Cradle-to-Cradle Stewardship of Drugs for Minimizing Their Environmental Disposition While Promoting Human Health. II. Drug Disposal, Waste Reduction, and Future Directions

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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. The growing, worldwide importance of freshwater resources underscores the need for ensuring that any aggregate or cumulative impacts on (or from) water supplies are minimized. Despite a 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 for reducing or minimizing 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 the lessening of medication expense for the consumer and improving patient health and consumer safety. In this article (the second of two parts describing the "green pharmacy") I focus on those actions and activities tied more closely to the end user (e.g., the patient) and issues associated with drug disposal/recycling that could prove useful in minimizing the environmental disposition of PPCPs. I also outline some recommendations and suggestions for further research and pose some considerations regarding the future. In this mini-monograph I attempt 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* **111:775–785 (2003). doi:10.1289/ehp.5948 available via** *http://dx.doi.org/* **[Online 12 December 2002]**

This article is part II of a mini-monograph on the many facets of a little-discussed but important aspect of the overall issue of pharmaceuticals and personal care products (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 by way of their use and disposal (Daughton 2001a; Daughton and Jones-Lepp 2001; Daughton and Ternes 1999; Heberer 2002; Kolpin et al. 2002; Kümmerer 2001; Servos et al. 2002), 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 can be taken to minimize or eliminate their further environmental disposition. 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 their occurrence as pollutants (Daughton 2002). This second of two parts focuses on those source control/reduction activities tied more closely to the end user (e.g., the patient and consumer) and issues associated with drug disposal/recycling rather than those that reside more under the control of the health care industry (further up the chain of events involved with a drug's cradle-to-grave disposition), which is the focus of part I (Daughton 2003). In this second part, I also outline some specific suggestions centering more on end use, present recommendations for further research, and pose some considerations regarding the future; the background and context for why pollution prevention is a topic worth considering for PPCPs are covered in part I.

Drug Disposal/Recycling/ Pollution Prevention

Responsible disposal and product stewardship. Of all the inquiries received from the public and the news media on the topic of PPCPs in the environment, the most frequent regards "proper" (ecologically sound) disposal of unused medications. Unfortunately, definitive, consistent guidance is not available. The age-old wisdom of flushing medication down the toilet (still recommended by many professionals), however, is probably the least desirable of all the alternatives, which include disposal in household trash and community hazardous waste pickup programs. Indeed, standardized nationwide or international guidance is needed for disposition of noncontrolled substances by end users of unused/expired drugs as well as by disposal companies. A formal but voluntary Product Stewardship program (previously known as Extended Product Responsibility; Hanisch 2000; U.S. EPA Office of Solid Waste 2002) implemented by all involved industries would be a proactive way to guide the disposal of unwanted, expired ("outdated") PPCPs by the public, state, local, and medical communities (e.g., nursing homes, hospitals, physician samples). National policies are usually directed solely at the internal generation of wastes by the medical care industry—not by the public. For example, Australia [National Health and Medical Research Council (NHMRC) 1999] advises, "Wherever possible, this waste should be incinerated. It should not be sent for landfill. Such waste should not be discharged into sewerage systems" (p. 14). Little exists in the peer-reviewed literature regarding drug disposal regulations and attendant issues. Within the gray literature (i.e., literature not captured by traditional means of archiving), four of the more informative resources are Musson and Townsend (1998), Smith (2002), Wang (2000), and the World Health Organization (WHO 1999). The ideas

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embodied in Extended Product Responsibility, incidentally, have evolved separately from those of "industrial ecology," but the principle of closing the loops for material flows is shared by both. The first professional society devoted to industrial ecology, the International Society for Industrial Ecology, was recently formalized (International Society for Industrial Ecology 2001).

Incentives. One of many possible approaches to fostering stewardship programs [those that tie both environmental and human health together—"ecology of health" (Daughton 2003)] would be to offer patent extensions to companies that formulate vibrant, comprehensive stewardship programs tailored for each particular drug. Precedent for this resides in what was the U.S. Food and Drug Administration (FDA)'s Pediatric Rule [an incentive-based rule that encouraged clinical trials designed for children (Center for Drug Evaluation and Research; CDER 2002), since replaced by the Best Pharmaceuticals for Children Act (U.S. FDA 2002a), which offers 6-month patent extensions for doing research that defines safe dosages for children. Interestingly and ironically, the rationale for this need is that it is not possible to predict the differing responses of children (compared with adults)—the same as what might very well be true for potential effects on nontarget organisms.

Expanded use and mission of reverse distributors. Many but not all U.S. pharmacies use "reverse distributors" for return of unsold/expired inventory [e.g., Returns Industry Association (RIA) 2002; RxWebPortal.com 2002]. This existing industry could serve as the foundation for an overarching returns industry—by its expansion into a larger, comprehensive disposal/recycling program, one that accommodates the consumer sector. Great value could be added by designing an integral database that compiled information mined from consumer returns, with the objective of ultimately improving health care; such data are traditionally extremely difficult to obtain.

Pharmaceutical "returns" result directly from the many issues associated with "unsaleables" (products unwanted by the consumer, for any of a wide spectrum of reasons, and products that have expired), a topic whose entire scope is not even understood by the involved industries, but one that has been captured in a report by Siecker (2001). The monetary costs associated with returns in the United States have been estimated at up to (or even exceeding) $2 billion per year, exceeding the actual market value of the products (Siecker 2001); these costs, however, have never been factored in to a cradle-to-cradle approach. Clearly, many inefficiencies exist in the distribution system. The many forces that cast a product into the unsaleable class have been enumerated by Siecker (2001); these range from simple expiry issues to new market forces (rapid obsolescence by market-entry of new products) to seasonal demand. Industry has brainstormed on ways to reduce the need for returns (Siecker 2001), and some of the ideas correspond with those presented in this mini-monograph. That the returns industry is so large and that it is driven by the many vagaries of consumerism perhaps cast some light on the scope and magnitude of the parallel issues with consumer creation of unused drugs. The total cost for drugs that are placed into the returns network amounts to a little more than 1% of total sales. The 2002 *Chain Pharmacy Industry Profile* [National Association of Chain Drug Stores (NACDS) 2002] reports US$164 billion in 2001 total retail pharmacy sales resulting from more than 3 billion prescriptions, representing 2-year increases of 13–16% in sales and 5–6% in scripts; $188.5 billion in sales are projected for 2002 (a 15% increase from 2001). Four of every five patients leave the doctor's office with a prescription (NACDS 2002), so the distribution of drugs through the consumer sector is clearly enormous.

Physician samples. Although physician samples (manufacturer samples distributed free to medical practices) constitute an unknown percentage of the overall disposal problem, distributors of physician samples often instruct physicians to dispose of outdated samples to the sewage system. This source should also be subject to any nationwide guidance or regulations.

Source separation for domestic wastes. Advancement in, and implementation of, new technologies for dealing with waste at the source (e.g., separation of distinct streams) holds the highest potential for the future minimization of waste flows to the environment. Sewage source separation schemes such as those involving toilet reengineering are but one example (e.g., Larsen et al. 2001; Novaquatis 2002; Otterpohl 2002).

Sewage recycling. Also under development are various "toilet-to-tap" plans for upgrading sewage to potable water (or at least to a level suitable for groundwater reinjection) (Drewes and Shore 2001; Greene 2000). By use of advanced water treatment technology such as reverse osmosis, nearly complete removal of all PPCPs can be achieved. However, all the solutes removed by reverse osmosis are concentrated in the rejected "brine"—a waste stream that must be disposed itself.

Improvements to sewage infrastructure. Straight-piping of sewage (e.g., Pressley 1999) to surface waters should continue to be identified and eliminated on an ongoing basis. Privies and septic systems should be converted to municipal systems when feasible. Improvements in capacity can reduce overflow events, a problem of escalating proportions in many urban areas (e.g., see one of an extensive news series on aging sewer infrastructure in Sforza et al. 2001). It has long been assumed that ocean discharge of sewage protects coastal exposure (by way of dilution). A recent study, however, shows the possibility of sewage plume redirection to coastal areas by tidal events (Boehm et al. 2002). As sewage discharges increase with expanding populations, the dilution previously afforded by receiving waters will continually diminish.

Recycling (reclamation). "Drug mining," such as hospital reclamation of highly toxic drugs from excreta and other wastes, could be pursued and expanded; a prototype example can be found in work by Pharmaceuticals.org (2002).

Responsible reuse, recycling, and donation. The entire area of charitable drug donations and pharmacy reuse (sometimes referred to as recycling) is a complex issue fraught with concerns, especially regarding safety, liability, and compensation. Donations are complicated by a morass of international regulations, politics, interconnected organizations and charities, and controversy (Reich 1999). One of the technical issues associated with drug donations and reuse is that of expiry. More information can be found at the website maintained by the Wemos Foundation (2002). Certain state legislation in the United States (e.g., Ohio General Assembly 2001) has been attempting to establish drug "repository" programs for collecting and redistributing unadulterated prescription drugs for subsequent represcribing to patients meeting eligibility requirements.

The reuse by pharmacies of previously prescribed, within-date drugs has been a contentious and complex issue for more than two decades—partly because of the rising costs of new-generation drugs and because of insufficient public resources dedicated to the medically indigent. There is also debate over who should benefit (in terms of compensation) from reuse, given that the original patients, insurance companies, or Medicaid programs originally paid for the unused medications.

Dispensing laws often run counter to responsible reuse of still-usable drugs (OSU 2000a) despite the fact that modern, tamper-evident packaging would greatly assist in the assurance of the quality of reused drugs. In Oklahoma alone, long-term care facilities (LTCFs) each month are directed by state law to dispose of millions of dollars of unused medications (and incur substantial personnel oversight/implementation costs); an unknown portion of the disposed drugs is directed to municipal sewers (OSU 2000a). At the same time, the medically indigent often do not receive medications that they may require,

and when they do, it is often with the use of public funds (OSU 2000a).

One rough estimate of the national monetary value of unused drugs in LTCFs is US$73–378 million (OSU 2000a); statistically based estimates are difficult to compile because of the proprietary nature of the industry. This estimate assumed wastage rates of 4–15%, which have been revealed by various state studies (OSU 2000a).

It is illegal in certain states (e.g., Oklahoma) to give away (e.g., donate to charity) any drug already obtained by prescription (OSU 2000a, 2000b). It is also illegal in certain states for pharmacies to accept returned unused drugs; this is a result of long-recognized, complex issues regarding quality assurance (particularly problematic is a drug's shelf history—whether it was stored in a controlled environment, especially regarding temperature and humidity—as well as the issue of counterfeiting). Because of these complicating factors, the FDA has no general policy governing reuse and instead prefers that each state set its own individual policy (OSU 2000b); the FDA does not disallow reuse—it simply highlights the dangers and pitfalls that require vigilance in establishing a reuse program. The American Medical Association (AMA) supports the reuse of drugs in LTCFs (AMA 2001). In light of this, it behooves the states to study and emulate best practices and try to align their practices accordingly.

Demonstrating the disparate implementation of drug reuse across the United States, it has proved difficult to ascertain exactly what state practices do entail. One survey maintains that as of the year 2000, 36 states allowed at least some form of drug reuse (recycling) or resale; 17 allowed both reuse and resale without restrictions, and 12 prohibited any reuse or resale (OSU 2001, 2000b). A subsequent survey (OSU 2001), however, revealed only six or so states with reuse/resale provisions. It is clear that the issue is complex, with different meanings, interpretations, and implementation across the states. Certain states have been actively working on legislation that would enable reuse; Ohio (Ohio General Assembly 2001) and Oklahoma (OSU 2001) are two examples.

Environmentally sound funeral practices. In countries practicing burial, cemeteries [which are a special landfill subclass (Ucisik and Rushbrook 1998)] can pose problems with respect to groundwater pollution if they have not been properly engineered and sited with local hydrogeologic processes in mind (Croukamp 1999). Although a number of investigations have examined the transport of pathogens from burial grounds to the groundwater (Santarsiero et al. 2000), little is known regarding the release of PPCPs, whose presence in dead bodies could be expected to be extensive as a result of long-term medication and heroic treatment measures. Furthermore, in North America, those areas where embalming is practiced commonly discharge withdrawn body fluids (containing whatever medications the dying patient had been administered) directly into municipal sewage systems (Funeral Consumers Alliance 2002). An analogous problem might exist with the disposal of carcasses from medicated or euthanized pets (see Daughton 2001a), where lethal concentrations of barbiturates such as sodium pentobarbital are often used.

Public outreach/education—heightening public awareness. A well-designed, concerted public outreach program for communicating the issues associated with PPCPs as environmental pollutants could accomplish dual aims: *a*) enhance the public's appreciation and understanding of a wide range of principles associated with environmental science, and *b*) increase the public's sense of environmental responsibility by showing how their actions as individuals collectively contribute to the burden of PPCPs in the environment, how PPCPs can possibly affect environmental processes (e.g., aquatic biota), and the collateral advantages (human health and economic) accrued by conscientious/responsible disposal and use of PPCPs. The educational aspects of the topic are summarized in Daughton/U.S. EPA (2002a).

Two additional potential opportunities exist with leveraging the public education aspect of PPCPs as environmental pollutants: First, the fact that drugs can theoretically be monitored in sewage now provides society for the first time with the science to quantify the actual extent and magnitude of community-wide use of illicit/abused drugs (Daughton 2001b); this would objectify the decades-old and emotionally charged national debate regarding the actual magnitude of drug abuse. Second, parallel to this is the fact that monitoring for illicit drugs in sewage or the environment could raise community awareness of inadvertent financial support to terrorism (Daughton/U.S. EPA 2001a; ONDCP 2002). These activities, in turn, would heighten the public's awareness that their combined, daily individual activities, actions, and behaviors can have immediate, intimate, and inseparable connections with the environment and with world events. With improved knowledge of these connections, behaviors (e.g., consumerism) affecting pollution prevention, disposal, and recycling may eventually become self-adjusting or self-regulating.

Drug Alternatives

A variety of alternatives to drug therapy, ranging from nutrition to advanced use of medical microbial ecology, could help reduce society's use of medications.

Nutrition and health maintenance. The key and critical disease-prevention role played by nutrition should continue to be explored and emphasized at all levels. A number of federal agencies and organizations are active in purveying information regarding the critical linkage between nutrition and health (wellness or disease prevention), including the U.S. Centers for Disease Control and Prevention (CDC 2002a), Health Canada (2002), and the U.S. Department of Agriculture (USDA 2002a, 2002b). This type of information could be made an integral, visible part of direct-to-consumer advertising for drugs (Daughton 2003). The connections between health maintenance/improvement via proper nutrition and the reduced need for medication are well documented.

Placebos. Although "alternative" medicine (e.g., standardized, bioactive, naturally occurring substances such as phytochemicals and other "nutraceuticals") has received much renewed attention (Daughton and Ternes 1999) and could eventually reduce the use of synthetic drugs, more emphasis could be placed on expanding the exploration of nonchemical alternatives to traditional medications. As an example, more research could be directed at reducing (or eliminating) drug dosages via the use of placebos (e.g., Christensen 2001; Leuchter et al. 2002).

Probiotics. Probiotics (beneficial, endogenous microflora) have long been used and studied for the protection of the gut [largely by blocking pathogen adhesion (e.g., Kaur et al. 2002)]. More recent work has expanded this important domain of clinical microbial ecology to other medical uses such as prophylaxis for postsurgical infection [in lieu of prophylactic antibiotics (e.g., Harder 2002; Reid et al. 2001)]. The U.S. FDA Center for Veterinary Medicine approved the first probiotic for animals (known as a "competitive exclusion culture" product) in 1998; still the only approved competitive exclusion product, it is known by the trade name Preempt, and its New Animal Drug Application number is 141-101 (U.S. FDA 2002b). Sometimes called "bacteriotherapy," the wide range of medical uses of probiotics for displacing pathogens is summarized in Beale (2002).

Research and Development

Further research and development on a wide range of fronts could contribute to the minimization of PPCPs in the environment. Several are summarized here.

Determining the relative importance of sources. **Disposal versus excretion/washing.** Determine the relative contributions to environmental loadings of PPCPs from direct, purposeful disposal to sewage (and trash) of unwanted/unused PPCPs versus inadvertent excretion and washing. That portion of the

overall environmental drug burden emanating from direct disposal versus end use is totally unknown. More extensive public surveys and actual monitoring could be used to tease these apart. For example, for those oral drugs that *a*) are efficiently absorbed and undergo extensive, nearly complete metabolism excrete low levels of the parent form (e.g., imipramine, morphine, itraconazole, isoproterenol, meperidine, verapamil, among many) and *b*) also are documented to occur in the environment, perhaps it could be concluded that direct disposal plays a significant role in their entering the environment. Bathing would be expected to be the most significant source for those drugs that are extensively applied externally (e.g., silver sulfadiazine burn cream) and other topically applied antibiotics (e.g., bacitracin) as well as for personal care products (e.g., synthetic musk fragrances), but disposal could play a role.

Disposal from LTCFs versus general population. The accumulation of unused medications at LTCFs presents major, well-documented problems for disposal. It is not known, however, how significant this source is compared with disposal from the general populace. This issue grows more important as our population's age structure becomes more inverted.

Maintenance versus short term. The relative overall contributions to the environment by long-term maintenance drugs (used extensively at LTCFs) versus short-term drugs is not known.

Hospitals versus domestic. The use of on-site waste reclamation and treatment varies greatly for hospitals and other medical care facilities. Hospitals especially might be expected to be more significant contributors for certain highly toxic drugs such as antineoplastics and other cytotoxic drugs.

Domestic animals versus humans. We should attempt to determine the relative contributions from veterinary animals (e.g., confined animal feeding operations, aquaculture, pets) versus that for humans. This is especially important regarding steroids (e.g., Renner 2002) and antibiotics (certain antibiotics and anabolic steroids are used exclusively for various domestic animals), where the overall loadings could be important. Although the discussion in this article has focused on human therapeutics, veterinary drugs clearly can be major contributors to environmental exposure (e.g., see Boxall et al. 2002).

Straight-piping and raw sewage versus treated sewage. Straight-piping sidesteps benefits that might exist in secondary and tertiary sewage treatment for further drug removal, so the relative contributions from straight-piping versus those for treated sewage would be useful to know. Overflow discharge of raw, untreated sewage is becoming more prevalent as aging and under-capacity treatment plants cannot keep pace with urban populations. Waivers for over-capacity overflows are frequently granted for discharges to marine environments, in contrast to straight-piping and malfunctioning septic systems, which can be found discharging into any type of receiving water. Another potential source of PPCPs from raw sewage (although more geographically confined) is cruise ships, which have a history of discharge of insufficiently treated sewage (Alaska Department of Environmental Conservation 2001a, 2001b, 2002; Nowlan and Kwan 2001).

Illicit versus licit drugs. The prevalence of illicit drugs in the environment is completely unknown (Daughton 2001b). Although the occurrence database for licit drugs continues to be expanded, with new publications appearing frequently, almost no effort has been devoted to illicit drugs.

Effect of health status on excretion. Health or disease status probably has a large but undetermined significance with respect to determining the extent of excretion of drugs in their unaltered states. Gastrointestinal disease can dramatically reduce uptake and thereby enhance excretion (or expulsion, e.g., through vomiting) of the parent drug. Sequestration (e.g., chelation of tetracycline by dairy products or of fluoroquinolones by divalent cations), alteration in gastrointestinal mobility, or alteration of gastric pH can similarly alter excretion. A better understanding of these parameters for the individual patient not only would better serve patients (e.g., by altered delivery routes) but also could reduce unnecessary excretion.

Release into waters with low versus high existing pollutant loads. An argument can be made that windows of aquatic toxicity vulnerability open as a dynamic function of the rate of change or status of overall cellular stress. Organisms that have accommodated to new stress (e.g., by synthesis of cellular stress proteins or overexpression of efflux pumps) may be significantly more resistant to the effects of newly present toxicants than those organisms equilibrated to a constant environment. For this reason, organisms in slowly changing, pristine environments may be more susceptible to new exposure to chemical stressors than are organisms experiencing ongoing exposure to many, changing stressors.

New drugs and ecotoxicology. Regardless of the environmental significance of the current universe of drugs, the anticipated continuing expansion in new drug entities (those from new chemical classes and with previously unknown mechanisms of action—whose development will be driven largely by advancements on the many fronts of "omics") provides the opportunity to develop ecologic toxicity testing approaches that are more capable of detecting the types of effects that could ensue. Particular attention should be paid to accounting for shared mechanisms of action (to accommodate cumulative exposure; see Daughton 2003, Figure 2). Also needed is attention to chemicals that are not necessarily toxic in their own right but can potentiate the toxicity of other substances ("chemosensitizers"). A good example of this concern is the possible need to screen for a pollutant's potential to inhibit multidrug efflux pumps, which serve as the first lines of defense for aquatic organisms (Daughton 2001a; Daughton and Ternes 1999; Epel and Smital 2001); this would obviously be important for the new generations of efflux pump inhibitors themselves but also would apply to any PPCP having efflux-pump inhibition potential. As just one example of a new therapeutic class of drugs that may pose environmental concern, consider the angiogenesis inhibitors (see links at NCI 2003). This broad therapeutic class consists of a number of synthetics—including legacy drugs such as thalidomide, as well as many new ones. These compounds have profound teratogenic potential (thalidomide being a well-known example), but little is known about their aquatic toxicology (especially important during embryogenesis and development).

Early warning monitoring. A nationwide, universal early-warning water monitoring system that can detect any newly appearing xenobiotic (including PPCPs) would be tremendously useful for detecting new trends (including illicit drugs) and for permitting early intervention as needed before adverse impacts might occur. A proposal on the utility of an early-warning monitoring system based solely on the simple approach of identifying anomalous constituents exclusively (largely ignoring all pre-existing constituents) has been outlined (Daughton/U.S. EPA 2001b). A collateral benefit from a real-time early-warning monitoring system is that it could be easily designed to serve double duty for homeland security—to detect any newly present chemical sabotage agent. A monitoring system is also a key component of any effort to measure the effectiveness of pollution prevention strategies that have been implemented [in keeping with the U.S. EPA's new Innovation Strategy (Gibson 2002; U.S. EPA 2002)]. In recent years, there have been a number of proposals for creation of a national health monitoring system—one based on epidemiology and environmental monitoring, illustrated recently by a meeting sponsored by the Institute of Medicine's Roundtable on Environmental Health Sciences, Research, and Medicine (IOM 2002). A nationwide early-warning monitoring system for previously unrecognized or newly emerging pollutants could be integrated within such a system. Furthermore, the system could

be expanded to include the tracking of environmental health in addition to human health pollutants because the argument can be made that the two are inseparable (Daughton 2003).

Guidance on groundwater recharge. With dwindling supplies of potable water supplies in many parts of the world, efforts to recycle water are accelerating (Drewes and Shore 2001). One approach is to store treated sewage in aquifers by a variety of active reinjection or recharge approaches. Although this approach seems straightforward, the fact that the environmental half-lives of many substances are increased in the subsurface domain (because of reduced microbial activity, lack of photolytic alterations), it is imperative that reinjected water be cleaned to standards protective of ecologic and human health. Consistent, national guidance (but which can be tailored to local geology) is therefore needed regarding the composition of active recharge waters.

Extended expiry. Extend the shelf life research already being performed for factory-sealed drugs under the Shelf-Life Extension Program (Daughton 2003) to see if expiration dates on public-sector factory-sealed drugs and pharmacy-dispensed drugs can be extended or maximized.

Excipients and "alternative" medicines. Even though registered drugs and diagnostics have a paucity of data regarding potential or actual environmental effects (other than for conventional ecotoxicologic tests), excipients (the nontherapeutic agents in formulated medicines), alternative drugs such as nutraceuticals and dietary supplements, and personal care products (except the synthetic musk fragrances, some surfactants, and sunscreen agents) have even less. Some research effort should be devoted to these underinvestigated classes of PPCPs in the environment to gage their possible importance. The diverse classes of bioactive chemicals in nutraceuticals and dietary supplements are growing as a result of renewed interest in "self-care." Several examples are summarized by Daughton and Ternes (1999). In contrast to the use of pharmaceuticals (with the exception of "cosmetic" or "lifestyle" pharmaceuticals), consumer use of personal care products is almost always one of personal discretion. Also unlike pharmaceuticals, most personal care products are used externally (or not ingested) and in larger quantities, maximizing their likelihood for release to the environment (via bathing or oral discharge).

Future Concerns/Opportunities

Molecular farming ("pharming"). The large-scale production (kilograms per hectare) of pharmaceuticals by transgenic organisms, especially plants and food crops (known as molecular farming or "pharming"), is currently aimed mainly at producing phytopharmaceuticals—"functional foods," "biologic" and other medically related reagents, diagnostics, and vaccines. Today, molecularly farmed pharmaceuticals are primarily recombinant proteinaceous therapeutics, such as enzymes, hormones, and monoclonal antibodies, that tend to be costly to produce by existing means (e.g., cultured mammalian cells) and more risky because of transference of human pathogens. For a listing of relevant web resources and reports on plant-made pharmaceuticals, see Daughton/U.S. EPA (2002b). Although these current-generation phytopharmaceuticals are proteins (and therefore at least have an innate susceptibility for degradation in the environment), questions must be asked as to the wisdom of mass biosynthesis of pharmaceuticals in food plants, whether the large quantities that can be produced will have the ability for direct escape to the environment (with the attendant unknowns of persistence and nontarget, unanticipated effects), and whether the technology will eventually gain the routine ability to synthesize small-molecule nonproteins, which may pose different concerns than for proteins.

Contamination of the common agricultural food-plant gene pool by cross-pollination has been established as a major concern (albeit hotly debated), especially if the therapeutic is bioactive at trace concentrations (e.g., hormones). This concern is reflected by the current U.S. regulations on intercrop distances and crop-cycle timing, as stipulated in regulations by the USDA (via the Animal and Plant Health Inspection Service) and the U.S. FDA (see links at Daughton/U.S. EPA 2002b). Furthermore, the crops most frequently used for molecular farming are corn, soybeans, and rice. Any progress in eliminating (vs. minimizing) the possibility of cross-pollination would be desirable—a true closed-loop system would be preferable because any controversy regarding contamination of the common food supply would then be negated. Although the primary concern regarding risk has focused on humans (centered around allergenicity, and toxicity in the form of direct endocrine disruption or other mechanisms), perhaps more imminent (but largely unanticipated) hazards could be present for nontarget organisms, whose interactions with crops are extremely difficult to prevent. Any failure of the systems in place to ensure the complete containment of plant-made pharmaceuticals could at the least lead to widespread distrust (and disruption) of the long-established and trusted U.S. food industry. Such concerns would at the least affect mass psychology. As an example, although a low level of contamination of nongenetically modified foodstuffs with herbicide-tolerant or insecticidal grain may be tolerable to some people, would the same level of tolerance continue if a drug for rheumatoid arthritis or a vaccine for hepatitis B were the contaminant? For in-depth discussions of the many complex facets of this topic, see CFIA (2001); Freese (2002); Golz (2001); Kirk (2001); McCalla et al. (2002); Pew Initiative (2002); see also other resources at Daughton/U.S. EPA (2002b).

Omics. As pointed out by Daughton and Ternes (1999), rapid and escalating advancements in genomics, proteomics, glycomics, and others, coupled with an inverting societal age structure, will contribute greatly to the commercial introduction of an ever-increasing array of new drug entities, many of which target new receptors and possess previously unforeseen mechanisms of action. As an example, novel (non-native, "mutated") proteins can now be theoretically engineered (using native biochemical machinery) by modification of existing proteins and incorporation of non-natural amino acids (e.g., Bessho et al. 2002). These "mutated" proteins may not be as easily catabolized as native proteins and therefore may have the potential for longer ecologic half-lives. This fact, in light of the precautionary principle, provides ample forewarning to institute measures for minimizing the risks that might be associated with introducing drugs to the environment—and at the same time improves consumer health and economy.

Personal "medical statistics card." A voluntary, personal "medical statistics card" containing an individual's medical treatment history could help minimize the overuse and inappropriate use of prescription drugs. The history stored on such a card (including, e.g., past and present medication, allergies) could assist an attending physician prevent redundant or ill-advised prescribing because of a lack of patient data; this would be especially valuable for those patients having multiple physicians and those who "self-medicate." It could even be used to help consumers in prescreening over-the-counter (OTC) drugs and food supplements that could lead to adverse interactions with prescription medication they are taking. Consumers would not need to understand the status of any of the medications and supplements they are taking as long as they were diligent in using their card when purchasing medications or supplements; the card would rely on accessing a standardized, up-to-date expert system of prescribing information. Such a card, whose information content could be stored anonymously (no need to encode with personal information) would not be confused with the concept long and hotly debated in the United States of a "national health card," which is intended more for obtaining medical services rather than ensuring efficiency and efficacy of medical treatment; national health cards have been successfully implemented for some time in a number of other countries but

have been controversial in the United States because of real or perceived issues with privacy protection. Patients could, however, also elect to store medical information keyed to their personal identity if they wished to avoid repeated requests for the same information by multiple medical care providers (and thereby also ensure a more accurate, thorough, and consistent portrayal of their medical histories across a continuum of providers).

Insights and Recommendations: Disposal of PPCPs by the End User

In North America, only a fragmented patchwork of often-contradictory regulations, guidance, and formal/informal advice attempts to direct the purposeful disposal of PPCPs. This uncoordinated guidance is geographically uneven and varies greatly among governing bodies. Regardless of what the best environmental disposition of expired/unwanted PPCPs might eventually be, clearly there would be benefits in having but one optimal approach. Much work is needed in formulating a single, cohesive set of nationwide (or global) regulations or guidance addressing disposal or recycling. Comprehensive regulations or guidance would address PPCPs that have entered the consumer chain, as well as those used in hospitals, medical practices (e.g., physician's samples), LTCFs (e.g., nursing homes), and humanitarian relief efforts.

Locating literature regarding drug disposal is not easy, primarily because there are no unique search words. To broaden success in key word searching of English documents available on the Internet and published in the printed literature, multiple terms must be used, including the coupling of the words "drug," "medicine" (or the adjective "medication"), or "pharmaceutical" with "disposal," "destruction," "recycling," "reuse," "return," "take-back," "outdated," or "expired." Once formal disposal/recycling program names have been identified (e.g., EnviRx or RUM, discussed below), they can be used in turn to locate many more references (this is especially useful for non-English-language web pages).

Current practice: patchwork of diametrically opposed approaches. To illustrate the disharmony of current practices, consider the following: Most existing laws directed at drug disposal are written around two concerns: *a*) the disposition of "controlled" substances or *b*) the imperative to keep expired/unwanted medication away from children (this is perhaps the major imperative for disposing of drugs to sewage that has been instilled in the public over the years). Environmental concerns are rarely cited (in the United States, California is one exception). Some states require nursing homes to dispose of unwanted drugs to the "toilet." For example, State of North Carolina (2002) regulations stipulate that "non-controlled substances shall be disposed of by incineration, flushing into septic or sewer system, or by transfer to a local pharmacy for destruction." Many pharmacy or health care websites recommend disposal to the sewer. Typical examples include "flush old drugs down the toilet; don't just toss them in the trash where little hands could get hold of them" (MSN 2002), and the California Poison Control System (2002), advocates flushing unwanted drugs down the toilet. Sometimes, the advice is nebulous and circular: "Contact your state board of pharmacy or your state Environmental Protection Agency office for the appropriate means of disposal of prescription samples. Local law enforcement may not be aware of specific disposal issues relating to prescription drugs" (Volunteers in Health Care 2001). In contrast, other websites give more proactive advice. For example, Great Pacific Industries' (2002; e.g., Save-On-Foods) pharmacy network has its own "take-back" program, more in line with a nationwide program that has been implemented in Canada since the mid-1990s and in Australia since 1998.

Take-back programs. Most British Columbia pharmacies belong to the Medications Return Program (MRP). The MRP was instituted in March 2001 as a relaunch of the formerly known EnviRx program, which was founded in November 1996 as a consumer-oriented stewardship program, established voluntarily by British Columbia's pharmaceutical industry. The program's most recent annual report can be found in Driedger (2002). The program was made mandatory in March 1997 by an expansion of the scope of the Post-consumer Residual Stewardship Program Regulation (Government of British Columbia 2002). It is designed to accept the free return of all prescription and OTC medications (and certain other medically oriented products); it does not, however, accept physician samples. The MRP derives from a true cradle-to-cradle philosophy in that "ecology of health" is the central focus (Daughton 2003). The MRP was formed to balance the concerns and objectives for ensuring or improving the health of the environment, consumer, and economy.

The MRP has been embraced by Canada's National Association of Pharmacy Regulatory Authorities (NAPRA) for a number of reasons, including consumer/child safety (accidental poisonings, unwitting consumption of expired product or product prescribed for someone else), reduced costs (encouraging purchase of manageable drug amounts that are fully consumed), improved therapeutic outcomes, and "reduced potential for environmental damage" (NAPRA 2002).

The Canadian take-back programs (as founded under EnviRx) have also had unforeseen benefits, especially for consumer health; such collateral benefits are characteristic of cradle-to-cradle approaches. For example, the Alberta Pharmaceutical Association has been mining the data compiled from their program to answer questions regarding what consumer sectors are discarding PPCPs and why they are not fully using their supplies (Driver 1998). For example, a major problem long faced by medical practitioners has been "patient noncompliance" (why patients do not finish their medication). The Alberta take-back program provided the rare opportunity to perform a follow-up, life-cycle analysis—the type of study normally missing from current prescribing practices. The knowledge gained could prove extremely beneficial to the health care consumer. At the same time, potential adverse environmental impacts are reduced. The study learned, for example, that geriatric patients return the most medications. This led to the recommendation for "trial prescriptions" that provide small initial quantities, enabling the physician to determine the suitability of the prescription for the patient before large quantities go unused.

There are also some take-back programs in Europe. Two major ones are Italy's Ass.Inde and France's Cyclamed (e.g., Macarthur 2000). The European Agency for the Evaluation of Medicinal Products (EMEA 2001, sec 5) also recommends that "unused preparations or old preparations should be returned to pharmacies." In Australia, a free "returns" program was launched in July 1998 using a not-for-profit organization (National Return and Disposal of Unwanted Medicines Ltd.) in partnership with the New South Wales Government and various pharmaceutical industry entities. Dubbed the RUM Project (Return Unwanted Medicines), the program plans to enlist more than 5,000 pharmacies nationwide. As with other take-back programs, RUM's mission is to lessen disposal to the environment, reduce child poisonings, and minimize inappropriate sharing of medicines (RUM 2002). A similar Australian program is Overseas Pharmaceutical Aid for Life (OPAL 2003)

Sparse literature. Surprisingly, the various facets of the topic of drug disposal have been infrequently addressed in the literature over the years, and the few reports that have been published in the open literature have received little attention outside the pharmacy community. Drug disposal has interested medical professions primarily because of insights it can yield on issues relating to patient compliance and economic costs to the consumer. The driving force has rarely emanated from the potential for environmental benefits (which are currently ill-defined because of the lack of science), although progress toward one aim is often relevant to the other—they are intimately tied. The two major issues in the

literature are misuse and inappropriate use (both resulting in overuse) and noncompliance (resulting in discharge of unused drugs to sewage and solid waste when a course of medication is not completed). Inappropriate use especially among the elderly has been a topic of continuing debate (e.g., Gurwitz and Rochon 2002; Pitkala et al. 2002). The public needs to be better informed regarding the appropriate use of medications to maximize the benefits for themselves and the environment. The following is a synopsis of some of these relevant studies.

Coambs et al. (1997) reported that for Canada's health care system, the economic annual costs that could be potentially avoided by better engineering of prescribing practices and patient education (i.e., inappropriate use and medication noncompliance) were estimated to be as high as Can$7–9 billion. More recent studies (e.g., CSHP 2002) corroborate the economic aspects: "Misuse of drugs is not only a major health concern, it is a major economic concern." In one of the earliest analyses of the economic costs of drug disposal, Kidder (1987) determined that monthly per-patient drug wastage costs ranged from US$1.52 to $5.67.

Boivin (1997) reports some of the only actual survey data on drug disposal. As many have noted, as the population age structure becomes more inverted, the number of prescriptions per patient also tends to increase; for example, those patients 75 years and older in 2000 received per capita the most new prescriptions—an average of 12 (NACDS 2002). But medication use not only rises with age; it also tends to result in more wastage (for a variety of reasons, most of which result from issues specific to geriatric medicine). Boivin (1997) discovered that substantial quantities of drugs go unused from both classes of therapeutics—acute (short term) and maintenance (long term). Many of the most frequently unused (returned) drugs also happened to be ones that have since been identified in environmental monitoring studies (e.g., Daughton and Ternes 1999). Factors that contribute to noncompliance include frequent physician alterations in dosage of existing drugs and prescribing of new drugs, patient death, patient improvement, and silent symptoms (those that the patient cannot detect as worsening or improving, e.g., high blood pressure, and that provide the patient with no feedback or incentive for continuing with their medication). The survey indicated that more than 63% of the population had disposed of medication in the past. The estimated annual cost of the wasted medication across the province of Ontario exceeded Can$40 million; if extended for all of Canada, the wastage could have exceeded Can$110 million. Regarding the method of disposal (before the Canadian take-back program), 46% had disposed of their unwanted medications to the toilet, 31% disposed them to trash, 17% had already been taking them back to the pharmacy, 2% to their physician, and 4% used other routes. The predominance of disposal to the toilet over other routes, corroborates the few other published studies, despite claims to the contrary (e.g., Velagaleti et al. 2002).

In a study of drug use at LTCFs, Paone et al. (1996) make a number of recommendations regarding the reduction of medication use. They found medication wastage to amount to 6.7% of the total cost of dispensed medications. This resulted partly from problematic "prn" (take as needed) medication and because medication was discontinued by physicians 27% of the time because it was no longer needed or suitable; the dose of medication was altered in 5% of patients. The researchers recommended that dispensing be limited to 10-day (instead of 30-day) supplies.

The AMA's Council on Scientific Affairs addresses the issue of drug "recycling" (AMA 2001) and reaches the conclusion that the costs associated with LTCF unused medications is between 4% and 10% of the total dispensed costs. Of the wastage, more than 90% results from "discontinuation or change in medication or death, transfer, or hospitalization of the resident." But they were not able to assess the method by which this substantial quantity of unreturned medication was disposed. The AMA encourages the use of tamper-evident seals on medication to facilitate return/recycling. The AMA policy is consistent with the policy of the American Society of Consultant Pharmacists, which "supports the return and reuse of medications to the dispensing pharmacy to reduce the waste associated with unused medications in LTCFs and to offer substantial cost savings to the health care system" (ASCP 1996).

Very sparse data are available that indicate the quantities of drugs that are purposefully disposed. The Australian RUM Project (RUM 2002) has recently been collecting more than 200 tons of unwanted drugs each year; this perhaps gives a glimpse of the magnitude of the disposal issue. In one of the only published surveys relevant to the United States, Kuspis and Krenzelok (1996) also surveyed community drug disposal. Of those surveyed, only 1.4% returned medications to a pharmacy, 54% disposed of medications in the garbage, and 35.4% flushed medications down the toilet or sink; 7.2% did not dispose of medications, and 2% said that they used all medications before expiration. Of the pharmacies surveyed, 97% had specific policies regarding disposal of undispensed medications, and these policies directed return to the producer. For medication that was not returnable, 15% was incinerated, 17% directed to hazardous waste handlers, and 68% disposed to solid waste or the toilet (but unfortunately, the two were not distinguished). In contrast to internal operating procedures, only 5% of the surveyed pharmacies had consistent recommendations for their customers. Little information on safe disposal of drugs was routinely relayed to the public. The authors recommend that uniform guidelines are needed for the safe disposal of expired medications and that these policies be included in consumer education provided by pharmacies and poison information centers alike. Indeed, note that the California Poison Control System (2002) advocates flushing unwanted drugs down the toilet. For the 12-month period before the COMPAS survey (for Health Canada), 19% and 20% of those surveyed disposed of unused/expired nonprescription and prescription drugs, respectively, to sewage (with higher percentages of women doing so than men), and 50% and 39% disposed of nonprescription and prescription drugs to the garbage, respectively (COMPAS 2002); interestingly, 26% and 37% disposed of these by a means other than garbage, recycling, sewage, or dumping/burying.

Only as recently as the late 1990s was the concept of "treating the environment as our patient" [in line with the "ecology of health" (Daughton 2003)] beginning to emerge from the pharmacy sector (e.g., Blanchard 1998). Blanchard (1998) noted a survey recommendation that reducing a prescription's supply to 28 days could reduce the need for discarding by as much as 30% (but also observed that progress in that direction is hampered by the desires of insurers and patients, both of whom want bulk filling of prescriptions). Also, with the issue of waste aside, 28-day supplies would also reduce inappropriate use of leftover medications and accidental poisonings (Blanchard 1998).

Disposal Guidance

Little formal guidance has been developed for drug disposal. The WHO was forced to develop guidance as a result of the humanitarian efforts during the Bosnia conflict. A major problem arose from the enormous quantities of expired and inappropriate medications that were received as part of humanitarian donations. But the WHO's (1999) guidance is more relevant to large-scale field situations.

The Canadian NAPRA has also taken a proactive stance toward drug disposal (e.g., NAPRA 2002); their philosophy is reflected in the consumer pamphlet prepared by the Canadian Pharmacists Association (CPhA 2002), which gives the consumer tips on disposal of unwanted drugs, including guidance to not dispose drugs in the garbage or to the toilet—because "it's not good for the environment."

The American Pharmaceutical Association coordinated the development of the 1998 Pharmacist Practice Activity Classification (PPAC) system (APhA 1998), which describes and classifies the activities of licensed pharmacists throughout the health care delivery system. Activity C.3.4. in the PPAC (to promote safe medication use, storage, and disposal) has two tasks involving drug disposal: task C.3.4.4 (educate groups about the proper disposal of medications and devices) and task C.3.4.5 (provide a general medication and device disposal service pursuant to state and federal laws and regulations). But specifics are not provided on their website.

For the most part, however, a large disjointed patchwork of often conflicting guidance and regulations exists for directing the disposal or destruction of drugs. It has long been common knowledge among pharmacists and physicians, at least in some states and locales, that oversight/regulatory authorities do recommend "proper disposal" of drugs, but at the same time, they contradictorily recommend disposal to sewage. Oversight regarding disposal/destruction usually resides in a variety of agencies and departments, and those that oversee pharmacies differ from those that oversee nursing facilities, and yet others sometimes oversee consumer end use (Light 1997).

The importance of uniform guidance for disposal of PPCPs is illustrated by one of the outcomes from the American Academy of Pediatrics (AAP) policy statement on the implications of mercury in pediatric health care (Goldman et al. 2001). One of the many sources for mercury in the environment is from personal care products and devices such as mercury thermometers. One of the recommendations set forth to pediatricians by the AAP policy statement was for "parents to remove mercury thermometers from their homes." Unfortunately, advice on the proper methods for disposal of elemental-mercury thermometers did not accompany the report. A follow-up study (DiCarlo et al. 2002) surveyed a variety of local, county, and state health officials to ascertain the advice that they would be giving to public inquirers regarding proper thermometer disposal. Only 24% would have made the correct recommendation (viz., turn thermometers in to hazardous waste pickup). The major (and incorrect) recommendation would have been to dispose in domestic trash (45%). This one example (which should have been clear-cut) shows the importance of unified, clear guidance regarding disposal or recycling of all medical products.

Hazardous Chemicals: A Special and Paradoxical Case regarding PPCPs

There does exist a special circumstance where the disposal of specific drugs and ingredients in personal care products is indeed regulated—namely, chemicals listed as hazardous under the Resource Conservation and Recovery Act (RCRA 1976). The U.S. Department of Justice's Drug Enforcement Agency (DEA) strictly regulates the disposal of unwanted controlled substances (but there are many exemptions, depending on such factors as whether the substance is used in a prescription medication, e.g., pentobarbital, phenobarbital, diazepam, codeine, and many others). The DEA disposal program is not discussed here; for more information, refer to DEA (2003). The Schedules of Controlled Substances can be obtained from the Code of Federal Regulations (CFR 2002a). The DEA classifies controlled substances into five categories (schedules I through V), indicating progressively lower potential for substance abuse. Schedule I substances have a high potential for abuse (and no recognized medical uses); the other schedules contain drugs with recognized medicinal uses.

For a drug to be RCRA listed, it generally appears on the RCRA "P" or "U" lists. P-List RCRA chemicals are deemed acutely hazardous in any concentration (40 CFR 261.33e); U-list chemicals are deemed less toxic (40 CFR 261.33f). Quite a number of PPCPs appear on these two RCRA lists primarily because of toxicity. In addition to P- and U-listing, a substance is subject to RCRA D-listing if it exhibits one or more of four RCRA characteristics: toxicity, ignitability, corrosivity, and reactivity. D-listing, however, usually applies not to active ingredients but rather to other ingredients (e.g., excipients such as solvents). Some RCRA-listed chemicals that have major medicinal therapeutic uses are listed in Table 1 (but note that many other nonmedicinal chemicals on these lists are commonly used in various other aspects of medicine and therapeutics). For the complete lists, refer to 40CFR§261.33 (CFR 2002b). Whether a PPCP is available only by prescription is not a determining factor for listing. Some listed PPCP ingredients are OTC constituents (e.g., nicotine). These issues are further discussed by Smith (1999, 2002).

These and other commonly used PPCP ingredients become hazardous waste at the time the decision is made to actually dispose. The responsibility for determining if the waste is indeed hazardous rests with the waste generator. As mentioned above, note that for controlled substances (e.g., codeine, opiates, tranquilizers, etc.), DEA regulations apply. Although RCRA directs the disposition of certain select PPCPs, this determines how distributors and pharmacies handle these drugs when they are outdated. Significantly, the law is not closed around the complete use cycle, because it has no impact on the actions of consumers. For example, mention is never made on a drug container that the ingredients are subject to RCRA. But even then, the fact that a drug is listed by RCRA and handled appropriately cannot completely prevent it from entering the environment—because the mere use of these substances by consumers results in direct input to the environment—by both excretion (currently unavoidable) and consumer disposal.

A paradox arises in that many regulated industrial chemicals have dual uses—as consumer nonfood products and as industrial chemicals. These chemicals are not subject to the same strict disposal standards for consumer use as they are for industrial use. Phthalic acid esters (phthalates) are but one example; others include a wide array of common solvents, including alkanes, alcohols, aldehydes, ketones, esters, and aromatics (all of which can be used in formulating cosmetics and for some drugs). The consequence is that substantial exposures to very high concentrations of industrially regulated substances can result from direct application of cosmetics to the body by unregulated consumer use.

The CDC published the first large-scale environmental contaminant human exposure study through direct biomonitoring of blood and urine (Blount et al. 2000; CDC 2000b).

Table 1. Some RCRA-listed chemicals that have major medicinal therapeutic uses.

P List[a]	U List[b]
Epinephrine (adrenaline) P042	Chlorambucil (Leukeran) U035
Nicotine P075	Cyclophosphamide (Cytoxan, Neosar, Procytox) U058
Nitroglycerine P081	Daunomycin (Dauorubicin, Cerubidine) U059
Physostigmine P204	Diethylstilbestrol U089
Physostigmine salicylate P188	Melphalan (Alkeran) U150
Warfarin > 0.3% P001	Mitomycin C (Mutamycin) U010
	Paraldehyde U182
	Phenacetin U187
	Reserpine U200
	Saccharin U202
	Selenium sulfide U205 (e.g., dandruff shampoos)
	Streptozocin (Zanosar) U206
	Uracil mustard U237
	Warfarin (Coumadin) < 0.3% U248

[a]Representative P-listed drugs (some have other uses). [b]The U list has a number of antineoplastic agents (among other PPCPs).

The study verified human exposure to chemicals via personal care products—namely, phthalates. These ubiquitous, high-volume industrial chemicals (often used as flexibility promoters in plastics) have a plethora of end uses in consumer products, including vinyl flooring, wall coverings, detergents, lubricating oils, solvents, food packaging, and medical devices. They also are frequently used in many formulations of PPCPs—for example, soap, shampoo, hair spray, sunscreens, antiperspirants, medication, and many types of nail polish; their uses are designed around the very abilities of phthalates to penetrate the skin and to act as humectants and emollients. They are incorporated into formulations at high concentrations. Their use has been so widespread for such a long time that they are frequent background contaminants in environmental analyses. The CDC study showed that human exposure is higher and spans a wider spectrum of phthalates than previously suspected. Exposure of wildlife is unknown, but given the widespread and heavy use of these compounds, exposures to a wide array of organisms can be inferred.

Conclusions/Recommendations

A patchwork of inconsistent and often conflicting advice, guidance, or regulations exists among and within countries to guide the disposal of PPCPs and ultimately determine their environmental disposition. Despite this patchwork, a wide array of actions could be taken both near term and longer term to lessen the introduction of PPCPs to the environment. Given the state of current information regarding the occurrence of PPCPs in the environment, disposal of drugs to domestic sewage systems is probably the *least* desirable way to dispose of any drug. In the United States, two better alternatives might include reworking existing regulations that prevent *a*) local pharmacies from taking back consumer medications (to either dispose of by medical incineration or return to "reverse distributors") or *b*) local hazardous waste collectors from collecting unwanted medications (e.g., community curb-side pickup programs, but not for RCRA- or DEA-listed PPCPs). As a last alternative, disposal in household trash destined for engineered landfills is probably more environmentally sound (but still not desirable) than disposal to sewage systems; landfills, however, are really a form of potential "pollution postponement"—as opposed to an ultimate solution. Coincidentally, efforts to reduce the introduction of PPCPs to the environment often could and can have unforeseen, collateral benefits for consumer health and economies. Protecting the health, safety, and pocketbook of the patient holds potential for protecting the environment—and vice versa. Such wide-ranging benefits are characteristic of cradle-to-cradle stewardship programs. Stewardship programs (centered around a cohesive take-back or returns program) would prove critical to the birth of the "green pharmacy." For true cradle-to-cradle stewardship of PPCPs, a holistic integration of all aspects of the production–consumption cycle is required—one that takes into consideration the needs and costs of the complete cycle from drug discovery/design to distribution, end use, and disposal/recycling. The economies and ecological/human health efficiencies of no single aspect can be optimized in isolation from the others. Although in this mini-monograph I survey many of the avenues for reducing the controllable introduction of PPCPs to the environment, I do not address the many other issues (especially the potential for adverse effects) associated with the unintended, uncontrollable excretion of PPCPs and their metabolites into the environment—a subject of a future publication. Supplementary and updated materials for this mini-monograph are available at the Green Pharmacy web page (Daughton/U.S. EPA 2003).

References

Alaska Department of Environmental Conservation. 2001a. Report to the Alaska Cruise Ship Initiative: Near-Field Dispersion of Wastewater Behind a Moving Large Cruise Ship. Cruise Ship Wastewater Science Advisory Panel, 26 June 2001. Juneau, AK:Alaska Department of Environmental Conservation. Available: http://www.state.ak.us/dec/press/cruise/scipanl2.htm [accessed 27 July 2002].

———. 2001b. Alaska Cruise Ship Initiative: Part 2 Report 1 July 2001. Juneau, AK:Alaska Department of Environmental Conservation. Available: http://info.dec.state.ak.us/DECPermit/ACSIReport.pdf [accessed 27 July 2002].

———. 2002. Cruise Ship Waste Disposal and Management. Juneau, AK:Alaska Department of Environmental Conservation. Available: http://www.state.ak.us/local/akpages/ENV.CONSERV/press/cruise/cruise.htm [accessed 27 July 2002].

AMA. 2001. Report 2 of the Council on Scientific Affairs (I-97) Full Text: Recycling of Nursing Home Drugs. Chicago:American Medical Association, 14 March. Available: http://www.ama-assn.org/ama/pub/article/2036–2527.html [accessed 10 May 2002].

APhA. 1998. Pharmacist Practice Activity Classification 1.0. Washington, DC:American Pharmaceutical Association. Available: http://www.aphanet.org//lead/practiceclass.html [accessed 10 May 2002].

ASCP. July 1996. ASCP Policy Statement—Statement on the Return and Reuse of Medications in Long-Term Care Facilities. Alexandria, VA:American Society of Consultant Pharmacists. Available: http://www.ascp.com/public/pr/policy/return.shtml [accessed 10 May 2002].

Beale B. 2002. Probiotics: their tiny worlds are under scrutiny. Scientist 16(15):20. Available: http://www.the-scientist.com/yr2002/jul/research_020722.html [accessed 22 July 2002].

Bessho Y, Hodgson DRW, Suga H. 2002. A tRNA aminoacylation system for non-natural amino acids based on a programmable ribozyme. Nat Biotechnol 20(7):723–728.

Blanchard B. 1998. Medication wasteland: can we care for the environment as our patient? Toronto, Ontario, Canada: Pharmacy Practice, Rogers Media. Available: http://www.pharmacyconnects.com/content/phpractice/1998/11–98/php119804b.html [accessed 10 May 2002].

Blount BC, Silva MJ, Caudill SP, Needham LL, Pirkle JL, Sampson EJ, et al. 2000. Levels of seven urinary phthalate metabolites in a human reference population. Environ Health Perspect 108:979–982. Available: http://ehpnet1.niehs.nih.gov/docs/2000/108–10/toc.html [accessed 10 May 2002].

Boehm AB, Sanders BF, Winant CD. 2002. Cross-shelf transport at Huntington Beach. Implications for the fate of sewage discharged through an offshore ocean outfall. Environ Sci Technol 36(9):1899–1906.

Boivin M. 1997. The cost of medication waste. Can Pharm J, May, 32–39. Available: http://www.napra.org/practice/toolkits/toolkit9/wastecost.pdf [accessed 10 May 2002].

Boxall ABA, Fogg L, Blackwell PA, Kay P, Pemberton EJ. March 2002. Review of Veterinary Medicines in the Environment. Bristol, UK: Environment Agency R&D Technical Report P6-012/8/TR. Available: http://www.webookshop.com/ea/rdreport.nsf/cb25ea8bb5cda7ce8025670d0046afca/ebb707d23d5c38f980256bf1005ca749?OpenDocument [accessed 2 August 2002].

California Poison Control System. 2002. How Can You Prevent Poisonings? San Francisco, CA:California Poison Control System. Available: http://www.calpoison.org/public/prevent.html [accessed 10 May 2002].

CDC. 2002a. Nutrition and Physical Activity. Atlanta, GA:Centers for Disease Control and Prevention. Available: http://www.cdc.gov/nccdphp/dnpa [accessed 10 May 2002].

———. 2002b. National Report on Human Exposure to Environmental Chemicals. Atlanta, GA:Centers for Disease Control and Prevention. Available:http://www.cdc.gov/nceh/dls/report/Highlights.htm [accessed 10 May 2002].

CDER. 2002. Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric "Rule," and Their Interaction. Washington, DC:Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available: http://www.fda.gov/cder/pediatric/faqs.htm [accessed 10 May 2002].

CFIA. 2001. Public Forum on Plant Molecular Farming. Ottawa, Ontario:Plant Biosafety Office, Plant Health and Production Division, Canadian Food Inspection Agency, 30 October 2001. Available: http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_fore.shtml [accessed 10 May 2002].

CFR. 2002a. 21 CFR Section 1308: Schedules of Controlled Substances. U.S. Code of Federal Regulations. Available: http://www.deadiversion.usdoj.gov/21cfr/cfr/2108cfrt.htm.

CFR. 2002b. 40 CFR—Chapter I—Part 261§ 261.33 Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Code of Federal Regulations. Available: http://www.access.gpo.gov/nara/cfr/cfrhtml_00/Title_40/40cfr261_00.html [accessed 10 May 2002].

Christensen D. 2001. Medicinal mimicry: Sometimes, placebos work—but how? Sci News 159(5):74–75,78. Available: http://www.sciencenews.org/20010203/bob9ref.asp [accessed 10 May 2002].

Coambs RB, Jensen P, Her MH, Ferguson BS, Jarry JL, Wong JSW, et al. 1997. Costs of Non Compliance and Inappropriate Use of Prescription Medication in Canada. Special Report prepared for the Pharmaceutical Manufacturers Association of Canada. Ottawa, Ontario, Canada:Canada's Research-Based Pharmaceutical Companies. Available: http://www.canadapharma.org/Media_Centre/Special_Reports/noncomp97_e.html [accessed 10 May 2002].

COMPAS. 2002. F&DA Environmental Assessment Regulations Project Benchmark Survey. A Report to Health Canada. POR-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].

CPhA. 2002. Your Medicine Cabinet. Ottawa, Ontario, Canada: Canadian Pharmacists Association. Available: http://www.pharmacists.ca/content/consumer_patient/resource_centre/working/pdf/medicine_cabinet.pdf [accessed 10 May 2002].

Croukamp L. 1999. Cemetery Site Investigations. Pretoria, Australia:Environmental-, Engineering- and Marine-Geoscience Division, Council for Geoscience. Available: http://www.geoscience.org.za/divisions/eemg/cemetery.htm [accessed 10 May 2002].

CSHP. 2002. Pharmacy Facts—Pharmacists—Making a Difference! . . . On Healthcare Costs. Ottawa, Ontario, Canada:Canadian Society of Hospital Pharmacists. Available: http://www.cshp.ca/advocacy/fact.html [accessed 10 May 2002].

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/nerlesd1/chemistry/pharma/book-summary.htm [accessed 10 May August 2002].

———. 2001b. 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/nerlesd1/chemistry/pharma/book-conclude.htm [accessed 10 May 2002].

———. 2002.Environmental stewardship and drugs as pollutants. Lancet 360:1035–1036.

———. 2003. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ Health Perspect 111:757–774.

Daughton/U.S. EPA. 2001a. 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].

———. 2001b. One Proposal for a Nation-wide Approach to Identifying Emerging, Nascent Risks: Pollutant Fingerprint Anomalies. Las Vegas, NV:U.S. Environmental Protection Agency. Available: http://www.epa.gov/nerlesd1/chemistry/pharma/science-issues.htm#One Proposal [accessed 10 May 2002].

———. 2002a. Teaching Environmental Science—Guide to Relevant Materials Located on This Web Site. Las Vegas, NV:U.S. Environmental Protection Agency. Available: http://www.epa.gov/nerlesd1/chemistry/pharma/teaching.htm [accessed 10 May 2002].

———. page 2002b. Molecular Farming (production of PPCPs by transgenic organisms). Las Vegas, NV:U.S. Environmental Protection Agency. Available: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Molecular Farming [accessed 10 May 2002].

———. 2003. Environmental Stewardship of PPCPs: The Green Pharmacy. Las Vegas, NV:U.S. Environmental Protection Agency. Available: http://www.epa.gov/nerlesdI/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].

DEA. 2003. Diversion Control Program. Washington, DC:U.S. Drug Enforcement Agency. Available: http://www.deadiversion.usdoj.gov/ [accessed 6 April 2003].

DiCarlo M, Ruck B, Marcus S. 2002. How should a fever mercury thermometer be disposed of? A survey of those likely to be asked. Pediatrics 109(5):e71. Available: http://www.pediatrics.org/cgi/reprint/109/5/e71.pdf [accessed 7 May 2002].

Drewes JE, Shore LS. 2001. Concerns about pharmaceuticals in water reuse, groundwater recharge, and animal waste. 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, 206–229.

Driedger R. 2002. Post-consumer Residual Stewardship Program Regulation Pharmaceuticals—Annual Report by the Director—2000 Reporting Period. Victoria, British Columbia, Canada:Pollution Prevention and Remediation Branch, Ministry of Water, Air, and Land Protection, Government of British Columbia. Available: http://wlapwww.gov.bc.ca/epd/epdpa/ips/meds/meds2000.html [accessed 10 May 2002].

Driver D. 1998. APhA Mines drug waste for data—pharmacy association to determine who's throwing out medications and why, based on data from province-wide EnvirX program. Toronto, Ontario, Canada:Pharmacy Post, Rogers Media.Available:http://www.pharmacyconnects.com/content/phpost/1998/06–98/ppo069820.html [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: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.

Freese B. July 2002. Manufacturing Drugs and Chemicals in Crops: Biopharming Poses New Threats to Consumers, Farmers, Food Companies and the Environment. Washington, DC:Genetically Engineered Food Alert Coalition. Available: http://www.gefoodalert.org/pages/home.cfm [accessed 15 July 2002].

Funeral Consumers Alliance. 2002. What You Should Know about Embalming. Hinesburg, VT:Funeral Consumers Alliance. Available: http://www.funerals.org/personal/embalm.htm [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].

Goldman LR, Shannon MW, and the Committee on Environmental Health. 2001. Technical report—mercury in the environment: implications for pediatricians. Pediatrics 108(1):197–205. Available: http://www.aap.org/policy/t109907.html [accessed 10 May 2002].

Golz C. 2001. Gene Farming: State-of-the-Art Report on Potential Risks and Risk Management Strategies. Conducted for the Federal Environmental Agency. Berlin:Umweltbundesamt. Available: http://www.biotech-consult.de/gene-farming-sum.pdf [accessed 10 May 2002].

Government of British Columbia. 2002. Medications Return Program. Victoria, British Columbia, Canada:Industry Product Stewardship, Ministry of Water, Air, and Land Protection, Government of British Columbia. Available: http://wlapwww.gov.bc.ca/epd/epdpa/ips/meds [accessed 10 May 2002].

Great Pacific Industries. 2002. Bright Ideas for Environment: Medication Disposal Program. Vancouver, British Columbia, Canada:Great Pacific Industries. Available: http://www.saveonfoods.com/1/brightlife/environment/medicationdisposal.htm [accessed 10 May 2002].

Greene LA. 2000. Controversy swirls around toilet-to-tap project. Environ Health Perspect 108(10):A447.

Gurwitz JH, Rochon P. 2002. Improving the quality of medication use in elderly patients: a not-so-simple prescription. Arch Intern Med 162(15):1671–1672.

Hanisch C. 2000. Is extended producer responsibility effective? Environ Sci Technol 34(7):170A–175A.

Harder B. 2002. Germs that do a body good: bacteria might someday keep the doctor away. Sci News 161(5):72–74. Available: http://www.sciencenews.org/20020202/bob9.asp [accessed 10 May 2002].

Health Canada. 2002. Office of Nutrition Policy and Promotion. Ottawa, Ontario, Canada:Health Canada. Available: http://www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/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.

International Society for Industrial Ecology. 2001. International Society for Industrial Ecology. Available: http://www.yale.edu/is4ie/ [accessed 1 August 2002].

IOM. 2002. Environmental Health Indicators: Bridging the Chasm of Public Health and the Environment. Workshop sponsored by the Institute of Medicine (IOM), Roundtable on Environmental Health Sciences, Research, and Medicine, Washington, DC. 10–11 April 2002. Available: http://www.iom.edu/iom/iomhome.nsf/pages/environmental+health+roundtable [accessed 10 May 2002].

Kaur IP, Chopra K, Saini A. 2002. Probiotics: potential pharmaceutical applications. Eur J Pharm Sci 15(1):1–9.

Kidder SW. 1987. Review of drug waste in long-term care facilities 1976–1983. J Geriatr Drug Ther 1(3):35–47.

Kirk DA. 2001. Potential Impacts of Plant Molecular Farming on Biodiversity. Ottawa, Ontario:Canadian Food Inspection Agency. Available: http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_kirke.shtml [accessed 10 May 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.

Kuspis DA, Krenzelok EP. 1996. What happens to expired medications? Vet Hum Toxicol 38(1):48–49.

Larsen TA, Peters I, Alder A, Eggen R, Maurer M, Muncke J. 2001. Re-engineering the toilet for sustainable wastewater management. Environ Sci Technol 35(9):192A–197A.

Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. 2002. Changes in brain function of depressed subjects during treatment with placebo. Am J Psychiatry 159:122–129. Available: http://ajp.psychiatryonline.org/cgi/content/abstract/159/1/122 [accessed 10 May 2002].

Light G. 1997. Conflicting information, regulations add confusion to the drug disposal question. The Consultant Pharmacist, American Society of Consultant Pharmacists 12(9). Available: http://www.ascp.com/public/pubs/tcp/1997/sep/letters.html [accessed 10 May 2002].

Macarthur D. 2000. Any old drugs? Two schemes for the disposal of unwanted medicines in Europe. Pharm J 264:223–224. Available: http://www.pharmj.com/Editorial/20000205/articles/olddrugs.html [accessed 10 May 2002].

McCalla DR, Beames RM, Lehman H, Christie B. 2002. Critique of the CBAC Interim Report, 4 January. Ottawa, Ontario, Canada:Canadian Food Inspection Agency, Public Forum on Plant Molecular Farming. Available: http://www.canadians.org/ge-alert/cbac_interim.html [accessed 10 May 2002].

MSN. 2002. Bitter pills. Redman, WA:WomenCentral, Microsoft Network. Available: http://womencentral.msn.com/babies/articles/toddler_0423.asp [accessed 10 May 2002].

Musson S, Townsend T. 1998. Management of discarded pharmaceuticals. Prac Period Haz Toxic Radioact Waste Manage 2(3):89–92.

NACDS. 12 August 2002. In 2001 Retail Pharmacies Filled over 3 Billion Prescriptions Totaling $164 Billion. News Release for 2002 Chain Pharmacy Industry Profile. Alexandria, VA:National Association of Chain Drug Stores. Available: http://www.nacds.org/wmspage.cfm?parm1 = 2489 [accessed 14 August 2002].

NAPRA. 2002. Pharmacy Practice: Recycling and Disposal of Dispensed Drugs. Ottawa, Ontario, Canada:National Association of Pharmacy Regulatory Authorities, Canada. Available:http://www.napra.org/practice/toolkits/pharm-toolkit9.html [accessed 10 May 2002].

NCI. 2003. Digest Page: Angiogenesis Inhibitors. Bethesda, MD:National Cancer Institute. Available: http://www.cancer.gov/clinicaltrials/digestpage/angiogenesis-inhibitors [accessed 6 April 2003].

NHMRC. March 1999. National guidelines for waste management in the health industry. Canberra, ACT, Australia:National Health and Medical Research Council, Commonwealth of Australia. Available: http://www.health.gov.au/nhmrc/publications/pdf/eh11.pdf [accessed 10 May 2002].

Novaquatis. 2002. Innovative Management of Anthropogenic Nutrients in Urban Water Management and Agriculture. Duebendorf, Switzerland:EAWAG (Swiss Federal Institute for Environmental Science and Technology). Available: http://www.novaquatis.eawag.ch/project.html; http://www.novaquatis.eawag.ch/index_e.html [accessed 10 May 2002].

Nowlan L, Kwan I. 2001. Cruise control—regulating cruise ship pollution on the Pacific coast of Canada. West Coast Environ Law, September 2001:1–33. Available: http://www.wcel.org/wcelpub/2001/13536.pdf [accessed: 27 July 2002].

Ohio General Assembly. 2001. H.B. No. 221: Prescription Drug Repository Program/Tax Credit. 124th Ohio General Assembly; Bill sponsored by Rep. J. Schuring; introduced to the House on 18 April 2001 and to the Senate on 24 April 2002. Available: http://www.legislature.state.oh.us/bills.cfm?ID = 124_HB_221 [accessed 24 July 2002].

ONDCP. 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].

OPAL. 2003. Overseas Pharmaceutical Aid for Life. Kilburn, South Australia:Overseas Pharmaceutical Aid for Life. Available: http://www.opal.org.au/i.cfm [accessed 6 April 2003].

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. Available:http://www.healthsciencesokstate.edu/telemedicine/Pub/chpr/chpr.0009.pdf [accessed 25 July 2002].

———. 2000b. Prescription Medicines and 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].

———. 2001. A 50-State Survey: Prescription Drug Re-use Policies. Health and Medicine Issue Paper Tulsa, OK:Oklahoma State University College of Osteopathic Medicine. Available:http://www.healthsciences.okstate.edu/telemedicine/Pub/chpr/chpr.0401.pdf [accessed 25 July 2002].

Otterpohl R. 2002. Options for alternative types of sewerage and treatment systems directed to improvement of the overall performance. Water Sci Technol 45(3):149–158.

Paone RP, Vogenberg FR, Caporello E, Rutkowski J, Parent R, Fachetti F. 1996. Medication destruction and waste measurement and management in long-term care facilities. Consult Pharm 11(1). Available: http://www.ascp.com/public/pubs/tcp/1996/jan/mdwm.html [accessed 10 May 2002].

Pew Initiative. 2002. Pharming the Field: A Look at the Benefits and Risks of Bioengineering Plants to Produce Pharmaceuticals. Conference held 17–18 July 2002, Washington, DC. Available: http://pewagbiotech.org/events/0717/ [accessed 19 July 2002].

Pharmaceuticals.org. 2002. Pharmaceuticals from Human System to Human System. Utica, MI:Pharmaceuticals.org, Inc. Available: http://www.toilets.com/pharmaceuticals.htm [accessed 10 May 2002].

Pitkala KH, Strandberg TE, Tilvis RS. 2002. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Arch Intern Med 162(15):1707–1712.

Pressley SA. 1999. North Carolina effort seeks to wipe out outhouses. Washington Post, 25 April, A3. Available: http://www.pmmag.com/CDA/ArticleInformation/features/BNP__Features__Item/0,2379,4222,00.html [accessed 10 May 2002].

RCRA. 1976. The Resource Conservation and Recovery Act. 42 U.S.C. § 321 et seq. Available: http://www.epa.gov/region5/defs/html/rcra.htm [accessed 4 April 2003].

Reich MR, ed. 1999. An Assessment of U.S. Pharmaceutical Donations: Players, Processes, and Products. Boston, MA:Harvard School of Public Health. Available: http://www.hsph.harvard.edu/faculty/reich/donations/ [accessed 10 July 2002].

Reid G, Howard J, Gan BS. 2001. Can bacterial interference prevent infection? Trends Microbiol 9(9):424–428.

Renner R. 2002. Do cattle growth hormones pose an environmental risk? Environ Sci Technol 36(9):195A–197A.

RIA. 2002. Returns Industry Association. Reston, VA:Returns Industry Association. Available: http://www.returnsindustry.com/ [accessed 10 May 2002].

RUM. 2002. Return Unwanted Medicines. Adelaide, South Australia:National Return and Disposal of Unwanted Medicines Ltd. Available: http://www.returnmed.com.au [accessed 29 May 2002].

RxWebPortal.com. 2002. Drug Suppliers Return Policies—Return-Goods Service Companies. Charlotte, NC:RxWebPortal.com. Available: http://www.rxwebportal.com/purchasing303.html [accessed 10 May 2002].

Santarsiero A, Minelli L, Cutilli D, Cappiello G. 2000. Hygienic aspects related to burial. Microchem J 67(1–3):135–139.

Servos MR, Innes E, Given J, Ostapyk 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].

Sforza T, Heisel W, Brennan P. 2001. The price of neglect. Orange County Register, 19 August. Available: http://www.asce.org/pressroom/honors/2002.cfm [accessed 10 May 2002].

Siecker, BR. 2001. Many Unhappy Returns—An Industry Report and Guide on Pharmaceutical Returned Goods. Reston, VA:HDMA Healthcare Foundation. Available via: http://web1.hdma.net/shop/cgi-bin/shopper.exe?preadd = action&key = PUBS1310–2001 [accessed 18 July 2002].

Smith CA. 1999. Rationale for inclusion of criteria for proper disposal of monograph pharmaceutical preparations based on the resource conservation and recovery act. Pharmacopeial Forum 25(3):8309–8312.

———. 2002. Pharmaceuticals Take Back Program. Presented at ASTSWMO (Association of State and Territorial Solid Waste Management Officials) State Hazardous Waste Conference, 29 July 2002, Minneapolis, MN.

State of North Carolina. 2002. .0207 Medication Requirements. Raleigh, NC:Pharmaceutical Services Branch, Division of Mental Health, Developmental Disabilities, and Substance Abuse Services, State of North Carolina. Available: http://www.dhhs.state.nc.us/mhddsas/pharm/medrules.htm [accessed 10 May 2002].

Üçisik AS, Rushbrook P. 1998. The Impact of Cemeteries on the Environment and Public Health. An Introductory Briefing. EUR/ICP/EHNA 01 04 01 (A). Copenhagen:WHO Regional Office for Europe. Available: http://whqlibdoc.who.int/euro/1998-99/EUR_ICP_EHNA_01_04_01(A).pdf [accessed 10 May 2002].

USDA. 2002a. Food and Nutrition Information Center home page. Beltsville, MD:U.S. Department of Agriculture and the Agricultural Research Service. Available: http://www.nal.usda.gov/fnic; Dietary Guidelines for Americans (http://www.nal.usda.gov/fnic/dga/) [accessed 10 May 2002].

———. 2002b. Nutrient Data Laboratory. Beltsville, MD:Agricultural Research Service, U.S. Department of Agriculture. Available: http://www.nal.usda.gov/fnic/foodcomp/index.html [accessed 10 May 2002].

U.S. EPA. 2002. Innovating 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 Solid Waste. 2002. Product Stewardship. Washington, DC:U.S. Environmental Protection Agency. Available: http://www.epa.gov/epaoswer/non-hw/reduce/epr/index.htm [accessed 10 May 2002].

U.S. FDA. 2002a. Best Pharmaceuticals for Children Act. Rockville, MD:U.S. Food and Drug Administration. Available: http://www.fda.gov/opacom/laws/pharmkids/contents.html [accessed 10 May 2002].

———. 2002b. Active Ingredients. 2002 Online Green Book. Rockville, MD:U.S. Food and Drug Administration. Available: http://www.fda.gov/cvm/greenbook/Chapter2.htm [accessed 10 July 2003].

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.

Volunteers in Health Care. 2001. Managing Medication Samples. Pawtucket, RI:Volunteers in Health Care. Available: http://www.volunteersinhealthcare.org/Manuals/sample.manual.pdf [accessed 10 May 2002].

Wang J. 2000. Unopened, Unused Prescription Drugs Destroyed at Taxpayer Expense. Houston, TX:Health Law and Policy Institute, University of Houston Law Center. Available: http://www.law.uh.edu/healthlawperspectives/Food/001129Unopened.html [accessed 10 May 2002].

Wemos Foundation. 2002. Wemos Foundation Drug Donations home page. Amsterdam:Wemos Foundation Pharmaceuticals Programme. Available: http://www.drugdonations.org/eng/ [accessed 10 July 2002].

WHO. 1999. Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies. Geneva:World Health Organization. Accessible: http://www.who.int/medicines/library/par/who-edm-par-99-2/who-edm-par-99-2.htm [accessed 10 May 2002].