Daughton/U.S. EPA (2002d). Science, in the face of uncertainty, must be melded with policy and political judgment to arrive at a course of further study or action. Many environmental issues, given their extreme complexity and the assurance that a thorough understanding of any isolated aspect (much less a truly needed, overarching systems-level, holistic understanding) may occur only far in the future, will require an approach based on an unorthodox, dichotomous mixture of subjective (and at times emotional) values wedded to reasoned, science-based logic; this point relates to the reasons for the difficulties associated with how science measures “real” hazard versus how society actually perceives risk (a topic thoroughly addressed in a broad body of work; e.g., Slovic 2001). A recent compilation of case histories shows how the precautionary principle did serve (or could have served) in a variety of situations (Harremoës et al. 2001).

To illustrate that chemicals can have unforeseen, subtle effects, consider estradiol, an endogenous hormone excreted to sewage. The work of Martinovic et al. (2003) went beyond the common practice of separating a treated population (male fish exposed to 25 ppt estradiol) from the untreated control. Although no significant effect was noted in the treated group in isolation, when the treated group was placed in competition with the untreated group, subtle differences became greatly amplified because of disparities in competitive advantage. In isolation, competitive advantages can remain masked, but in the wild they serve as strong selective pressures. Martinovic et al. (2003) showed that subtle effects resist unmasking by using reductionist approaches. Only systems-level, holistic approaches can reveal inter-organism interactions, pointing to the need for more attention to subtle effects (Daughton and Ternes 1999).

The precautionary principle has a long and still extremely controversial history. Its adoption by Europe, Canada, and the United States has proved extraordinarily uneven, influenced largely by differences in cultural and political histories and imperatives. But regardless of the heated debate surrounding the precautionary principle, deep-rooted fundamental changes in

corporate philosophies are beginning to emerge in the way that environmental considerations are melded with market imperatives—the two are beginning to merge as it becomes apparent that many economic advantages (and seemingly unrelated, and often unforeseen, societal advantages) can be gained by employing environmental stewardship as a foundation for corporate philosophy. A proactive, voluntary holistic stewardship program for PPCPs [first alluded to by Daughton (2002a)] would also be preferable to a reactive, prescriptive regulatory program. By focusing on developing a mind set toward holistic, thoughtful environmental responsibility rather than rote compliance to regulations, all aspects of society can play integral roles. This approach is also in keeping with the U.S. EPA’s new Innovation Strategy (Gibson 2002; U.S. EPA 2002). Indeed, avoiding the syndrome of insidious, cumulative environmental degradation by way of “small decision effects” (“multitude of small pin pricks”) may be possible only in embracing a holistic view of the world around us (Odum 1982).

The fusion of ecologic and marketplace imperatives has perhaps emerged most noticeably in the relatively recent product management philosophy termed “cradle to cradle”—in contrast to the “cradle-to-grave” approach that has long been the objective of recycling.

Water Quality: Key to Many Doors in the 21st Century

The growing, cardinal importance of water for sustaining societies is becoming more widely recognized as recently evidenced by its central role in the Broadway musical *Urinetown* (2002). The story is set at a time when “water is worth its very weight in gold”:

A depletion of the earth’s water supply has led to a government enforced ban on private toilets. The privilege to pee is regulated by a single, malevolent corporation, which profits by charging admission for one of mankind’s most basic needs.

A backdrop to the precautionary principle is the growing imperative for water reuse, which will prove to be the key, critical driving force for management of water quality in the 21st century. The NRC, as requested by the National Science Foundation (NRC 2001), synthesized the broad expertise from across the many disciplines embodied in environmental science to offer its judgment as to the most significant environmental research challenges of the next generation—based on their “potential to provide a scientific breakthrough of practical importance to humankind if given major new funding.” Of the eight “grand challenges” identified in the NRC’s report, two involve water quality issues, both relevant to PPCPs: *a*) hydrologic forecasting (for predicting changes in freshwater resources as a result in part of chemical contamination) and

b) reinventing the use of materials. The impetus driving the second is that

new compounds and other substances are constantly being incorporated into modern technology and hence into the environment, with insufficient thought being given to the implications of these actions. All of these issues assume added importance in urban areas, which concentrate flows of resources, generation of residues, and environmental impacts within spatially constrained areas. From a policy standpoint, reliable predictive models of material cycles could be invaluable in guiding decisions about . . . topics relating to human-environment interactions. . . . This grand challenge centrally encompasses questions about societal-level consumption patterns, since consumption is the primary force driving human perturbations of material cycles. (NRC 2001, p. 55)

Likewise, the World Health Organization’s (WHO) World Water Day Report draws international attention to the intimate connection between water and health:

Due to a mix of geographical, environmental and financial factors, as well as to increased pollution from municipal and industrial waste, the leaching of fertilizers and pesticides used in agriculture, only about one-third of the world’s potential fresh water can be used for human needs. As pollution increases, the amount of usable water decreases. (WHO 2001, p. 7)

Links to numerous resources regarding freshwater can be found at the World’s Water website (2002). The concept of the “ecological footprint” (Wackernagel and Rees 1995) also highlights the central importance of water. Residents of industrialized countries may need an average of 10–22 acres per capita to support an urban lifestyle. One of the major issues facing water resource managers in the 21st century will be to understand the overall impact of the urban ecologic footprint on water resources. Although there are numerous consequences of the footprint, a major concern may be the continued use of urban waterways as “waste receptacles”—merely for diluting and transporting downstream the by-products of urban consumption.

Although this background material emphasizes the aquatic environment, it is important not to lose sight of the other environmental compartments with which PPCPs can interact. The most significant of these secondary concerns is sewage sludge, to which certain PPCPs can sorb or partition. Subsequent application of sewage sludge (“biosolids”) to land (e.g., as a soil amendment) holds the potential for exposure of terrestrial ecosystems. The NRC revisited the issue of biosolids (NRC 2002b; see especially chapters 5 and 6) with respect to reevaluating the approach used by the U.S. EPA in setting its chemical standards for the biosolids rule (U.S. EPA Office of Wastewater Management 2002b). The NRC recommended that “a research program be

developed for pharmaceuticals and other chemicals likely to be present in biosolids that are not currently included in routine monitoring programs.” The NRC also recommended that alternative (i.e., nontraditional) toxic end points be considered.

Health of Ecology versus Ecology of Health

The intimate, inseparable connections between humans and the environment (actually, humans can be viewed as an integral part of the environment) have been discussed widely in many contexts. By applying principles of medicine and public health to the environment, David Rapport formalized the concepts of “ecologic health” and “ecosystem medicine” (Rapport 2002). The “health of ecology” refers to ecosystem health; the “ecology of health” refers to human health as determined partly by the condition of ecology (creation and transmission of antibiotic resistance is one example). Ecologic stress is reflected by stress in humans—the two are intimately tied. Adverse effects in one are eventually reflected in the other. The Institute of Medicine (IOM), a private, nonprofit institution that provides health policy advice under a congressional charter granted to the National Academy of Sciences, has called for a revolution and is reengineering all aspects of the health care system in the United States. A major objective of the IOM Committee on Quality of Health Care in America (formed in June 1998) was to develop a national strategy to radically improve the quality of U.S. health care within 10 years. To date, their recommendations (e.g., IOM, 2001; Kohn et al. 2000) address the many aspects of patient safety and how the concepts of quality systems can be applied. Although the IOM’s goals are far-reaching and urgently needed, they do not include the concept of ecology of health. Safety of the patient is pursued out of context of the safety of the ecology. With a little expansion of the IOM vision, an integration of human and ecologic health could be formalized at a national level through their efforts. High-quality health care and environmental protection need not be competing goals—they are intimately linked.

Connecting Health of Ecology and Human Health: Health Promotion and Social Entrepreneurs

The specific environmental issues and the example solutions posed in this mini-monograph are not as pertinent to those parts of the world where PPCPs are little used, such as economically disadvantaged regions [except in areas where large-scale drug disposal occurs, e.g., from humanitarian operations (WHO 1999)] or where illicit drug

manufacturing or use is prevalent (Daughton 2001c). Nonetheless, the basic, universal concept of a “health state” (rather than an “absence of illness”)—one of a balanced and interconnected physical, mental, social, and spiritual well-being—is equally applicable to Western cultures and could have a profound impact on overall drug use (both licit and illicit). Treatment of physiologic and psychologic symptoms and even the curing of diseases are just one dimension of holistic health—and in many respects, preventive and curative approaches are but stop-gap measures in the absence of a sustainable environment. For example, one can argue that the single most important limitation in the continual quest to eliminate infectious diseases is not the lack of medication but rather the failure to address poverty and its attendant liabilities of hygiene and malnutrition.

Many people actively engaged in advancing the principles of “sustainability” (sometimes defined as meeting society’s needs in ways not diminishing the capacity of future generations to meet theirs) have strongly felt that without empowering people to take charge of the basic aspects of their own lives, sustainable improvements in health are not possible. A model effort (Comprehensive Rural Health Project) begun in 1970 by the Indian medical doctors Raj Arole and Mabelle Arole has demonstrated how a holistic approach builds a foundation for sustainable living and only then is advancement in improving health possible. Health cannot be dissociated from all the other aspects of sustainable living (Arole 2001); the burgeoning field of sustainability is captured by the Initiative on Science and Technology for Sustainability (ISTS 2002), among others. Social entrepreneur projects in health promotion (vs. illness/disease prevention), such as those begun by the Aroles, abandon narrow technical objectives aimed at preventative and curative measures in pursuit of wider-ranging holistic goals that emphasize the interconnectedness of social systems.

Cradle-to-Cradle Stewardship

Guided by the interrelationships among the precautionary principle, the ever-increasing and key worldwide importance of water, and the idea of “ecology of health,” the incorporation of “eco-effectiveness,” “ecologic intelligence,” or cradle-to-cradle design concepts into life-cycle considerations for product development and use has gained momentum in the last decade. The idea of cradle-to-cradle stewardship has most recently been embraced by many international corporations. Some of the more visible and successful proponents of cradle-to-cradle concepts have been William McDonough and Michael Braungart (MBDC 2002; McDonough and Braungart 2002). They have been leaders in implementing the

idea of full life-cycle product design, referring to this approach as the “next industrial revolution.” One of the tenets of this philosophy for a truly sustainable industry is that it benefit not just the environment but also consumer and corporation; this is one reason for the expression sometimes used for these programs: “waste to wealth.” Numerous similar efforts have been successfully under way; examples include those with such monikers as “Zero-Waste” and “Zero Emissions,” being implemented in Canada by the Recycling Council of British Columbia (RCBC 2002). Another effort toward directing organizations toward sustainability is being led by the international organization The Natural Step (TNS 2002). Of the “four system conditions” that The Natural Step framework is based on, the second states that “in a sustainable society, nature is not subject to systematically increasing concentrations of substances produced by society.” It is worth noting from an historical perspective, however, that the idea of sustainability was put forth decades ago, as early as 1966 (Blutstein 2003).

The United Nations Environment Programme (UNEP 2002) notes that although significant efforts in reducing environmental footprints have been made by a few companies across many industrial sectors, a gap continues to widen between these few and the vast majority that continue “doing business as usual.” Among the five major areas for advancement toward true sustainability identified in UNEP (2002), the fourth is the “integration of social, environmental and economic issues.” These efforts hint that a sustained future viability of this product life-cycle philosophy can be expected. A wide range of strategies that could foster a cradle-to-cradle approach for stewardship of PPCPs by the pharmaceutical/medical care industries could be adopted. Some could be implemented quickly (requiring only a collective will to implement them); others would require sustained research and development efforts (which in some cases are already under way, albeit for reasons unrelated to environmental benefits), and some would require major attention by the numerous agencies involved with a patchwork of laws and regulation of drug recycling and disposal. Several examples are outlined in various sections of this mini-monograph.

Viable Options for Minimizing the Introduction of PPCPs to the Environment

Numerous actions could be implemented in the near term for reducing what risks might exist from introducing PPCPs to the environment. In the longer term, a number of research avenues could be pursued regarding drug design, packaging, and delivery—all of

which could provide environmental (as well as consumer) paybacks. Indeed, some of these are already being pursued. Many would yield direct benefits to human health for reasons unrelated to any environmental imperative, including reducing inappropriate drug use and lowering therapeutic dosages [thereby lessening adverse drug reactions (ADRs) and reducing consumer costs].

Many pharmaceutical producers and organizations have “product stewardship” as an integral part of their business. These programs, however, although sometimes acknowledging the issues associated with consumer use of PPCPs, tend to focus on aspects of the manufacturing process (vs. distribution and use) as well as on hospital waste (Daughton/U.S. EPA 2002e). A potential mechanism for effecting change in the health care industry (starting with hospitals) is via an existing program established under a program agreed to in 1998 by the American Hospital Association and the U.S. EPA and administered by the Hospitals for a Healthy Environment (H2E 2002). This program’s overall goal is to reduce the impact of health care facilities on the environment. Although the program initially focused on eliminating mercury and reducing total waste volume, a future area to consider is development of model chemical waste minimization plans such as that developed for mercury by H2E (2002).

Some of the ideas presented below may prove controversial. I highlight them solely to generate an active dialog or debate across the many disciplines that must become involved to successfully address this topic. Many of these disciplines have never before had reason to interact or collaborate with each other. With the increasing visibility of PPCPs as pollutants, I hope these disparate professional communities will find compelling reasons to cross-communicate and, in doing so, expand their knowledge and effectiveness in their own fields.

Avenues for Progress toward a “Green Pharmacy”

The last decade has seen tremendous progress in advancing the practice of “green chemistry” (e.g., minimizing the use of ecologically hazardous reagents and designing alternate synthesis pathways, some of which are based on aqueous chemistry) (U.S. EPA Office of Pollution Prevention and Toxics 2002). In fact, the pharmaceutical industry has a strong history of applying environmentally responsible chemistry (which also turns out to be economically advantageous) to drug synthesis and manufacturing. The same principles could be logically extended and applied to drug design, delivery, package design, dispensing, and disposal so that their benefits could accrue to the end user and not just the manufacturer. Some of these ideas for minimizing the release of

PPCPs to the environment have already been put forth (Daughton and Ternes 1999) but are reiterated and expanded on here because all these ideas have never been brought together in one document. Unfortunately, despite the many avenues of advancement that could be—and sometimes are already being—made toward a green health care system, the transfer of new knowledge and technology to clinical practice is notoriously slow; as one example, new knowledge gained from clinical trials takes an average of 17 years to become incorporated into routine practice (IOM 2001).

Drug Design

New drug design (chemical structure and properties) and formulation (combination of the active, therapeutic ingredient with the inert, nonactive ingredients known as excipients) should factor in new considerations for “environmental friendliness” or “environmental proclivity.” Such “green” PPCPs would maintain or improve therapeutic or cosmetic efficacy while also maximizing their susceptibility to biodegradation, photolysis, or other physicochemical alterations to yield innocuous end products. Design of more labile drugs (e.g., those that would ordinarily be degraded by or poorly transported across the gut) would further reduce excretion. Current drugs that do undergo initial structural alterations (e.g., via phase I or phase II metabolism) often yield broad arrays of metabolites, some of which are the actual active drug form and some of which are environmentally persistent; compared with what little is known regarding effects to nontarget species by parent drugs, even less is known about metabolites. Drugs could be designed with better physiologic sorption characteristics (to lessen direct excretion of the parent compound). Using smaller doses by enhancing the delivery exclusively to the target site or receptor is an objective being pursued on many fronts, including better drug design to accommodate existing membrane transporters (e.g., XenoPort 2002) and “creating” *in situ* synthetic transporters (Alper 2002). Sometimes the formulation of a drug can impede its sorption, especially for those with ill health or impaired gastrointestinal function. Rapid-dissolve tablets are one example of an improvement over formulations that can impede or prevent dissolution; for example, the common excipient stearic acid often impedes dissolution (Daughton 2001a). New formulations are particularly needed for insoluble drugs [about 30% of U.S. Pharmacopeial Convention, Inc. (USP) drugs and 50% of prospective drugs are poorly water soluble]; current examples include liposomal delivery, polymer-drug conjugate prodrugs (with release at the target site), and special formulating approaches, such as “insoluble drug delivery” (SkyePharma 2003). Other examples include

novel targeting approaches such as patient re-infusion of autologous erythrocytes that have been altered to encapsulate drugs and permit a steady, low-drug concentration to be attained for a period of weeks and that can selectively target certain sites such as macrophages (Magnani et al. 2002).

The future of omics. The rapidly advancing “omics” revolution [e.g., genomics, proteomics, glycomics, metabolomics; Cambridge Healthtech Institute (CHI) 2002] will probably lead to the development of countless new classes of drugs (some with mechanisms of action never before encountered by any organism, and therefore posing the attendant questions as to the possibilities for previously unconsidered effects on nontarget organisms). But at the same time, identification of genetic idiosyncrasies will allow the selective targeting of specific subpopulations of patients for treatment with these same new drugs—thereby allowing for their reduced use across the larger population. “Pharmacogenomics” holds great promise to *a*) greatly increase the numbers of low-use drugs (those specifically tailored to narrowly defined patient populations, effectively vastly increasing the number of therapeutic niches), and *b*) increase the numbers of high-use (blockbuster) drugs (by addressing therapeutic targets of minimal genetic variability across the population to yield drugs of extremely broad tolerability). By increasing the efficiency of drug discovery (minimizing failures), the reduced costs will in turn catalyze yet more new-drug discovery. “Genomics” is also recognized by the U.S. EPA as providing new opportunities for risk assessment and predictive toxicology and will continue to gain new applications (U.S. EPA Science Policy Council 2002).

Dirty drugs to designer drugs. With better-designed drugs (vs. those with a broad spectrum of molecular actions—“dirty” or “promiscuous” drugs), by increasing the specificity of drug action at the target receptor, not only could adverse reactions be minimized, but with extremely narrow MOAs it would also prove easier to predict the potential for effects on nontarget species. Another example (regarding drug discovery/design) is the development of drugs with higher potencies (and therefore lower doses) as a result of greater systemic availability. Drug potency is partially a function of absorption efficiency (lower doses necessitated by higher absorption efficiency). Recently, as reported by Veber et al. (2002), reduced molecular flexibility (as measured by the number of rotatable bonds) coupled with lower polar surface area (or total hydrogen bond count) was shown to reflect good oral bioavailability— independent of low molecular weight (MW) or lipophilicity. Absorption had been thought to be a strict function of MW (e.g., MW > 500 daltons led to poor absorption; low MW was

required for good systemic availability). At least in rats, however, Veber et al. (2002) showed that it is not necessarily MW but rather the rigidity of the molecule (which is partly an indirect function of MW) that is a prime determinant. This points to the possibility that higher-MW drugs for humans are possible as long as the number of rotatable bonds is minimized. For rats, the more rigid molecules (those with 10 or fewer rotatable bonds and lower polar surface area) show the better oral absorption; lowest absorption occurs with those having more than 10 (“flexible” compounds). The rule of five (Lipinski et al. 1997) as a predictor of oral bioavailability posits that either the number 5 or a multiple of 5 was involved in the predictive parameters (but there were only four rules in the “rule of five”): “In the discovery setting ‘the rule of 5’ predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight . . . is greater than 500 and the calculated Log P . . . is greater than 5.” The number of rotatable bonds (Veber et al. 2002) would add the fifth rule.

Chirality’s role. Design that lessens therapeutic doses without increasing overall potency is already occurring with the emphasis on enantiomerically pure drugs (homochiral drugs), which can have therapeutic advantages over their conventional racemic mixtures. One of the first commercial examples was (*R*)-albuterol or levalbuterol (Xopenex; Sepracor, Inc., Marlborough, MA), the homochiral version of racemic albuterol; broncodilation could be achieved with levalbuterol at one-fourth the dose of racemic albuterol (and with fewer side effects) (Handley et al. 2000). A more recent example is esomeprazole (Nexium; AstraZeneca, Södertälje, Sweden), the homochiral form of omeprazole (Prilosec; AstraZeneca). This approach not only cuts the overall dose by at least one-half (sometimes more, depending on the number of isomers) and totally eliminates exposure to the other (nontherapeutic) isomer(s), which frequently has completely different mechanisms of action, but can also yield benefits to the patient by removal of nontherapeutic isomers that were also responsible for unwanted side effects. The commercial-scale production of homochiral drugs, however, is fraught with scale-up difficulties; advances in economic racemic separation efficiencies will prove useful (e.g., see Lee et al. 2002). The development of enantiomerically pure drugs to reduce environmental loadings has a parallel with pesticides. Optically pure pesticides have been approved by the U.S. EPA (e.g., *S*-metolachlor) under the U.S. EPA’s Reduced Risk Pesticide initiative (under the Food Quality Protection Act; U.S. EPA Office of Pesticide Programs 1996). For metolachlor, this might lessen its overall use by 35%.

Emulating nature. Another design strategy would be “smart” drugs that better emulate the nonanthropocentric, native chemistries of natural products. As examples, consider *a*) the newer classes of antimicrobial peptides modeled after the endogenous antimicrobials (e.g., defensins, piscidins, and cathelicidins; Toma 2001), *b*) bacteriophages (viruses that infect only bacteria; e.g., see Intralytix 2002), and *c*) the enzymes used by phages to destroy their bacterial hosts (e.g., highly species-specific lysins). One new approach uses synthetic cyclic peptides (some with the non-native optical isomers) to disrupt cell wall/membrane function or physical integrity (Fernandez-Lopez et al. 2002). Although naturally produced antimicrobials and analogs may not be sufficient on their own, their use could serve to potentiate the action of existing synthetic antibiotics and thereby reduce overall use. These natural products could also reduce overall antibiotic use by prophylaxis—in preventing the onset of infection. Another example is the synthetic musk fragrances. The two classes that have been used extensively are the nitro musks and the polycyclic musks. Certain members of these classes (or their metabolites) are known to persist and bioaccumulate (Daughton 2001a; Daughton and Ternes 1999). A third class that is not used as extensively because of its cost comprises the macrocyclic musks (15–18 carbon cycles closed as either a carbonyl or lactone), which better emulate natural musks and are purportedly more biodegradable.

Avenues to resurrection. “Resurrection” of “retired” drugs that are no longer efficacious (e.g., because of development of pervasive pathogen or tumor resistance) could allow for the continued use of older-generation drugs that could be more environmentally friendly. Resurrection could be accomplished by developing potentiators that are not inherently toxic but that overcome, for example, the defensive strategies used by resistant target organisms or tissues. An example is the development of multidrug efflux pump inhibitors (EPIs) (Daughton and Ternes 1999). One (of many) example class of existing EPIs is that containing certain selective serotonin reuptake inhibitor antidepressants (Munoz-Bellido et al. 2000), which synergize the activity of some antibiotics. But strategies designed to counteract general defensive strategies (such as efflux pumps) must be assessed carefully in light of their potential for compromising the health of nontarget species, many of which (especially in the aquatic realm) employ efflux pumps as a first line of defense against toxicants (Daughton 2001a; Daughton and Ternes 1999; Epel and Smital 2001).

Alternative medicines missing from the radar. The WHO developed a strategy for addressing issues of policy, safety, efficacy,

quality, access, knowledge preservation/protection, and rational use of “traditional, complementary, and alternative medicine” (TM/CAM) (WHO 2002b). That the WHO put forth this first global strategy clearly signals that TM/CAM has gained substantial stature. The popularity of TM/CAM in less developed countries is widely appreciated; its growth in more developed countries over the last two decades is reflected by the proliferation of websites devoted to it. Because many active ingredients in natural medicines are highly bioactive, the same concerns regarding environmental fate and ecologic effects apply (Daughton and Ternes 1999) and should therefore be subject to similar scrutiny. But the WHO strategy does not address any issues concerning disposal or pollution prevention.

In many countries, environmental risk assessments of varying degrees are required at least for new drug entities meeting certain criteria. Although the existing regulations for these assessments (e.g., see discussions in Velagaleti and Gill 2001; Velagaleti et al. 2002) as well as those under consideration (e.g., CSTEE 2001; Health Canada 2002) have the potential to evolve over time in response to new science regarding environmental impacts, similar assessments for dietary supplements, “alternative” medicines, and other personal care products do not exist. Given that the biologic activity of many of these chemicals can rival that of drugs (e.g., Daughton and Ternes 1999), it would be prudent to also submit these diverse chemical classes to environmental risk assessments; currently, they are completely free of any oversight regarding ecologic hazard, and many escape assessment of human health risk. Indeed, the fact that nutritional supplements can elicit profound biologic effects is becoming codified in medical references (e.g., PDR 2002a, 2002b) where commonly recognized cross-reactions with conventional drugs have already been noted—for example, with Saint John’s wort (a potent inhibitor of certain drug-activating enzymes).

Drug Delivery

Eco-friendly strategies to implement in the area of drug delivery include those relevant to prescribing, dispensing, patient compliance, and medication delivery mechanisms. Some advanced ideas regarding delivery mechanisms can be gained from Mort (2000).

Prescribing. Both physicians and the public could be made more aware and better informed as to the medical and environmental consequences of overprescribing medications. Better ways need to be found to engage the medical community and the public in this issue. Guidelines could be developed and promulgated for minimizing inappropriate drug use (misuse, overuse, and abuse). Regarding the linkage between human and ecologic health,

progress on this front has been most developed for the issue of antibiotics (see links in Daughton/U.S. EPA 2002f), where physician knowledge and patient expectations are commonly at odds and antibiotics are sometimes prescribed (because of patient expectations) in situations where they are not justified. Imprudent use also involves failure to identify putative pathogens and to perform susceptibility testing before selecting the most effective antibiotic. The literature continues to document circumstances where antibiotics have long been used but should not have been; a recent example is their inappropriate use for bronchitis (Evans et al. 2002). Others who should attempt to minimize the misuse of antibiotics are veterinarians, aquaculturists, and agriculturists to lessen the incidence of resistance development in native bacteria and human pathogens (e.g., Lipsitch et al. 2002; Smith et al. 2002). An example of a creative approach to minimizing the use of antibiotics for the common cold is presented by Arroll et al. (2002). By giving patients antibiotic prescriptions that could be filled only 3 days thence, overall use was 48% as opposed to 89% for those having immediate access to antibiotics for “treating” common cold symptoms—nearly halving their use and avoiding exposing the patient to unnecessary medication.

Lower versus established dosing. Numerous studies show that the therapeutically effective dose for many drugs can be significantly lower than that initially recommended by the manufacturer. There are many reasons for this (including some stemming from regulatory requirements during clinical trials), which are summarized by Crutchfield (2001). Sometimes the effective dose for a drug can be many orders of magnitude lower than previously realized, largely a result of incomplete knowledge of MOAs. An excellent example is the conventional therapeutic dosage of morphine to achieve analgesia—typically about 1–10 mg/kg. With simultaneous administration of an opioid receptor antagonist (i.e., naltrexone) at the ultra-low dosage of 0.1 ng/kg, the same conventional level of analgesia can be achieved with morphine at 1 µg/kg—6 orders of magnitude lower (a dosage that can be sustained without risk of addiction); similar effects can be achieved with 0.1 µg/kg morphine coupled with 1 pg/kg naltrexone (Crain and Shen 2001; Pain Therapeutics 2002). This is an excellent example of research that could markedly reduce patient risk by reducing side effects or ADRs and even addiction while minimizing the potential for environmental effects. Most hospital ADR-related deaths are related to dose, and ADRs may be a leading cause of hospital death in the United States (Lazarou et al. 1998). Indeed, deaths from medication errors occurring both in and out of hospitals exceed 7,000 annually in the United States—exceeding those

from workplace injuries (Kohn et al. 2000). Moreover, Kohn et al. (2000) maintain that extrapolation of certain statewide studies to the United States as a whole shows that annual excess costs of preventable hospital ADRs are about \$2 billion (and hospital patients represent only a small portion of the at-risk general population).

Precision formulation/dosing. Current technology for formulating drug dosages is incapable of high accuracy or precision, especially that needed for ultra-low doses. Nonhomogeneous formulation or inconsistent delivery can lead to undesirable repeated dosing and improper dosing (e.g., Alliance Pharmaceutical 2002). New technologies such as “three-dimensional printing” can formulate accurate, precise, and minuscule amounts of drugs into one delivery device to achieve better temporal and spatial control of drug release via any combination of sustained, controlled, targeted, or cyclical methods. With the ability to control the drug release “profile” (tailored to a variety of factors, including time after ingestion or circadian rhythm), more effective and lower doses can be achieved (MIT 3DPTM Laboratory 2002; MIT News 1997).

Individualization of therapy. Drug manufacturers could provide the medical community with more easily implementable information (and requisite unit doses) to tailor drug dosages for the individual (especially for long-term maintenance drugs) on the basis of the sometimes complex interplay among body weight, age, sex, health status, nutritional status, timing/circadian rhythm, subtle genetic distinctions (e.g., accommodation for single-nucleotide receptor polymorphisms using new toxicogenomics tools), and known individual drug sensitivities. Several companies are currently involved in approaches based on genetic variabilities to personalize drug therapy (e.g., Genaissance Pharmaceuticals 2002; Orchid Biosciences 2002). Currently, customized doses and formulations are often obtainable only from private pharmacy “compounders”—not drug manufacturers—and are not subject to FDA rules for quality. Such individualization of therapy (also known as “calibrated dosing”) can minimize the requisite therapeutic dose (which is frequently higher than need be) (Phillips et al. 2001). Available tests for drug metabolizing enzymes (e.g., the cytochrome P450 superfamily of monooxygenase isoforms) can distinguish fast, normal, and slow variants. These enzyme systems play major roles in the speed with which certain drugs are metabolized (whether leading to detoxification and excretion or to activation) and therefore determine the proper dosage. Advances in detection of other physiologic and metabolic characteristics of a patient can also allow for the specific targeting of a drug

for its intended site (to reduce unnecessary systemic exposure).

Individualized therapy can also help to address the growing trend of the healthy population that medicates on a long-term basis using a wide array of drugs as preventive measures (attempting to prevent the onset of various health problems). Outcomes from the use of medications by healthy people for durations spanning decades prompt numerous questions regarding patient safety and the consequent issue of imprudent introduction of drugs to the environment. But long-term studies (those lasting for decades) are rarely performed because patents do not offer protection sufficiently long to justify the cost. It is possible that in place of new studies, the vast collection of individual, small reports already in the published literature could be distilled into useful knowledge. Much of what exists in the published literature is never “mined” and applied (Daughton 2001b, 2002b). An example of one step in the direction of mining the existing literature and using it to predict adverse drug outcomes is an approach called “evidence-based care,” where recommendations are collectively made by physician experts who continually scan the broad medical literature and synthesize recommendations (evidence-based rules) regarding drug use across patients comprising a wide spectrum of health status (e.g., ActiveHealth Management 2002).

Developing alternative delivery mechanisms. Dosages could be reduced with better targeted delivery routes (e.g., expanding the utility of pulmonary and transdermal/mucosal delivery), mechanisms of release (e.g., rapid-dissolving formulations, controlled release), and mechanisms for delivery of drugs to the target (e.g., antibody-linked drugs; *in situ* implants) (e.g., Mort 2000). Advancement in eluding the blood–brain barrier would vastly expand the universe of available central nervous system drugs, which are currently restricted to a small galaxy of drugs smaller than 500 daltons; selective disruption of the blood–brain barrier, either via momentary enlargement of the endothelial cell junctions or by use of native membrane transporters, is one example (Miller 2002). Although advancement in drug delivery has received concerted attention over the years (e.g., see ACS 2002; CRS 2002), expanded efforts in this area (e.g., by leveraging with nanochemistry) could yield significant rewards, especially with respect to resurrection of “retired” or underused drugs.

A potential future route/mechanism is the use of “click chemistry” for the self-assembly of drugs *in situ*, where the nonbioactive precursor reactants required to synthesize a drug are self-assembled directly at the receptor target (the “templating” site; e.g., Borman 2002).

Such assembly that mimics enzyme-catalyzed synthesis is sometimes called “bioinspiration.” This approach for drug delivery perhaps holds the ultimate potential for minimizing dosage. *In situ* click chemistry (a new rendition of *in situ*, site-catalyzed synthesis) uses the specific conformational locations within biochemical receptor molecules as templates for guiding the formation of a chemical product with high affinity for the site. Candidate drugs generated in this manner also would have a higher probability for specificity—avoiding the propensity for promiscuity (“dirty” drugs), a problem that has plagued drug discovery for years—and thereby further reducing required doses (McGovern et al. 2002). Interactions with receptors that do not provide intended therapeutic effects are sometimes called “sites of loss” and are often the cause of ADRs. The work done with current *in situ* click chemistry shows the ease with which small molecules with ligand interactions at the femtomolar level could be achieved. An acetylcholinesterase inhibitor formed via click chemistry proved to be the most potent noncovalent inhibitor ever found for this enzyme. It may eventually prove possible to set the conditions for the self-assembly of reactants at the desired site of biochemical action within the living organism, to prevent reaction with nontarget sites. Such an approach would effectively achieve the lowest possible dose for a drug (forming the ultimate “smart” drug), thereby minimizing or even eliminating the possibility for excretion to the environment.

Patient compliance and education. Patients frequently fail to finish their courses of medication—for a wide variety of reasons (Daughton 2003). This problem not only increases health care costs and can jeopardize patient health but also leads to unnecessary accumulation of unused drugs, which then require disposal [this is a major problem at long-term care facilities, discussed in Daughton (2003)]. Further education of patients might reduce patient noncompliance. Additional patient education regarding appropriate drug use (as defined in USP 2001) and drug abuse (consumption of more frequent or higher doses than prescribed, or use of illicit drugs) could reduce unnecessary excretion or disposal. A recent example of proactive guidance on minimizing commonly overprescribed drugs is the U.S. Centers for Disease Control (CDC) campaign called Promoting Appropriate Antibiotic Use in the Community (CDC 2002). By showing the linkages between human and ecologic health benefits, perhaps more progress can be made in minimizing overuse/misuse of legal drugs (e.g., antibiotics) and illicit drugs; also of relevance is the linkages between illicit drug use and terrorism [Daughton/U.S. EPA 2001; Office of National Drug Control Policy (ONDCP) 2002].

Education of health care practitioners. Hand-in-hand with education of the public is education of those working in the health care industry (not just pharmacists, but all health professionals and technicians, federal and state policy makers and regulators, organization managers, and governing boards). A good way to teach the importance of dose minimization and proper disposal would be through formal, continuing education courses, where the interface between medicine and environmental science and the synergies accrued from cradle-to-cradle stewardship of medications could be taught. Along these lines, Smith (1999) proposed that the USP include hazardous waste criteria in its monographs; this recommendation could be extended to include disposal guidance for all nonhazardous, noncontrolled drugs as well.

Marketing

Guidance on packaging for disposal. Consumer-oriented packaging for OTC and prescribed drugs in the United States lacks guidance for disposition of unused medication contents. Standardized nationwide guidance regarding recommended routes for responsible disposal (which could be custom tailored depending on the ingredients) could be easily added to package labeling/inserts. The use of consumer guidance on labeling for protecting the environment has long been common with other consumer products throughout the world, especially for pesticides and industrial chemicals. Standards that cover the entire packaging system are developed and promulgated by the USP. The many complex aspects of packaging are summarized in Okeke (2002). In the United States, consumer warning and use information regarding drugs is conveyed not just on affixed labels but also on attendant documents such as prescription “leaflets,” the minimum information content for which is set by the U.S. FDA. For prescription drugs, these leaflets are supposed to contain (at a minimum) the FDA-approved prescribing information (also called a package insert). Various other sources of consumer (as well as physician) information on drugs can be found in *a*) the *Physicians’ Desk Reference* (PDR 2002a), which contains the required prescribing information for most but not all drugs (the printed version is updated three times per year, the online version monthly, and the personal digital assistant version daily); *b*) any of the various compendia such as *Drug Facts and Comparisons* (Facts and Comparisons 2002), which is updated with labeling changes monthly; and *c*) MedWatch (U.S. FDA 2002b). The U.S. FDA’s new labeling requirements for OTC drugs are one example of labeling status in U.S. drugs (U.S. FDA 2002c). These are all examples of information resources that could convey information regarding possible environmental

ramifications and disposal advice—comporting with the ideas of ecology of health and health of ecology.

Steps in this direction are already being taken. For example, EMEA (2001) has already taken this step in recommending labeling provisions. A consumer survey sponsored by Health Canada showed that a large majority of respondents read drug labels, but fewer than 50% read labels for personal care products (COMPAS 2002). Although most consumers claim to read labels for ingredients, when unprompted by the interviewer, few (only 8%) claim to read them for information regarding “environmental-friendliness/impact.” But when prompted, 57% said they do read labels for guidance regarding disposal (in Canada).

Guidance on packaging to prevent unnecessary dosing (aggregate and cumulative). Inadvertent ingestion of multiple drugs sharing the same MOA (joint action from cumulative exposure; Figure 2) or ingestion of the same drug from different sources (aggregate exposure) can occur when consumers use multiple medications without fully understanding the formulated contents. This multiple-exposure pathway scenario is especially problematic when patients are prescribed medications by multiple physicians; for patients with multiple health care providers, poor communication can also lead to represcribing of medication that has already been shown for the patient to be nonefficacious. Besides prominently listing contents on labeling, it would also be useful to consumers to list the actual therapeutic end points. For example, analgesics are often formulated into multiple classes of medications, including those such as pain killers, antihistamines, and cold/flu preparations, and consumers sometimes take all of these together, getting doses higher than needed. By better alerting the consumer to those drugs intended for different therapeutic end points but which share the same active ingredient or that share ingredients with the same mechanism or mode of action, the use of certain drugs could be lessened and the likelihood of consuming doses higher than necessary could be reduced. This is analogous to the current practice of alerting consumers to adverse interactions between drugs having different mechanisms of action. The significance of this type of combined (aggregate and cumulative) exposure is captured by the concept of the Risk Cup (Figure 2), a term that establishes by analogy of water in a cup the sum total of stressor exposure evoking a particular effect or end point (and therefore the remaining exposure that could be tolerated before the cup becomes full). One possible mechanism for reducing this problem is presented in Daughton (2003).

More informative and less confusing drug names. The IOM recommends that better efforts be made to eliminate drug names that

sound similar and formulated drugs that look similar, as well as confusing labels and packaging that foster mistakes by consumers, health care providers, and dispensers (Kohn et al. 2000). Although these problems can jeopardize patient safety, they also lead to unnecessary (and inappropriate) use of drugs and their eventual discharge to the environment, as well as to the purchase of medications that might not have been made by a better-informed consumer.

Reducing package sizes. Consideration could be given to providing a broader selection of package sizes of PPCPs. Some PPCPs are perhaps more likely to be discarded because they are prescribed or purchased in quantities too great to be used before expiration or because they tend to expire more rapidly. A common example is aspirin and certain nonsteroidal anti-inflammatory drugs, which are available in such large package sizes that the contents may frequently go unused before reaching expiration. Alternatively, bulk-size packaging could incorporate individually factory-sealed subpackages whose expiration dates are maintained even when the seal to the main container is broken. Consumer education might also be useful here—to encourage purchase of only needed amounts of PPCPs (e.g., package sizes conducive to avoiding expiration). Consideration should therefore be given to not penalizing consumers monetarily for purchasing small-quantity package sizes (or perhaps offering “introductory size” samples).

Improved packaging. Package materials and sealing mechanics could possibly be improved to enhance both factory-sealed and dispensed shelf lives (e.g., more effective exclusion of humidity and heat, which are major factors limiting the storage life of drugs in bathrooms). Ideally, packaging could integrate inexpensive sensors (customized for each drug) that are capable of detecting breakdown products indicative of degraded drug performance or formation of products presenting adverse risk.

Advertising. Since the 1800s, PPCP direct-to-consumer (DTC) advertising in the United States has played an increasingly significant role in relaying information to the public regarding the many aspects of improved health, fitness, and appearance, as well as the prevention of disease (Duke University 2002). Only more recently have advertisers been required to highlight the caveats associated with their products (e.g., side effects or contraindications). DTC advertising purportedly empowers consumers, leading them to better-informed decisions and improved quality of care (e.g., National Health Council 2002; PhRMA 2003). But critics of DTC advertising (which is one of the most heated topics in the medical care industries of many countries) maintain that it can interfere with the physician–patient relationship (e.g., leading to “doctor shopping”) and lead to the

pressuring of physicians to prescribe expensive and sometimes unnecessary medications for demanding, poorly informed patients (Rosenthal et al. 2002); some countries have banned or minimized DTC advertising (e.g., Galbally 2000; Meek 2001). Regardless of the fate of DTC, a logical next step for advertisements could be to include information for the public regarding the proper disposition of unused products and the imperative for environmental stewardship.

Advertising can also educate consumers in decisions to use a new drug. A criticism of the reporting of controlled drug trials involves the significance of treatment outcomes. Two measures of significance are often used—not in conjunction with each other, but separately—without explaining their relative meanings. The measure of a new drug’s effectiveness is usually expressed in comparison with an accepted standard treatment. If the new drug is more effective, its comparative effect can be expressed in terms of either absolute risk reduction (ARR; or its reciprocal, number needed to treat) or relative risk reduction (RRR). RRR data often seem to have a much higher percentage of effectiveness than ARR data (Nuovo et al. 2002). Sometimes, when the RRR might convey to the consumer a major advance in treatment, in reality it might be minuscule in terms of absolute improvement (ARR) over current therapy.

Drug Dispensing

Internet dispensing. The availability of licit and also illicit drugs via the Internet (via both legal and illegal “Internet pharmacies”) and black markets continues to escalate and expand, undoubtedly leading to overdispensing and dispensing without a prescription (U.S. FDA 2002a). The added influx of drugs to the environment via illegal sales that were never anticipated by FDA during new drug approval is undoubtedly contributing to the overall environmental exposure burden. That many of these sales come from overseas may have ramifications for performing environmental risk assessments for drugs. Uncontrolled drug distribution channels also have profound ramifications for consumers in terms of safety and expense (e.g., “fake,” counterfeit, or unstated dangerous ingredients) and also could be a major factor in both the accumulation of unused drugs and the excretion of drugs that ordinarily might never have been ingested. Both the public and the pharmacy communities might benefit by more definitive education on these issues and understanding the possible environmental consequences. This awareness could minimize unneeded drug use and attendant disposal. One way for consumers to verify the quality of Internet pharmacies is to check for the presence of the Verified Internet Pharmacy Practice Sites (VIPPS) hyperlink

seal. The National Association of Boards of Pharmacy developed this certification program for Internet pharmacies in 1999; few Internet pharmacies are VIPPS certified (NABP 2002).

Detection of counterfeiting. Regarding the gray- and black-market distribution of drugs, industry experts suggest that some 25% of the unauthorized distribution of pharmaceutical drugs takes place online (Cyveillance 2001). Although development of deterrents for black-market distribution of drugs (and counterfeits) has always made economic sense for manufacturers (e.g., Green and Murray 2001), it would also clearly reduce the quantities of drugs available for eventual introduction to the environment (by both direct disposal and excretion). Advancements are needed in detecting molecular counterfeiting; an example is Biocode’s anticounterfeiting efforts (Biocode 2002).

Nationwide database of drug sales. A publically accessible, central database that compiles and tracks geographic OTC and prescribed drug sales as well as drug use (not to be misconstrued as a patient-level database) would be extremely useful for predicting the actual quantities of drugs that could be entering the environment (by using pharmacokinetic models based on ADME/Tox—adsorption, distribution, metabolism, excretion, and toxicity) (Daughton/U.S. EPA 2002g). Such a database would have great added utility for environmental scientists if it were integrated on a geographic information system platform to enhance the geographic utility of the data; first steps in this direction have been made and reported by Schowanek and Webb (2002). Data from the *Prescription Drug Atlas* (Express Scripts 2001) show that for some drugs, regional preferences in use can vary by severalfold. First steps in this direction include proprietary databases such as the extensive ones developed by Quintiles (2002). The Quintiles Rx Market Monitor (Quintiles 2000) uses near–real-time patient claims transactions to mine accurate drug use statistics at the geographic level.

Nationwide database of drug returns. An active “returns” industry (Daughton 2003) expanded to the consumer level would have obvious positive ramifications for the environment. Less appreciated, however, is that a cohesive nationwide policy encouraging the return of unused drugs to pharmacies or directly to reverse distributors (see links at Daughton/U.S. EPA 2002h) yields a number of consumer health and economic benefits by mining the data generated by a nationwide, integrated “returns” network. In the United States, however, a morass of sometimes conflicting and competing oversight and liability concerns from numerous state and federal agencies stymies the creation of a cohesive approach to returning/recycling medication from the end user (Daughton 2003).

Geographic variability in drug use: ramifications for calculating EECs/PECs. As mentioned above, environmental assessments for approval of new drug applications are required by the U.S. FDA only when the concentration of a drug predicted to enter the aquatic environment (EEC) is 1 ppb or greater. But calculation of the EEC (or PEC) assumes a uniform use of a drug across the United States. Data from the *Prescription Drug Atlas* (Express Scripts 2001) show that for some drugs, regional preferences in use can vary by several-fold. This means that for highly populated metropolitan areas with use of a particular drug exceeding that expected by a normal distribution, the EEC could be higher than predicted. This problem is further compounded by the fact that calculation of the EEC does not take into consideration cumulative exposure to drugs sharing the same MOA—where the risk from a drug's nontarget effects does not exist in isolation but should at least be considered in the context of all drugs of like MOA. The calculation of EECs could be yielding underestimates also because of the expanding purchase and use of drugs from the gray and black markets, in large part via the Internet. These use figures cannot currently be accounted for in environmental assessments.

Dispensing and expiry. The disposal of drugs is necessitated by two major factors: *a*) excess inventory of nonexpired drugs (i.e., unwanted, unneeded but still usable drugs) and *b*) outdated drugs [those whose expiration (expiry) dates have been exceeded]. Minimizing the need to dispose as a result of these two factors can be addressed by minimizing inventory (by pharmacies and consumers alike) and by ensuring that expiration dates are based on actual, empirical data rather than projections. The issue of expiry is not as simple as it may seem because there are a number of issues involved with setting the time periods for which a drug can be safely maintained (and these differ for factory-dispensed vs. consumer-dispensed forms). In practice, the time periods for shelf lives are determined not entirely empirically but also by estimates and projections. Shelf life is important as it dictates whether a therapeutic dose of the active ingredient is still present and whether degradation products with adverse therapeutic outcomes are absent.

Conservative dispensed amounts. The need for disposal could be lessened by reducing prescribed/purchased quantities too great to be used before expiration or increasing shelf life. Reasonable, minimal quantities of medication could be purchased or prescribed until the effects of the medication and its therapeutic effectiveness are understood by both the physician and patient. Overprescription of quantity (or frequent change in medication type) is a major reason for accumulation of

unused drugs by geriatric patients (Daughton 2003). Consideration should be given to not penalizing consumers for small-quantity package sizes. This recommendation, however, runs counter to mail-order dispensing businesses run by insurers, where multimonth supplies are favored because of short-term cost considerations.

Re-engineering of dispensing. A reengineering of pharmacy practice with respect to the mechanics of drug dispensing could greatly reduce drug wastage. Progressing from previous advancements in dispensing (such as blister packs, also known as “bingo cards”) and hospital unit-dose systems to the new generation of “automated medication dispensing” programs is demonstrated to have a dramatic impact not just on waste but also on reducing the hours required by nurses and caregivers devoted to mundane chores such as “med passing,” and on assuring accurate medication distribution. This has been the case especially in long-term care facilities where the accumulation of unused medications may be significant. An example is given by Saffel (1999). Certain U.S. states such as Georgia do not allow return of unused portions of 30-day medication packages. A shorter 7-day exchange cycle provided by point-of-use “automated medication dispensing” obviates this problem (e.g., Pyxis 2002). One of the recommendations of Kohn et al. (2000) is that all hospitals and health care organizations implement the use of automated drug-ordering systems.

Science-based expiry dates. Expiry dates could be investigated to see if they can be extended to reflect true stability durations. Scientifically sound protocols need to be implemented for the public sector to define, determine, predict, and/or monitor actual expiration periods for both factory-sealed and unsealed drugs. There have been very few scientific studies on the chemical stability of drugs in their formulated states. Guidance for establishing shelf lives has been developed by the U.S. FDA (2001). The significant point, however, is that there is no requirement to establish the *maximum* shelf life for a drug product—only to establish *a* documented shelf life. The major study, still ongoing, for determining shelf lives is the Shelf Life Extension Program (SLEP) (JRCAB 2002), a stability testing program administered by the U.S. FDA for the U.S. Department of Defense (for noncivilian purposes). The SLEP has documented that the actual shelf lives for some drug formulations exceed the times dictated by the labeled expiration dates (under ideal storage conditions). The cost savings in being able to increase the life-cycle times for drug restocking purportedly claimed by the Department of Defense have been substantial.

The SLEP program has been highlighted by the American Medical Association (AMA)

Council on Scientific Affairs as the type of study requiring expansion (AMA 2001). The AMA emphasizes, however, that

expiration dates only apply when the drug product is stored under defined conditions. Regardless of the feasibility of extending expiration dates, this strategy applies only to the date of packaging in the original factory container. For most U.S. drug products, expiration dating ranges from 12 to 60 months from the time of original manufacture. . . . Once the manufacturer's container is opened and drug product is transferred to another container for dispensing or repackaging, the expiration date no longer applies. The USP has developed recommendations for pharmacists to place a “beyond-use” date on the label of the new container. There is little scientific basis for “beyond-use” dates. However, the American Pharmaceutical Association (APhA) encourages, and 17 states require, that pharmacists place a “beyond-use” date on the label of the prescription container that is dispensed to the patient. (AMA 2001)

For more detailed information, see Okeke (2002).

Once the pharmacist transfers the drug to a consumer-use container (including, sometimes, heat-sealed blister packs), an expiration date is applied (usually 1 year from date of sale) not based on science; a USP standard for blister packs is 6 months or one-quarter of the manufacturer's original date [Oklahoma State University (OSU) 2000a, 2000b]. Thus it would be beneficial when marketing larger-unit, bulk drugs (e.g., those purchased by consumers in membership “club” warehouses) that the bulk container comprise a number of smaller, factory-sealed packages so as to extend the usable life. An article in the *Medical Letter* (Abramowicz 2002) surmises that most medications stored in their original, unopened packaging under proper conditions retain 70–80% of their potency for at least 10 years. Once removed from original packaging, most tablets and capsules (dry-formulated drugs) retain 70–80% of their potency (in low humidity—i.e., preferably not in a humid bathroom, which is where most “medicine cabinets” reside) for 1–2 years after the expiration date. Note, however, that these points do not address the issue of consumer safety (e.g., changes in formulation quality) but rather point to the fact that chemical stability of the parent drug can be much longer than implied by expiration dates.

Reduce/phase out controversial uses of drugs. Historically, drugs or drug classes often undergo expanded use beyond their original targeted purposes; this usually results from off-label prescribing. With certain other drugs or classes, the original intended use may have seemed logical at one time—only to be challenged later as unforeseen consequences emerged (as the known risk–benefit equation changed). Respective examples of both scenarios are the postmenopausal use of

combination hormone replacement therapy (HRT) and subtherapeutic antibiotics in animal feed for growth promotion.

HRT's use to prevent cardiovascular disease has long proved contentious. The long presumed benefits of combination HRT recently have been called into question by a number of studies, one of which is the 15-year Women's Health Initiative (WHI) sponsored by the National Institutes of Health's National Heart, Lung, and Blood Institute (see various published papers and links provided at NHLBI 2002). The WHI study set out to examine the presumed long-term beneficial effects of combination HRT (involving estrogen and progestin) on the prevention of heart disease and hip fractures, but the study was terminated early when HRT was found instead to increase a woman's risk of breast cancer, heart attack, stroke, and blood clots; the study did find that HRT reduced the risk of colorectal cancer and bone fractures.

The long-running debates regarding the use of subtherapeutic antibiotics and of anabolic steroids in animal feed have resulted in a number of actions in certain countries to reduce or abolish their use. An example is the National Antimicrobial Resistance Monitoring System, a joint nationwide monitoring program of the FDA, CDC, and U.S. Department of Agriculture for detecting the extent and trends in both human and animal enteric bacteria susceptibilities to 17 antimicrobial drugs (CVM 2002; also see links at Daughton/U.S. EPA 2002f, 2002i). From time to time, other drugs develop notoriety as a result of excessive or profound ADRs or other problems (thalidomide's original use is a classic example).

Vigilance and ongoing expedited review of the expansive literature (not limited solely to the various fields of medicine and health care but also including the biologic and ecological literature) coupled with reasoned debate are important responsibilities of science for detecting possible future problems with respect to the use of new drugs and the continued use of established drugs, especially for those that provide nonessential benefits. The soundness of current approaches used for determining whether drugs should be used for purposes never originally intended might benefit from continual reevaluation.

Supplementary and updated materials for this mini-monograph are available at the Green Pharmacy web page (Daughton/U.S. EPA 2003b).

Conclusions

The need for life-cycle stewardship of PPCPs is driven partly by the growing importance of preserving freshwater resources coupled with a water treatment and distribution infrastructure in need of major maintenance, repair, and upgrading. "Cradle-to-cradle"

stewardship is prudent not just as a derivative of the precautionary principle and the concept of environmental surprise but also because it holds the potential for major collateral benefits to consumer health care. In fact, parallels exist between human health care and the health of ecology. The options available for minimizing or preventing the release of PPCPs to the environment reside in a multitude of components composing the manufacturing and service sectors of the health care system—including everything from drug design, drug delivery, prescribing, dispensing, individualization of therapy, packaging, advertising, marketing, education for health care practitioners, and establishment of real-time PPCP use databases, among many others. Regardless of the consequences of the current generation of PPCPs that continually make their way to the environment and add to the overall pollutant burden and play a role in exposed organisms' 4Ts (toxicant–totality–tolerance–trajectory), we now have the knowledge and the opportunity to more thoroughly consider the potential for ecologic or human health effects from new classes of drugs with unique mechanisms of biologic action and to begin setting in place mechanisms for minimizing their introduction to the environment.

REFERENCES

- Abramowicz M (ed). 2002. Drugs past their expiration date. *Med Lett (On Drugs and Therapeutics)* 44(W114B):93–94. Available: <http://www.medletter.com/freedocs/expdrugs.pdf> [accessed 10 May 2002].
- ACS. 2002. Future Directions of Drug Delivery Technologies: Molecular Design, Cellular Response and Nanotechnology. American Chemical Society ProSpectives Conference Series, 13–16 October 2002, Boston, MA. Available: <http://www.acsprospectives.org> [accessed 3 September 2002].
- ActiveHealth Management. 2002. Evidence Based Medicine. New York: Active Health Management, Inc. Available: <http://www.activehealthmanagement.com/treatingphys.asp> [accessed 28 July 2002].
- Alliance Pharmaceutical. 2002. Drug Formulation Technology for Compounds Administered by Inhalation. San Diego, CA:Alliance Pharmaceutical Corp. Available: http://www.allp.com/PulmoSpheres/PS_WHITE.HTM [accessed 10 May 2002].
- Alper J. 2002. Breaching membranes. *Science* 296:838–839.
- AMA. June 2001. Report 1 of the Council on Scientific Affairs (A-01): Pharmaceutical Expiration Dates. AMA Policy H-115.983. Chicago:American Medical Association. Available: http://www.ama-assn.org/ama1/upload/mm/interim01/CSA_Reports.pdf [accessed 10 May 2002].
- Arole R. 2001. Community based health and development: the Jamkhed experience. *Health Promotion J Austral* 11(1):5–9.
- Arroll B, Kenealy T, Kerse N. 2002. Do delayed prescriptions reduce the use of antibiotics for the common cold? A single-blind controlled trial. *J Fam Pract* 51(4):324–328.
- ASCE. 2001. 2001 The 2001 Report Card for America's Infrastructure. Washington, DC:American Society of Civil Engineers. Available: <http://www.asce.org/reportcard> [accessed 10 May 2002].
- Biocode. 2002. Applications: Pharmaceuticals. Bethlehem, PA:Biocode. Available: <http://www.biocode.com/> [accessed 10 May 2002].
- Blutstein H. 2003. A forgotten pioneer of sustainability. *J Cleaner Prod* 11(3):339–341.
- Borman S. 2002. *In situ* click chemistry. *Chem Eng News* 80(6):29–34. Available: <http://pubs.acs.org/cen/coverstory/8006/8006clickchemistry.html> [accessed 10 May 2002].
- Bradley D. 2002. Computational toxicology. *Alchemist*, 6 June. Available: <http://www.chemweb.com/alchemist/articles/102229169054.html?> [accessed 11 June 2002].
- Buchanan M. 2001. *Ubiquity: The Science of History . . . or Why the World Is Simpler Than We Think*. New York:Three Rivers Press.
- Buhner SH. 2002. *The Lost Language of Plants: The Ecological Importance of Plant Medicines to Life on Earth*. White River Junction, VT:Chelsea Green Publishing.
- CDC. 2002. Promoting Appropriate Antibiotic Use in the Community. Atlanta, GA:Centers for Disease Control and Prevention. Available: <http://www.cdc.gov/drugresistance/community/> [accessed 10 May 2002].
- CHI. 2002. -Omes and -Omics Glossary. Newton Upper Fall, MA:Cambridge Healthtech Institute. Available: <http://www.genomicglossaries.com/content/omes.asp> [accessed 10 May 2002].
- COMPAS. March 2002. F&DA Environmental Assessment Regulations Project Benchmark Survey. A Report to Health Canada. PDR-02-13. Ottawa, Ontario, Canada:Office of Regulatory and International Affairs, COMPAS Inc. Available: http://www.hc-sc.gc.ca/ear-ree/fda_report_e.pdf [accessed 3 July 2002].
- Crain SM, Shen K-F. 2001. Acute thermal hyperalgesia elicited by low-dose morphine in normal mice is blocked by ultra-low-dose naltrexone, unmasking potent opioid analgesia. *Brain Res* 888(1):75–82.
- CRS. 2002. Home page. Minneapolis, MN:Controlled Release Society. Available: <http://www.geriatrictimes.com/g010709.html> [accessed 3 September 2002].
- Crutchfield DB. 2001. Patients respond to lower doses of medications. *Geriatr Times* 2(4). Available: <http://www.geriatrictimes.com/g010709.html> [accessed 10 May 2002].
- CSTEE. 2001. Opinion on: Draft CPMP Discussion Paper on Environmental Risk Assessment of Medicinal Products for Human Use [Non-Genetically Modified Organism (Non-GMO) Containing]. 24th Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) plenary meeting, 12 June 2001, Brussels, Belgium. Available: http://europa.eu.int/comm/food/fs/sc/sct/out11_en.pdf [accessed 10 May 2002].
- CVM. 2002. NARMS: National Antimicrobial Resistance Monitoring System. Rockville, MD:U.S. FDA Center for Veterinary Medicine. Available: http://www.fda.gov/cvm/index/narms/narms_pg.html [accessed 10 May 2002].
- Cyveillance. 5 June 2001. Cyveillance Partners with Biocode to Serve Pharmaceutical Industry [press release]. Arlington, VA:Cyveillance, Inc.
- Daughton CG. 2001a. Pharmaceuticals in the environment: overarching issues and overview. In: *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues* (Daughton CG, Jones-Lepp T, eds). Symposium series 791. Washington DC:American Chemical Society, 2–38. Available: <http://www.epa.gov/nerled1/chemistry/pharma/book-summary.htm> [accessed 10 May August 2002].
- . 2001b. Literature forensics? Door to what was known but now forgotten. *Environ Forensics* 4(2):277–282. Available: <http://www.epa.gov/nerled1/chemistry/pharma/images/forensics.pdf> [accessed 10 May 2002].
- . 2001c. Illicit drugs in municipal sewage: proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequences. In: *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues* (Daughton CG, Jones-Lepp T, eds). Symposium series 791. Washington DC:American Chemical Society, 348–364. Available: <http://www.epa.gov/nerled1/chemistry/pharma/book-conclude.htm> [accessed 10 May 2002].
- . 2002a. Environmental stewardship and drugs as pollutants. *Lancet* 360:1035–1036.
- . 2002b. Literature forensics: navigating through flotsam, jetsam, and lagan. *Scientist* 16(4):12. Available: http://www.the-scientist.com/yr2002/feb/opin_020218.html [accessed 10 May 2002].
- . 2003. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. II. Drug disposal, waste reduction, and future directions. *Environ Health Perspect* 111:775–785.
- Daughton/U.S. EPA. 2001. Commentary on Illicit Drugs in the Environment: A Tool for Public Education—Societal Drug Abuse and Its Aiding of Terrorism. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://>

- www.epa.gov/nerlesd1/chemistry/pharma/book-post.htm [accessed 10 May 2002].
- . 2002a. Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants: Pollution from Personal Actions, Activities, and Behaviors. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm> [accessed 10 May 2002].
- . 2002b. Summary of Media Coverage Regarding PPCPs in the Environment. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/media.htm> [accessed 10 May 2002].
- . 2002c. Origins and Fate of PPCPs in the Environment. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf> [accessed 10 May 2002].
- . 2002d. The Precautionary Principle ("Reverse Onus"). Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#ThePrecautionaryPrinciple> [accessed 10 May 2002].
- . 2002e. Perspectives from the Pharmaceutical Industry and Examples of Corporate Stewardship Programs. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Perspective> [accessed 14 August 2002].
- . 2002f. Antibiotics: Prudent/Judicious Use. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#antibiotics> [accessed 10 May 2002].
- . 2002g. Factors Complicating Prediction of Drug Elimination from the Body. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/images/slides/part3.pdf> [accessed 10 May 2002].
- . 2002h. Disposal and New Ideas in PPCP Recycling and Pollution Prevention. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Disposal> [accessed 10 May 2002].
- . 2002i. Confined Animal Feeding Operations. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#ConfinedAnimalFeedingOperations> [accessed 10 May 2002].
- . 2003a. Biological Systems and Stressors. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/stressors.htm> [accessed 13 April 2003].
- . 2003b. Environmental Stewardship of PPCPs: The Green Pharmacy. Las Vegas, NV:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/greenpharmacy.htm> [accessed 3 April 2003].
- Daughton CG, Jones-Lepp T, eds. 2001. Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. Symposium Series 791. Washington DC:American Chemical Society. Available: <http://www.oup-usa.org/isbn/0841237395.html> [accessed 10 May 2002].
- Daughton CG, Ternes TA. 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? *Environ Health Perspect* 107(suppl 6):907–938. Available: <http://www.epa.gov/nerlesd1/chemistry/ppcp/images/errata.pdf> [accessed 10 May 2002].
- DisabilityResources.org. 2002. Prescription Drug Assistance Programs. Center each, NY:DisabilityResources.org. Available: <http://www.disabilityresources.org/RX.html> [accessed 10 May 2002].
- Duke University. 2002. Medicine and Madison Avenue. Available: <http://scriptorium.lib.duke.edu/mma> [accessed 10 May 2002].
- EMEA. 2001. Draft CPMP Discussion Paper on Environmental Risk Assessment of Non-Genetically Modified Organism (Non-GMO) Containing Medicinal Products for Human Use. CPMP/SWP/4447/00 draft corr. London: The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use. Available: <http://www.emea.eu.int/pdfs/human/swp/444700en.pdf> [accessed 7 June 2002].
- Epel D, Smital T. 2001. Multidrug/multixenobiotic transporters and their significance with respect to environmental levels of pharmaceuticals and personal care products. In: *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues* (Daughton CG, Jones-Lepp T, eds). Symposium series 791. Washington, DC:American Chemical Society, 244–263.
- Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. 2002. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet* 359:1648–1654.
- Express Scripts. 2001. Prescription Drug Atlas. Maryland Heights, MO:Express Scripts Inc. Available: http://www.express-scripts.com/other/news_views/outcomes_research/atlas2002/atlas_ex_sum.htm [accessed 10 May 2002].
- Facts and Comparisons. 2002. Drugfacts.com, Facts and Comparisons. St. Louis, MO:Facts and Comparisons. Available: <http://www.drugfacts.com/shop.asp> [accessed 2 June 2002].
- Fernandez-Lopez S, Kim H-S, Choi EC, Delgado M, Granja JR, Khasanov A, et al. 2002. Antibacterial agents based on the cyclic d,l- α -peptide architecture. *Nature* 412:452–455.
- Fong PP. 2001. Antidepressants in aquatic organisms: a wide range of effects. In: *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues* (Daughton CG, Jones-Lepp T, eds). Symposium series 791. Washington DC:American Chemical Society, 264–281.
- Galbally R. December 2000. National Competition Review of Drugs, Poisons and Controlled Substances Legislation. Final Report Part A. Wodan, ACT:Commonwealth of Australia. Available: <http://www.health.gov.au/tga/docs/pdf/rdfpna.pdf> [accessed 10 May 2002].
- Genaisance Pharmaceuticals. 2002. Personal Medicine from Genomics. New Haven, CT:Genaisance Pharmaceuticals. Available: http://www.genaisance.com/home_index.html [accessed 10 May 2002].
- Gibson T. 2002. The innovation imperative. *Environ Forum*, March/April, 23–31. Available: <http://www.epa.gov/opei/eli2002mar.pdf> [accessed 10 May 2002].
- Gleick J. 1987. *Chaos: Making a New Science*. New York:Viking Penguin.
- Green JV, Murray BH. 2001. Online Distribution of Counterfeit Pharmaceuticals. Arlington, VA:Cyveillance, Inc. Available: http://www.cyveillance.com/web/downloads/Online_Pharmaceuticals.pdf [accessed 10 May 2002].
- H2E. 2002. Memorandum of Understanding: EPA-AHA. Washington, DC:Hospitals for a Healthy Environment. Available: <http://www.h2e-online.org/about/mou.htm> [accessed 16 July 2002].
- Handley DA, Tinkelman D, Noonan M, Rollins TE, Snider ME, Caron J. 2000. Dose-response evaluation of levalbuterol versus racemic albuterol in patients with asthma. *J Asthma* 37(4):319–327.
- Harremoës P, Gee D, MacGarvin M, Stirling A, Keys J, Wynne B, et al., eds. 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Environmental issue report no. 22. Copenhagen:Office for Official Publications of the European Communities. Available: http://reports.eea.eu.int/environmental_issue_report_2001_22/en [accessed 10 May 2002].
- Health Canada. 2002. Environmental Assessment Regulations (EAR): Food and Drug Products and the Environment. Ontario, Canada:Environmental Assessment Regulations Project. Available: http://www.hc-sc.gc.ca/ear-ree/index_e.html [accessed 10 May 2002].
- Heberer T. 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicol Lett* 131(1–2):5–17.
- Holling CS. 1986. The resilience of terrestrial ecosystems: local surprise and global change. In: *Sustainable Development of the Biosphere* (Clark WC, Munn RE, eds). Cambridge, UK:Cambridge University Press, 292–317.
- Intralytic. 2002. Bacteriophage Research & Development. Baltimore, MD:Intralytic, Inc. Available: <http://www.intralytic.com> [accessed 10 May 2002].
- IOM. 2001. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC:Committee on Quality of Health Care in America, Institute of Medicine, National Academy Press. Available: <http://www.nap.edu/books/0309072808/html> [accessed 2 June 2002].
- ISTS. 2002. Initiative on Science and Technology for Sustainability. Cambridge, MA:Belfer Center for Science and International Affairs, Kennedy School of Government, Harvard University. Available: <http://sustsci.harvard.edu/index.html> [accessed 4 September 2002].
- JRCAB. 2002. DOD/FDA Shelf Life Extension Program. Joint Readiness Clinical Advisory Board, U.S. Department of Defense. Available: <http://www.jrcab.army.mil/fda/page1.html> [accessed 10 May 2002].
- Kohn LT, Corrigan JM, Donaldson MS, eds. 2000. *To Err Is Human: Building a Safer Health System*. Washington, DC:Committee on Quality of Health Care in America, Institute of Medicine, National Academy Press. Available: <http://www.nap.edu/books/0309068371/html> [accessed 2 June 2002].
- Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, et al. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance. *Environ Sci Technol* 36:1202–1211.
- Kümmerer K, ed. 2001. *Pharmaceuticals in the Environment—Sources, Fate, Effects and Risks*. Heidelberg, Germany:Springer-Verlag Heidelberg. Available: <http://www.epa.gov/nerlesd1/chemistry/pharma/kummer/default.htm> [accessed 20 May 2002].
- Landis WG. 2002. Uncertainty in the extrapolation from individual effects to impacts upon landscapes. *Human Ecol Risk Assess* 8(1):193–204.
- Lazarou J, Pomeranz BH, Corey PN. 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *J Am Med Assoc* 279:1200–1205.
- Lee SB, Mitchell DT, Trofin L, Nevanen TK, Söderlund H, Martin CR. 2002. Antibody-based bio-nanotube membranes for enantiomeric drug separations. *Science* 296:2198–2200.
- Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev* 23(1–3):3–25.
- Lipsitch M, Singer RS, Levin BR. 2002. Antibiotics in agriculture: when is it time to close the barn door? *Proc Natl Acad Sci USA* 99(9):5752–5754.
- Lorenz E. 1963. Deterministic nonperiodic flow. *J Atmos Sci* 20:130–141.
- Magnani M, Rossi L, Fraternali A, Bianchi M, Antonelli A, Crinelli R, et al. 2002. Erythrocyte-mediated delivery of drugs, peptides and modified oligonucleotides. *Gene Therapy* 9(11):749–751.
- Martinovic D, Schoenfeld HL, Sorensen PW. 2003. Exposure to low levels of water-borne estrogen suppresses the competitive spawning ability of male fathead minnows. In: *Proceedings of the 3rd International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water*. Minneapolis, MN:National Ground Water Association, 125–132.
- MBDC. 2002. *Transforming Industry: Cradle to Cradle Design*. Charlottesville, VA:McDonough Braungart Design Chemistry. Available: http://www.mbdc.com/c2c_home.htm [accessed 10 May 2002].
- McDonough W, Braungart M. 2002. *Cradle to Cradle—Remaking the Way We Make Things*. New York:North Point Press.
- McGovern SL, Caselli E, Grigorieff N, Shoichet BK. 2002. A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. *J Med Chem* 45(8):1712–1722. Available: <http://pubs.acs.org/cgi-bin/jcenc/jmcar/asap/html/jm101533y.html> [accessed 10 May 2002].
- MEEK C. November 2001. Direct-to-consumer advertising of prescription medicines: a review of international policy and evidence. Supplement to a report for the Royal Pharmaceutical Society of Great Britain. London:Royal Pharmaceutical Society of Great Britain. Available: <http://www.rpsgb.org.uk/pdfs/dtcarev.pdf> [accessed 10 May 2002].
- Miller M. 2002. Breaking down barriers. *Science* 297:1116–1118.
- MIT 3DPTM Laboratory. 2002. Three Dimensional Printing. Cambridge, MA:Massachusetts Institute of Technology. Available: <http://web.mit.edu/tdp/www/medical.html> [accessed 10 May 2002].
- MIT News. 1997. MIT Scientists "Print" Drugs Into Pills. 13 April [press release]. Cambridge, MA:Massachusetts Institute of Technology. Available: <http://web.mit.edu/newsoffice/nr/1997/43521.html> [accessed 10 May 2002].
- Mort M. 2000. Multiple modes of drug delivery. *Mod Drug Discov* 3(3):30–32,34. Available: <http://pubs.acs.org/hotartcl/mdd/00/apr/mort.html> [accessed 10 May 2002].
- Munoz-Bellido JL, Munoz-Criado S, Garcia-Rodriguez JA. 2000. Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors. *Int J Antimicrob Agents* 14(3):177–180.
- NABP. 2002. Verified Internet Pharmacy Practice Sites. Park Ridge, IL:National Association of Boards of Pharmacy.

- Available: <http://www.nabp.net/vipps/intro.asp> [accessed 4 June 2002].
- National Health Council. 2002. Direct-To-Consumer Prescription Drug Advertising. National Health Council statement. Washington, DC:National Research Council. Available: <http://www.nhcouncil.org/advocacy/dtc.htm> [accessed 10 May 2002].
- National Research Council. 2001. Grand Challenges in Environmental Sciences; Committee on Grand Challenges in Environmental Sciences. Oversight Commission for the Committee on Grand Challenges in Environmental Sciences, Washington DC:National Academy Press. Available: <http://www.nap.edu/books/0309072549/html> [accessed 10 May 2002].
- . 2002a. Oil in the Sea III: Inputs, Fates, and Effects. Washington, DC:National Academy Press. Available: <http://www.nap.edu/books/0309084385/html> [accessed 29 May 2002].
- . 2002b. Biosolids Applied to Land: Advancing Standards and Practices. Washington, DC:National Research Council. Available: <http://www.nap.edu/books/0309084865/html> [accessed 3 August 2002].
- NCSE. 2001. Recommendations for Achieving Sustainable Communities: Science and Solutions. A Report from the Second National Conference on Science, Policy, and the Environment, 6–7 December 2001. Washington, DC:National Council for Science and the Environment. Available: http://cnie.org/nscconference/2001conference/report/2001_conf_report.pdf; <http://cnie.org/nscconference/2001conference/report/page.cfm?FID=1692> [accessed 29 May 2002].
- NHLBI. 2002. Facts about Postmenopausal Hormone Therapy. Bethesda, MD:National Heart, Lung, and Blood Institute, National Institutes of Health. Available: <http://www.nhlbi.nih.gov/whi/hrtupd/index.htm> [accessed 4 June 2002].
- Nuovo J, Melnikow J, Chang D. 2002. Reporting number needed to treat and absolute risk reduction in randomized controlled trials. *JAMA* 287:2813–2814. Available: <http://jama.ama-assn.org/cgi/reprint/287/21/2813.pdf> [accessed 10 June 2002].
- Odum WE. 1982. Environmental degradation and the tyranny of small decisions. *Bioscience* 32(9):728–729. Available: http://www.netpage.net.au/~jnevill/Tyranny_of_small_decisions.doc [accessed 10 May 2002].
- Okeke CC. 2002. Current USP requirements and proposals on packaging systems. *Am Pharm Outsourcing* 3(2):34–38.
- ONDCCP. 2002. Drugs and Terror. Rockville, MD:Office of National Drug Control Policy, National Youth Anti-Drug Media Campaign. Available: http://www.theantidrug.com/drugs_terror/index.html [accessed 10 May 2002].
- Orchid Biosciences. 2002. Profiling Genetic Uniqueness. Princeton, NJ:Orchid Biosciences. Available: <http://www.orchid.com> [accessed 10 May 2002].
- OSU. 2000a. Prescription Medicines and Nursing Homes: A Problem . . . a Solution. Health and Medicine issue paper. Tulsa, OK:Oklahoma State University College of Osteopathic Medicine. September. Available: <http://www.healthsciences.okstate.edu/telemedicine/Pub/chpr/chpr.0009.pdf> [accessed 25 July 2002].
- . September 2000b. Prescription Medicines & Nursing Homes: Laws—Letters—Reports—Policies. An Issue Paper Resource Supplement. Tulsa, OK:Oklahoma State University College of Osteopathic Medicine. Available: <http://www.healthsciences.okstate.edu/telemedicine/Pub/chpr/chpr.0009a.pdf> [accessed 25 July 2002].
- Pain Therapeutics. 2002. Pain Therapeutics. South San Francisco, CA:Pain Therapeutics, Inc. Available: <http://www.paintrials.com/index.html> [accessed 10 May 2002].
- PDR. 2002a. 2002 Physicians' Desk Reference. 56th ed. Montvale, NJ:Thomson Medical Economics.
- . 2002b. Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements. 23rd ed. Montvale, NJ:Thomson Medical Economics.
- Phillips KA, Veenstra DL, Oren E. 2001. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 286:2270–2279.
- PhRMA. 2003. Direct-to-Consumer Advertising Archives. Washington, DC:Pharmaceutical Research and Manufacturers of America. Available: <http://www.phrma.org/mediaroom/press/index.cfm?archive=DtoCAd> [accessed 3 April 2003].
- Pyxis. 2002. Pyxis. San Diego, CA:Pyxis Corp. Available: <http://www.pyxis.com> [accessed 10 May 2002].
- Quintiles. 2000. Quintiles Launches Commercial Version of Rx Market Monitor. Durham, NC:Quintiles Transnational Corp. Available: <http://www.quintiles.com/pressrelease> [accessed 10 May 2002].
- . 2002. Quintiles. Durham, NC:Quintiles Transnational Corp. Available: <http://www.quintiles.com> [accessed 10 May 2002].
- Rapport DJ. 2002. The health of ecology and the ecology of health. *Human Ecol Risk Assess* 8(1):205–213.
- RCBC. 2002. Zero Waste. Vancouver, British Columbia, Canada:Recycling Council of British Columbia. Available: <http://www.rcbc.bc.ca/zerowaste/zerowaste.htm> [accessed 10 May 2002].
- Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. 2002. Promotion of prescription drugs to consumers. *N Engl J Med* 346:498–505.
- Saffel D. 1999. Improving outcomes, managing drug costs, and achieving success under PPS. *Consultant Pharmacist* 14(6). Available: <http://www.ascp.com/public/pubs/tcp/1999/jun/improving.shtml> [accessed 10 May 2002].
- Schneider SH, Turner BL. 1994. Surprise and Global Environmental Change: Report of the 1994 Aspen Global Change Institute Summer Session on Surprise and Global Environmental Change. Thematic Guide to Integrated Assessment Modeling, Draft 3.0. University Center, MI:Center for International Earth Science Information Network. Available: <http://sedac.ciesin.org/mva/iamcc/articles/surprise.html> [accessed 10 May 2002].
- Schowaneck D, Webb S. 2002. Exposure simulation for pharmaceuticals in European surface waters with GREAT-ER. *Toxicol Lett* 131(1–2):39–50.
- Servos MR, Innes E, Given J, Ostapky K, Topp E, McInnis R, et al. 2002. Assessment and Management of Pharmaceuticals and Personal Care Products in the Canadian Environment: Proceedings of a Multi-stakeholder Workshop. Environment Canada and Health Canada Special Publication. NWRI Contribution 02-334. Burlington, Ontario, Canada:National Water Research Institute, Environment Canada. Available (Executive Summary of Proceedings): <http://www.nwri.ca/announce/pharmaceuticals-e.html> [accessed 2 August 2002].
- SkyePharma. 2003. Solubilization. London:SkyePharma PLC. Available: www.skyepharma.com/solubilization.com [accessed 1 April 2003].
- Slovic P. 2001. The risk game. *J Hazard Matter* 86(1–3):17–24.
- Smith CA. 1999. Rationale for inclusion of criteria for proper disposal of monograph pharmaceutical preparations based on the Resource Conservation and Recovery Act. *Pharm Forum* 25(3):8309–8312.
- Smith DL, Harris AD, Johnson JA, Silbergeld EK, Morris JG Jr. 2002. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria [Abstract]. *Proc Natl Acad Sci USA* 99(9):6434–6439. Available: <http://www.pnas.org/cgi/content/abstract/082188899v1> [accessed 10 May 2002].
- Straub JO. 2002. Environmental risk assessment for new human pharmaceuticals in the European Union according to the draft guideline/discussion paper of January 2001. *Toxicol Lett* 131(1–2):137–143.
- Thornton J. 2000. Beyond risk: an ecological paradigm to prevent global chemical pollution. *Int J Occup Environ Health* 6(4):318–330.
- TNS. 2002. The Natural Step. San Francisco, CA:The Natural Step. Available: <http://www.dettaturligastegest.se> [accessed 27 June 2002].
- Toma T. 2001. Cathelicidin and dermicin are antimicrobial proteins that enhance skin defense against invasive bacteria. Philadelphia, PA:The Scientist.com. Available: <http://www.biomedcentral.com/news/20011123/03> [accessed 10 May 2002].
- Toxicology Letters. 2002. *Toxicol Lett* 131(1–2):1–146 [Abstracts]. Available: <http://www.elsevier.com/locate/toxlet?menu=cont&label=Table> [accessed 16 August 2002].
- UNEP. 2002. Industry as a Partner for Sustainable Development—10 Years after Rio: The UNEP Assessment. Paris:United Nations Environment Programme. Available: http://www.unep.org/outreach/wssd/docs/global/UNEP_report-english.pdf [accessed 6 June 2002].
- UrineTown. 2002. Home page. Greg Kotis (playright); John Rando (director); Mark Hollmann (score). Available (description): http://www.urinetown.com/flash/home_1a.html [accessed 10 May 2002].
- U.S. DHHS. July 1998. Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications. CMC 6, Revision 1. Rockville, MD:U.S. Department of Health and Human Services. Available: <http://www.fda.gov/cber/gdlns/enviro.pdf> [accessed 10 May 2002].
- U.S. EPA. 2000. U.S. EPA Strategic Plan. EPA 190-R-00-002. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/ocfopage/plan/plan.htm> [accessed 10 May 2002].
- . 2002. Innovation for Better Environmental Results: Innovating a Strategy to Guide the Next Generation of Innovation at EPA. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/opei/strategy> [accessed 10 May 2002].
- U.S. EPA Office of Pesticide Programs. 1996. Reduced Risk, IPM and Pollution Prevention. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/oppfead1/fqpa/rripmp.htm> [accessed 10 May 2002].
- U.S. EPA Office of Pollution Prevention and Toxics. 2002. EPA's Green Chemistry Program. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/greenchemistry> [accessed 10 May 2002].
- U.S. EPA Office of Wastewater Management. 2002a. Combined Sewer Overflows. Washington, DC:U.S. Environmental Protection Agency. Available: http://cfpub.epa.gov/npdes/home.cfm?program_id=5 [accessed 10 May 2002].
- . 2002b. A Plain English Guide to the EPA Part 503 Biosolids Rule. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/OW-OWM.html/mtb/biosolids/503pe/index.htm> [accessed 10 May 2002].
- U.S. EPA Office of Water – Ground Water and Drinking Water. 2002. Unregulated Contaminant Monitoring Rule. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/safewater/ucmr.html> [accessed 10 May 2002].
- U.S. EPA Science Policy Council. 2002. Interim Genomics Policy. Washington, DC:U.S. Environmental Protection Agency. Available: <http://www.epa.gov/osp/spc/genomics.htm> [accessed 5 August 2002].
- U.S. FDA. 2001. Guidance for Industry—Q1A Stability Testing of New Drug Substances and Products. Revision 1. Rockville, MD:U.S. Food and Drug Administration. Available: <http://www.fda.gov/cder/guidance/4282fnl.htm> [accessed 10 May 2002].
- . 2002a. Buying Medicines and Medical Products Online. Rockville, MD:U.S. Food and Drug Administration. Available: www.fda.gov/oc/buyonline [accessed 10 May 2002].
- . 2002b. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Rockville, MD:U.S. Food and Drug Administration. Available: <http://www.fda.gov/medwatch/> [accessed 10 May 2002].
- . 2002c. The New Over-the-Counter Medicine Label: Take a Look. Rockville, MD:Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available: <http://www.fda.gov/cder/consumerinfo/OTClabel.htm> [accessed 10 May 2002].
- USGS. 2002. USGS Toxic Substances Hydrology Program: What's in Our Wastewaters and Where Does It Go? Denver, CO:U.S. Geological Survey. Available: <http://toxics.usgs.gov/highlights/whatsin.html> [accessed 10 May 2002].
- USP. 2001. A USP Council of Experts Statement of Scientific Policy—Guiding Principles Supporting Appropriate Drug Use at the Patient and Population Level. Rockville, MD:U.S. Pharmacopeia, 12 March 2001. Available: http://www.usp.org/information/drug_principle.pdf [accessed 10 May 2002].
- Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. 2002. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem* 45(12):2615–2623.
- Velagaleti R, Burns PK, Gill M, Prothro, J. 2002. Impact of current good manufacturing practices and emission regulations and guidances on the discharge of pharmaceutical chemicals into the environment from manufacturing, use, and disposal. *Environ Health Perspect* 110:213–220.
- Velagaleti R, Gill M. 2001. Regulatory oversight for the environmental assessment of human and animal health drugs: environmental assessment regulations for drugs. In: *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues* (Daughton CG, Jones-Lepp T, eds). Symposium series 791. Washington DC:American Chemical Society, 320–332.
- Wackernagel M, Rees W. 1995. Our Ecological Footprint: Reducing Human Impact on the Earth. Philadelphia,

- PA:New Society Publishers.
- WHO. 1999. Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies. Geneva:World Health Organization. Available: <http://www.who.int/medicines/library/par/who-edm-par-99-2/who-edm-par-99-2.htm> [accessed 10 May 2002].
- . 2001. World Water Day Report 2001: Water for Health—Taking Charge. Geneva:World Health Organization. Available: <http://www.worldwaterday.org/2001/report/index.html>; <http://www.worldwaterday.org/2001/report/wwwreport.pdf> [accessed 10 May 2002].
- . 2002a. Global Assessment of the State-of-the-Science of Endocrine Disruptors (Damstra T, Barlow S, Bergman A, Kavlock R, Kraak, GVD, eds). WHO/PCS/EDC/02.2. Geneva:International Programme on Chemical Safety. Available: http://www.who.int/pcs/emerg_site/edc/global_edc_TOC.htm [accessed 13 August 2002].
- . 2002b. WHO Policy and Strategy on Traditional Medicine. Essential Drugs and Medicines Policy. Geneva:World Health Organization. Available: <http://www.who.int/medicines/organization/trm/orgtrmmain.shtml> [accessed 18 May 2002].
- World's Water. 2002. Information on the World's Freshwater Resources. Oakland, CA:Pacific Institute. Available: <http://www.worldwater.org/links.htm> [accessed 10 May 2002].
- XenoPort. 2002. Home page. Santa Clara, CA: XenoPort, Inc. Available: <http://www.xenoport.com/> [accessed 10 May 2002].
-