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## Chapter 33

### PPCPs in the Environment: Future Research – Beginning with the End Always in Mind C. G. Daughton

#### 33.1

##### Introduction and Background

Pharmaceuticals and personal care products (PPCPs) are an extraordinarily diverse group of chemicals used in veterinary medicine, agricultural practice, and human health and cosmetic care. The various sources and origins of PPCPs as pollutants in the environment are depicted in the illustration "Origins and Fate of PPCPs" (available: <http://www.epa.gov/ppcp/pdf/drawing.pdf>; note: all of the URLs cited in the text of this chapter are from the web site Daughton/EPA 2003a). PPCPs are ubiquitous pollutants, owing their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals (and domestic animals) and from other uses such as pest control. Therapeutic drugs in current use comprise more than 3 000 distinct bioactive chemical entities formulated (using a wide array of so-called inert "excipients") into tens of thousands of registered end-use products; the definitive listings of drugs regulated in the US is maintained by the US FDA (2003). Personal care products contribute untold numbers of additional ingredients and formulations.

After supplying some fundamental background and perspective to the overall topic, the focus of this chapter is intended to be on knowledge gaps and future research needs (in both the near and longer term) for this "emerging" field; its focus is not on the wealth of accomplishments that have been reported to date; this chapter should therefore not be misconstrued as a review. Research, which began in earnest in the 1980s and has escalated dramatically in the early 2000s, was largely driven by analytical chemists and tended to focus on establishing the occurrence (and sources) of PPCPs in the environment – primarily in the aquatic domain (as a result of sewage discharge to receiving waters, which is the main route for pharmaceuticals used in human medicine) and much less so in the terrestrial environment (as a result of land application of biosolids; US EPA 2003). Only more recently has emphasis begun to shift to defining fate and transport, to assessing the effectiveness of and means of improving source control (e.g. sewage treatment), and to pollution prevention.

Attention to developing a better understanding of the toxicology issues has been hindered by challenges posed by problematic issues involving low-dose multigenerational exposure to multiple chemical stressors (simultaneously or sequentially). This limitation prevents

development of a comprehensive understanding of what human and ecologic risks might be posed by these galaxies of chemicals, many of which are designed with exquisite physiologic activity imparted by bewildering arrays of mechanisms of action. It is also worth noting that the issues posed by PPCPs partly intersect with those of "endocrine disrupting compounds" (EDCs). Although a small sub-set of PPCPs does indeed comprise direct-acting EDCs, most interact with endocrine systems "from a distance"; that is, they are not ligands that bind directly with hormone receptors, but rather they indirectly modulate these receptors via one or many intermediary cellular signaling pathways. Consideration should be given, therefore, to more narrowly defining EDCs to prevent the term "endocrine disruption" from expanding in scope to such a point where it loses useful meaning. As with any developing field of environmental research, new questions are often generated at a faster pace than are answers. In the exponential phase of publication, it is very difficult (if not impossible) to develop a comprehensive, lucid picture of all the facets of an emerging topic. With this said, the background to many of the aspects of PPCPs as environmental pollutants is captured in this book and in previous compendia and stand-alone research articles and grey-literature documents, many of which are available at or through the US EPA's web site devoted to PPCPs (Daughton/ EPA 2003a). The current state of knowledge regarding the occurrence of PPCPs as environmental pollutants and what little is known regarding the potential for human and ecologic effects has been summarised in a number of review articles and is not the focus of this chapter. Some of the more recent reviews and overviews (which in turn cite previous reviews) include Daughton (2001a), Daughton and Ternes (1999), Halling-Sørensen et al. (1998), Heberer (2002), Kümmerer (2001), Servos et al. (2002a) (some of these and many other overview materials are available from Daughton/EPA 2003a). This chapter will therefore not dwell on what *has been* accomplished in this "emerging" field, but rather what *could be* accomplished in the near and longer term.

### 33.2

#### PPCPs as "Emerging" Pollutants?

The occurrence of PPCPs in the environment is undoubtedly not a newly emerging phenomenon. Rather, it is one that has been made more widely evident (during the last decade) because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of trace xenobiotics in environmental matrices (Daughton 2001a). Antibiotics and oestrogenic steroids constitute well-known examples of but two of many broad classes of PPCPs, each of which poses its own unique concerns. There is no reason to believe that certain PPCPs have not had a steady presence in the environment since they were first introduced to commerce. In this sense, the issue is "emerging" only in terms of widespread discussion or recognition – *not* in the sense of a new environmental phenomenon (Daughton 2001b). It is important to note, however, that even though ecological effects attributable to PPCPs may not be manifest, it cannot be concluded that effects are nonexistent. The case for subtle effects that accrete over time has been advanced by Daughton and Ternes (1999) and by Daughton (2003a).

### 33.3

#### Drivers and Outcomes – A Perspective from a Regulatory Agency (US EPA)

The major US federal agencies involved in various aspects of PPCPs as pollutants are the CDC (Centers for Disease Control and Prevention), EPA (Environmental Protection Agency), FDA (Food and Drug Administration), USDA (US Department of Agriculture), and USGS (US Geological Survey). One of the EPA's major roles to date has been to catalyse and foster interest among research organisations and to advance the research agenda in the US and internationally. This has been attempted through a variety of publications and by implementing (in April 2000) the first publicly accessible web site devoted to the many issues associated with

PPCPs as environmental pollutants (Daughton/EPA 2003a). This web site serves somewhat as a clearinghouse for new information, as a repository for published documents, as a public outreach/education tool, and as a means of fostering collaboration among interested scientists. It is also hoped that by having access to centralised information, duplication of effort can be reduced and resources focused more effectively.

The body of work accomplished to date by researchers worldwide (as an outgrowth of the early and continuing work of analytical chemists) has served to prompt many more questions than it has resolved. These questions span a very large spectrum of scientific disciplines (many far removed from analytical chemistry). These questions can be distilled into a set of research needs and gaps, which can be arranged around the framework of the "risk assessment paradigm." These needs and gaps serve as the focus for this document.

### 33.4

#### **The Logic Model – Beginning with the End Always in Mind**

The overarching question for the scientist is "what research remains to be conducted?" But this seemingly simple question falls prey to a simple, circular trap – what exactly are the societal imperatives or concerns requiring attention – what are the ultimate outcomes that are sought? Herein lies the heart of the matter. It is one that can best be addressed by employing a widely used and universal planning/evaluation tool known as the "Logic Model". The Logic Model has been widely used for several decades in many private and public sectors to ensure that those research projects or activities that are planned are properly linked to needed "outcomes" – to align mission with desired final outcome. After all, in the final analysis, it is only the significance or impact of the outcomes from research that matters to the public – not *what* research was conducted or *how* it was performed (Daughton 2001b, 2004). Employing the Logic Model for research planning ensures that what research is conducted (termed "inputs" for the model) provides results (leading to eventual outcomes) that are valued by clients and beneficiaries of the original investment of resources. Government organisations in the US only more recently adopted the Logic Model to better guide development of their research and activities because the Model dramatically increases focus on accountability – the judicious allocation of public resources.

There are many web-based resources that present the Logic Model construct and how it is employed to design a research program (e.g. see McCawley (no date); University of Wisconsin 2003). The Model is actually employed in a manner that at first might seem backwards – to first determine the desired outcomes (short-, middle-, and long-term) and to look from the perspective of these outcomes back toward the beginning (i.e. the research required to catalyse attainment of the outcomes); note that the descriptors for these outcomes (short-, middle-, and long-term) do not necessarily refer to how long they will take to be achieved, but also the duration of the significance of their impact. Only with the desired outcomes pre-established can the requisite inputs and resources for achieving them be rationally determined. So in effect, the Model ensures that all work is planned and performed with the *end always foremost in mind*.

So with the Logic Model as the guide for the discussion here, a presentation will be made of the outcomes that *could* be sought, followed by the research that *might* be required for achieving the outcomes. This presentation is not intended to be comprehensive or complete, but rather its intent is to foster further thought and discussion so that the most important outcomes can eventually be agreed upon and the required research consequently prioritised. An essential aspect of determining outcomes is to understand who comprise the clients, customers, beneficiaries, stakeholders, and partners. This can be a complex undertaking in itself, one that

has been formalised under a process called "strategic customer value analysis" (further information can be found by searching for "SCVA" at: CCHPO 2002).

### 33.5

#### **Drivers, Gaps, Needs, and Outcomes**

The research needs summarised in this document represent a synthesis of those developed by the US EPA (Office of Research and Development, Las Vegas) and by various other organisations. Successful completion of research, development, and other related activities driven by these needs could lead to any number of *outcomes* – some with far-reaching ramifications – spanning a wide spectrum of disciplines and aspects of society. It is the outcome of research that is so important to society. Consideration of the desired outcome needs to guide problem-directed research, and the proper focus must be applied to communicating its significance or utility (see Daughton 2001b for more discussion regarding impact, significance, and outcomes).

This document intentionally makes no attempt at setting priorities because relative importance will be dictated by the outcome sought, which in turn is a function of the particular organisation having interest in PPCPs. Nor does this document pretend to present a comprehensive, exhaustive summary of the most important outcomes or research needs. Rather, its intent is to catalyse a more thorough, ongoing discussion and development of this topic by others, and to provide a window onto the available literature so that specific topics can be pursued in more depth.

Significantly, approaches for minimising the disposition of PPCPs to the environment could be implemented in the near term in the absence of obtaining any further understanding regarding their occurrence or environmental fate or effects. These far-reaching approaches (many of which would have collateral cost and healthcare efficiencies) have been summarised in a 2-part mini-monograph on the broad topic of environmental stewardship of drugs (see Daughton 2003a,b) and in a number of other documents, all of which can be located at the US EPA's *Green Pharmacy* web page (Daughton/EPA 2003b).

The EPA's involvement with the larger issue of PPCPs as environmental pollutants is driven by a number of scientific concerns as well as four major regulatory mandates (Daughton 2003c). Via the mandates, desired environmental and public health outcomes regarding PPCPs as pollutants could be achieved if warranted. It is important to separate two distinct and unrelated pathways for the entry of PPCPs to the environment – end-use vs. manufacturing. The focus of this document is primarily on PPCPs originating from end-use rather than from manufacturing. Emphasis is on use/disposal of PPCPs as originating primarily from activities/actions of individuals and to a lesser degree from hospitals – not from the PPCP manufacturing sector (whose waste streams are much better defined, confined, controlled/controllable, and already regulated by the EPA). The timely development of a scientifically sound knowledge base allows for more proactive engagement rather than reactive response – pollution prevention versus remediation/restoration.

### 33.6

#### **Science Drivers**

The major Science Drivers include identification of:

- "Hidden", previously unrecognised, or "emerging" environmental concerns before they become critical. Potential (future) environmental concerns (anticipatory research). (While current monitoring data primarily reveal PPCPs with environmental presences already established, such data serve another important purpose in demonstrating the potential for *any* consumer-use

chemical to enter the environment, and thereby give us the advance opportunity to be watchful regarding the future introduction to commerce of drugs with new mechanisms of action and everincreasing biochemical potencies.)

- Pivotal sources of uncertainty (esp. the potential for ecological/environmental "surprise") that affect assessment of risk to human health and ecological integrity (Daughton 2003a).
- Efficient means of reducing risk (preferably via voluntary stewardship measures or ultimately by regulation) first in the near-term and then in the longer-term.

### 33.7

#### Research and Development

In the US, R+D is currently being accomplished by:

- In-house research programs at (and contractors for) the CDC, EPA, FDA, USDA, and USGS.
- Federal external grants programs
- In-house research by municipal water utilities
- Fostering interdisciplinary research and collaboration among academe, private sector, government – nationally and internationally. Collaboration catalyses synergies, reduces the duplication of effort, and facilitates a more efficient focusing of resources. Progress will rely on concerted and coordinated efforts from an unusually broad spectrum of disciplines, including: Analytical and Environmental Chemistry, Environmental and Human Toxicology, Pharmacology, Hydrology, Medical Sciences, Sanitary Engineering, Risk Assessment and Communication, Policy Makers. The European Union, as an example, has a mechanism in place (EU 2002) that holds great potential for fostering research networks that could address many of the needs outlined in this document.

### 33.8

#### Supporting Data

Necessary Supporting Data could be collected via programs such as:

- The USGS Emerging Contaminants Water Monitoring program
- Existing EPA monitoring programs (e.g. under the Contaminant Candidate List – CCL).
- Emerging state programs with monitoring components (e.g. see California's proposed requirement for groundwater recharge
- Contributions from the numerous environmental scientists involved with the many aspects of PPCPs in the environment

### 33.9

#### Outcomes

Successfully addressing the various research questions and needs outlined in this document would provide the potential or wherewithal for achieving a wide spectrum of outcomes focused primarily on public and ecological health. Although some outcomes would be possible solely as a result of advances in PPCPs research, others would require expanded knowledge from other fields as well, and as such, PPCPs research would serve to contribute to a larger effort. The critical importance of planning research with the end (outcome) in mind is discussed under the *Logic Model* (above). Note, however, that in addition to planned or foreseen outcomes, often unanticipated, unplanned outcomes can and do result from research. These unanticipated or unforeseen outcomes can sometimes prove to be the most significant. There are many possible foreseen environmental and public health outcomes that could be achieved by an effective R+D program in PPCPs. Note that an important component to the Logic Model is formulating clear measures of success for each outcome; but each outcome could require a different approach for formulating appropriate measures. The following are provided as examples of possible outcomes (no attempt was made to categorise these according to short- or long-term).

Significant possible outcomes (both *longer-term* and *shorter-term*):

- Providing the knowledge necessary to address the paramount public concern: Does the occurrence of trace levels of multiple PPCPs in source waters pose risks to human health (especially for at-risk subpopulations such as fetuses, infants, and those with severely compromised health such as caused by immunosuppression)? Likewise, do they pose risks to ecological integrity?
- Reducing, minimising, or eliminating human exposure to PPCPs (via drinking water and foods) and ecologic exposure to PPCPs (especially the aquatic domain), and
- Improving consumer health and safety, while also reducing healthcare expenses (via "cradle-to-cradle" stewardship programs designed to integrate human and ecological health) (see Daughton 2003a,b and other materials at Daughton/EPA 2003b).
  - Voluntary creation of environmental stewardship programs for the responsible use and disposal of PPCPs and for reducing their introduction to the environment (see extensive information at Daughton/EPA 2003b).
  - Development of formal rules, decisions, and guidance for pollution prevention (where voluntary stewardship proves ineffective).
  - Antibiotic (mis)usage or inappropriate use is reduced for humans and CAFOs (confined animal feeding operations). Development of and genetic transfer of microbial pathogen antibiotic resistance is reduced.
  - Municipal sewage and drinking water treatment facilities are upgraded to remove PPCPs, and in the process, more uniform and extensive removal of other (collateral) micropollutants (such as consumer pollutants) is also achieved.
  - Incidence of straightpiping, septic systems, and unpermitted privies are further reduced.
  - Technologies for source separation of wastes (e.g. via toilet re-engineering) are developed.
- Avoiding introduction to commerce of new PPCPs possessing what would have otherwise been unforeseen environmental consequences ("environmental surprise"; see Daughton 2003a).
  - Furthering the debate on what role (if any) the Precautionary Principle should play in the US in guiding environmental stewardship programs for drugs.
- Facilitating widespread/universal public acceptance of water recycling/reuse (ultimately, direct on-site "toilet-to-tap" programs; see Daughton 2004):
  - Development of next-generation risk communication approaches (geared specifically to water re-use) (Daughton 2003d, 2004).
  - More effective understanding of the process of effectively communicating risk to the public especially with regard to the recycling of sewage for drinking water (cognitive sciences may play a key role in facilitating effective communication). Bridging the knowledge/communication chasm that separates the understanding of real hazards from public perception of risk (Daughton 2003d, 2004); see Sect.33.23.
  - Appropriate standards/guidance developed for determining and specifying the quality of water destined for active groundwater recharge and direct re-use programs (e.g. for toilet-to-tap).
- Changing public/consumer behaviour to lessen collective contributions to dispersed pollution. Public gains better understanding for their intimate, inseparable, and immediate interconnectedness with the environment. Improving vigilance regarding the public's collective individual role in diffuse-source pollution. Public gains understanding that some pollution is caused by the actions, activities, and behaviours of individuals collectively – "The Imperative of the Individual". PPCPs serve as an unexpectedly superb tool for capturing the public's attention in learning the principles of environmental science and protection:
  - Outreach programs and education improve public science literacy especially in regard to environmental science via:

- Increasing and broadening the public's understanding of exposure to potential toxicants
- Schools/universities incorporating PPCPs into environmental sciences curricula.
- Implementing a proactive rather than reactive approach for dealing with "emerging" water pollutants and chemical agents of water sabotage:
  - Foster development of a nation-wide, geographically networked early-warning water monitoring systems for detecting "emerging pollutants" as well as for detecting changes in status and trends of existing pollutants; such a system could be based on "change detection" (e.g. see Daughton 2001c). Such monitoring systems would also provide a major collateral benefit of providing early warning for protecting water supplies against chemical sabotage.
  - Establishing the safe land uses of "biosolids," and gaining public acceptance for those uses.
  - Determining the significance (if any) of PPCPs in biosolids (US EPA 2003a); because many PPCPs possess multiple functional groups, offering many mechanisms for complex intermolecular attraction, the predicted distribution of PPCPs between phases is not necessarily possible by conventional computational approaches.
  - Removing PPCPs from sewage by improved sewage treatment processes serves to also remove an array of unrelated but previously unidentified pollutants – a collateral benefit.
  - Emergence of a new paradigm for regulating chemical pollutants (evolution away from current chemical-by-chemical approach, whose continued feasibility may not be tenable) such as one based on specific, critical mechanisms of action.
  - Risk assessment better reflects real-world exposure scenarios, where routine exposure is traditionally assessed without regard to exposure history ("trajectory") and on the basis of a solitary chemical stressor in isolation from all others (not accounting for "exposure totality"). Rather, risk should be determined as a function of multiple (or a multitude) of stressors, each perhaps at "low," individual concentrations (fM-pM-nM), while also accounting for prior exposure history.
    - Environmental assessment guidance for new drug entities adopts more ecological relevance (multiple stressors, low concentrations, subtle effects, systems-level effects).
    - Paradigm shift from risk assessment based on a reductionist approach to one based on a systems-level understanding of organisms, populations, communities, and ecosystems, especially with regard to subtle effects that are greatly amplified by interspecies interactions (Daughton 2003a,d). Placing toxicology in a larger, holistic context.
    - Toxicological significance of environmental fate is modified to account for those chemicals that are continually released to the environment and therefore possess a "pseudo-persistence" independent of how refractory they might be to transformation processes (Daughton 2003d).
      - Scientific and regulatory view of chemical "persistence" is modified to encompass all pollutants introduced to the environment on a continual basis (e.g. via treated sewage) – not just those with structural stability – and which therefore exhibit "pseudo-persistence".
    - Chemical analysis technology evolves to the point where the traditional (and limited) target-based approach can be replaced with a comprehensive non-target approach that better serves holistic risk-assessment :
      - Pre-enrichment methods for concentration of ultra-trace concentrations of polar pollutants become widely available to chemists. Chemists gain better methods for monitoring trace levels of polar pollutants (e.g. Jones-Lepp et al. 2001).
      - Better determinative chemical methods developed for solving problematic "environmental forensics" mysteries (e.g. see Grange/EPA 2002).
      - Standardisation of methods for PPCP chemical analysis and monitoring – analogous to any of the various standard methods of analysis created by the US EPA and other organizations.
    - Capitalise on the fact that PPCPs occurring as trace pollutants can be used as a "tool" to address issues unrelated to PPCPs themselves as pollutants:

- Foster the use of PPCPs as analytical "tools" for a variety of environmental uses, such as surrogates, markers, or tracers for tracking surface water sewage plumes, leaking septic systems, or treatment thoroughness for recycled water.

- Occurrence of illicit drugs as pollutants used to advance the long-stalled and highly emotional national debate regarding the prevalence of illicit drug use. Catalyse the development of the first objective tools for measuring societal, anonymous community-wide illicit drug use. PPCP environmental monitoring data used as means of educating the public as to pervasiveness of licit and illicit drug use (see Daughton 2001d) and use of sewage drug monitoring to raise community awareness of the possible linkages between illicit drug use and terrorism.

### 33.10

#### Overarching Issues and Generalisations

Most of the research (up until 2002) on PPCPs as pollutants has focused on establishing their occurrence in sewage and receiving waters (primarily surface waters); a comparatively smaller effort had also been devoted to waste treatment investigations. This is largely a result of the fact that most of the research has been driven by analytical chemists, not by risk managers or regulators. In contrast, extremely little research has been devoted to establishing the health risks associated with any of the multitude of therapeutic classes of drugs or nontherapeutic PPCPs.

If risks exist, they are presumed to be much more imminent and prevalent for aquatic organisms (because of continual, multigenerational exposure) than for humans (because of much lower, intermittent exposure – primarily via drinking water). What little data that does exist and which indicates a potential for adverse effects by low concentrations of drugs points to a number of possibilities for aquatic organisms, ranging from direct to indirect. For example, certain classes of drugs (e.g. antidepressants) have the potential for profoundly disrupting signaling pathways in a wide array of aquatic organisms, leading to a multitude of adverse behavioural effects (Daughton and Ternes 1999); as another example, see Chaps. 16 and 19. Others having no intrinsic toxicity of their own (e.g. efflux pump inhibitors, from many different chemical classes) but could overcome the first line of defense for aquatic organisms, compromising their ability to cope with *any* type of toxicant. There is, however, one class of drugs for which a sufficient body of evidence exists showing that their trace environmental concentrations have the ability to impart adverse effects on aquatic organisms – the sex steroids (primarily oestrogenic but also androgenic).

Whether PPCPs pose risks to humans is much less understood. Perhaps the worstcase exposure scenario is where potable water is drawn from source waters containing maximised PPCP concentrations (especially during low-flow seasonal periods where dilution is minimal) and subjected to little if any further treatment or polishing. This scenario may occur where untreated sewage (from STWs or from CAFOs) is discharged directly to source waters for downstream communities. This happens with "straight-piping" (generally to receiving waters in rural areas), where direct hydraulic connection of septic leachate with groundwater occurs (a problem becoming more widely recognised throughout the country – since about one-third of all US residences use septic tanks), and where unexpected and permitted overflow events occur.

The many unanswered questions regarding health risks associated with exposure to trace concentrations of multiple drugs (and other pollutants as well) is hampered greatly because of the complexities involved in their study – especially because any effects that might occur could be subtle and therefore not amenable to detection or measurement by conventional toxicology, especially in reductionist assays (those that do not factor in systems-level aspects of inter-



organism signaling) (Daughton 2003a). Subtle effects resist unmasking by using reductionist approaches. Only systems-level, holistic approaches can reveal inter-organism interactions. It is important to realise that the broad topic of PPCPs as environmental pollutants comprises many dimensions, all of which are interrelated and cannot be separated from each other. A reductionist approach will not suffice in searching to reveal ultimate toxicologic outcomes. The overall issue is much more complex than appears on first examination.

The Knowledge Needs, Gaps, Uncertainties, Questions, and Issues summarised in this document are broadly applicable across all groups of PPCPs, whether they are categorised according to chemical class/structure, therapeutic end-point, or mechanism/mode of action. For each of these individual categories, however, an increasingly detailed list of gaps and needs could be fleshed out and which would be specific or unique for that particular category. Entire research strategies could in turn be written for each of the resulting needs (or those outlined here). Two obvious examples are antimicrobials (which includes antibiotics) and anabolic steroids – the effects that can result from these two classes are unique to each alone.

It is also important to note that PPCPs, while comprising a very diverse spectrum of "non-conventional", unregulated pollutants – a spectrum that is continually expanding as new chemical entities are discovered and brought to market – are only one of many other chemical groups that have been largely ignored. In addition, some other categories of pollutants intersect with PPCPs in that certain members of both groups share similar or the same mechanism of action (MOA). An obvious example is the intersection of PPCPs with EDCs (endocrine disrupting compounds) – with regard to synthetic therapeutic reproductive and anabolic steroids. This can lead to confusion when the same chemicals occur under different "classification" systems simply because each categorisation system "slices" the chemical-universe pie in a different way (e.g. sliced according to manufacturing sector, chemical structural class, toxicological endpoint, MOA, etc.).

Another generalization important to note is that most of the science issues and concerns are more relevant to ecological health than to human health. Antimicrobials are an obvious exception (because of the selection for human pathogen resistance), and this is the primary reason that this class of therapeutics has captured the predominant interest. The science to date indicates that human exposure to PPCPs via drinking water is probably one of the lower-priority areas in terms of actual, real-world hazard or risk. But this does not mean that it is not an *extremely* important issue. This seeming contradiction is because the public perceives the presence of pollutants in drinking water (especially those previously not known to occur and those whose origins trace obviously and directly to human or animal excreta) as posing imminent and significant risks to their health – regardless of concentration. This perception is based on profound, deep-seated emotional responses, not necessarily on logic, and even holds the potential for effecting genuine, adverse health effects (through the "nocebo" response; see Daughton 2004). Indeed, recognition of the fact that many PPCPs occur as pollutants solely and uniquely because of their use by humans has resulted in efforts to capitalise on their use as "tools" or "tracers" to accomplish other purposes unrelated to any concern related to them as pollutants. The issues involved with the perception of risk (regardless of any real hazard that these chemicals may or may not pose) are among the more important that society faces today in the environmental arena and ones that will continue to grow in importance – because of the escalating importance of water re-use (with the ultimate goal of recycling sewage for use directly as drinking water – so-called "toilet-to-tap" programs). Any work that can (i) better define the real hazards involved (if any, i.e. establish an absence of hazard) and (ii) better align public perceptions with those actual hazards, will prove extremely valuable, especially as freshwater resources continue to diminish and the pressure to re-use water escalates (Daughton 2004).

We must also keep in mind that the many issues associated with emerging contaminants are interwoven with those of water "sabotage" (homeland security). Any progress made on one front will frequently prove directly applicable and useful to the other. In some senses the two issues could even prove to be one and the same. So pursuit of drinking water issues is certainly an opportunity for leveraging on several fronts (i.e. increasing public acceptance of toilet-to-tap water reuse projects, as well as advancement of homeland security). Concerns regarding drinking water also supply an added rationale and justification for research directed at: (i) improving badly needed, nation-wide end-of-pipe sewage treatment technologies and decaying waste/water infrastructure, (ii) developing early-warning monitoring systems [generically applicable to both emerging pollutants as well as sabotage agents (an early warning system approach would be equally applicable to both emerging contaminants and to agents of water sabotage if it were based on an advanced form of "change detection" (Daughton 2001c); it is also worth noting that some of the agents that would be desirable for a saboteur to employ in water sabotage include drugs, especially those that can impart profound, irreversible delayed effects, e.g. thalidomide is but one example], (iii) wide-scale transfer of advanced point-of-use treatment technology (i.e. at the faucet) to the public (which would also serve as a defensive barrier of last resort against water sabotage), and (iv) better communication of risk to the public as well as an improved reciprocal understanding by scientists of how the laity perceives risk.

Finally, regardless of what concerns (if any) PPCPs may eventually prove to pose as environmental pollutants, there are a number of important collateral benefits that would automatically accrue simply by pursuing research on a variety of fronts. This means that resources invested in the study of PPCPs can achieve other outcomes not discussed here. These collateral benefits were first highlighted in a commentary published in the *Lancet* (Daughton 2002a). One important collateral benefit not mentioned in the *Lancet* article is that by reducing or eliminating the introduction of PPCPs and other chemicals to water (whether by stewardship, pollution prevention, or control technologies), having fewer anthropogenic chemicals in our water supplies would make it easier to detect ones that were not supposed to be present – namely chemical sabotage agents – by the use of early-warning "change-detection" monitoring. Another underappreciated connection of PPCPs with Homeland Security has to do with illicit drugs and public education.

### 33.11

#### **Summary of Specific Research/Knowledge Needs, Gaps, Uncertainties, Questions, and Issues**

A wide array of research needs/gaps and other activities must be addressed to delineate the scope and magnitude of environmental and human health issues derived from the occurrence of PPCPs in the environment. Presented below is a summary of some of the major needs/gaps arranged according to disciplines and according to the risk assessment paradigm; no relative priorities are implied by their order of presentation. This compilation of research needs and gaps is categorised mainly for sake of semantic convenience (organised around the many aspects of the risk paradigm) rather than reflecting real-world significance or priorities. This compilation is meant to serve as a catalyst for further discussion and debate rather than as a roadmap to research priorities. While this listing is in no way comprehensive, it should provide researchers with ideas as to where initial and continuing efforts need to be invested. It also serves as a framework that can be expanded upon.

The major deficiency of this document is that it does not attempt to provide any guidance as to priority setting. Undecided would be which avenues to pursue first. This will be largely determined by the short- and long-term outcomes (outlined earlier) that are sought. The priority

drivers could be the acquisition of monitoring data (to establish prevalence of PPCP occurrence), or development of sufficient toxicological data (but this is difficult in the absence of occurrence and concentration data), or the Precautionary Principle, which would dictate actions to minimise or eliminate the introduction of certain PPCPs to the environment in the absence of any further data. More likely, however, will be a continuing period of time where research is advanced on many fronts at once, eventually coalescing at a point where it becomes more obvious as to what specific areas require concerted focus. The future will bring more emphasis on the formulation of research plans guided by the Logic Model – *especially those with outcomes that can be measured.*

Many of the research needs outlined here are relevant not just to PPCPs but also to other unregulated pollutants and chemical stressors in general. *In that respect, they represent universal unmet needs in environmental science.* This compilation of needs and gaps results primarily from prior and current work of the US EPA but also as augmented by lists developed from other organisations (cited below). The resulting synthesis serves as a more comprehensive view of the complexity of the overall issue and its many and varied dimensions. Some of the pre-existing sources that delineated certain research gaps and needs include the following: Ayscough et al. (2000), Boxall et al. (2002), CDC (2001), CSTEE (2001), Daughton (2002b), Daughton/EPA (2002), Servos and Innes (2001), and Servos et al. (2002b). Also note that a major-needs list specifically for the topic of antimicrobials resistance was prepared by ITFAR (2001).

### **33.12**

#### **Needs and Gaps**

(Captured in abbreviated bullet format and categorised roughly around the risk paradigm.)

#### **33.12.1**

##### **Research Coordination**

Beginning in the late 1990s, the pace of research escalated (but primarily with respect to the analytical chemistry and environmental occurrence of PPCPs). The proliferation of research, especially in Europe, Scandinavia, Canada, and the US, points to the urgent need for an internationally coordinated research strategy to minimise duplication of efforts and maximise the impact of limited research resources. The outline presented here could serve as a starting point for such a strategy.

- A critical need exists for the development of a comprehensive relational database that captures all the published work that is directly and indirectly relevant to PPCPs (e.g. physicochemical characteristics, occurrence, fate/transport, exposure, and relevant toxicological data, especially effects from low-dose, chronic exposure). Such a database should be continually updated as the literature is scanned, and it should be made freely available via the Internet; note that Environment Canada has embarked on developing a database (Servos et al. 2002a). The literature relevant to PPCPs as pollutants is not easy to access for three major reasons: (1) it is not amenable to keyword searching (the vast medical literature is mostly irrelevant since it deals with therapeutic dosages and therapeutic endpoints), (2) it is spread out across the disparate and largely non-intersecting literatures pertaining to environmental science and medicine, and (3) much is published in non-English languages, such as German and Danish.
- A parallel, web-based relational database should be developed that captures in realtime all projects and associated activities (worldwide) relevant to PPCPs. This database should be freely accessible from the web. It is significant to note that scientists and regulators in the human and domestic animal health communities have traditionally been disconnected from those in the environmental arena.

This leads to two major consequences:

1. Knowledge is not shared across disciplines; non-intersecting literatures remain largely unexplored;
2. Accountability is often absent for issues emanating from the interface of human medicine and the environment (important issues, especially those of regulatory nature, can "fall through the cracks"). This is exactly one of the frequent concerns expressed regarding the historical lack of interaction between the US FDA and the US EPA (with respect to environmental assessment of new drugs and any followup [e.g. monitoring] regarding the possible presence of PPCPs in the environment).

### 33.12.2

#### Sources/Origins

Most of the environmental sources and origins of PPCPs in the environment are captured in this illustration: <http://www.epa.gov/ppcp/pdf/drawing.pdf>.

- Determine relative contributions to environmental loadings from direct (controllable) disposal of unwanted PPCPs (to sewage and trash) vs. indirect excretion and washing (to sewage). The relative significance of direct disposal versus excretion is a major unanswered question (Daughton 2003b).
- Relative contributions from hospitals vs. municipal sewage.
- Relative contributions from confined animal feeding operations (CAFOs) vs. human use (especially for antibiotics). Resolve debate regarding the continued use of CAFO growth promoters.
- Relative contributions from straightpiping (and overflow events) vs. treated sewage.
- Relative contributions of licit vs. illicit drugs.
- Relative importance of excipients (so-called "inert" ingredients). [As an example of how the "inactive" or "inert" ingredients in consumer products can pose risks not previously recognised, consider the solvents/carriers in personal care products. Personal care products are becoming established as a larger source of air pollution than previously recognised. While the active ingredients in PPCPs (with the exception of certain anaesthetic gases and synthetic musk fragrances) are undoubtedly almost without impact on air, the more prevalent "inert" ingredients can contribute to general indoor air pollution and serve as precursors to smog. California regulators are now discovering that the inert ingredients in personal care products are in part responsible for significant air pollution. Regulators are also becoming more concerned with the individually minuscule but significant combined effects of the chemicals released by consumerism (CARB 2003).]
- Need for nation-wide database (GIS) showing prescription/OTC sales data and usage (necessary for both modeling and target-based monitoring). Real-time, accurate data on nation-wide drug usage (and disposal) are unavailable to researchers and regulators; the first-ever study published on geographic variation (across the US) of prescription drug usage is subscription-based: "*Prescription Drug Atlas*" (Express Scripts 2001). Neither the absolute usage rates for PPCPs nor their geographic variations are known. Geographic drug usage patterns are partly a function of local prescribing customs and patient preferences and fads. A real-time GIS database showing drug usage by geographic locale would greatly aid modeling and monitoring efforts; but the proprietary nature of the pharmaceutical industry, widespread OTC availability of veterinary and agricultural drugs (especially antibiotics), and the availability of drugs outside manufacturer distribution networks are major barriers.
- Need for a better understanding of the factors leading to the excretion of drugs and transformation products to the environment. Absorption, distribution, metabolism, and excretion (ADME) pathways and profiles can differ greatly among drugs even of the same class as well as among organisms. Database capturing the salient features of ADME of drugs in humans and non-target organisms would be invaluable. Such ADME information would allow for prediction of

the relative proportions of parent drug and significant bioactive metabolites that could be excreted to the environment.

- Identify "hidden reservoirs" of PPCPs in the environment (e.g. microbial deglucuronidation of un-hydrolysed metabolic conjugates, or material sorbed to soil, sediments, and suspended particulates).
- The emergence of the molecular farming ("biopharming") industry poses a host of unanswered questions (and possibly unforeseen risks, primarily centered around allergenicity and consumer toxicity in the form of direct endocrine disruption or other mechanisms) with regard to the production of pharmaceuticals and allied chemicals in transgenic plants. Current transgenic biotechnology has potential for using food crop species (primarily corn, soybeans, rice) for producing hundreds of distinct proteinaceous therapeutics (especially enzymes, hormones, monoclonal antibodies) by genetically altered plants. Concerns that are less-discussed, however, include (i) the largely unanticipated hazards presented to non-target organisms, whose interactions with crops are extremely difficult to prevent, and (ii) future ability to "pharm" small-molecular non-proteins, which would pose concerns different from those for proteins. See discussions and references in Daughton (2003b).

### 33.12.3

#### Occurrence

- Significance of target-based monitoring versus comprehensive chemical characterisation  
Attaining a more comprehensive picture of occurrence is currently prevented by the nature of "target-based" chemical monitoring (in contrast to the laborious but more comprehensive and informative approach of chemical characterisation, such as used in environmental forensics (Grange/EPA 2002).
- Two major realms of PPCP environmental occurrence need to be understood: ecological and human (drinking water). As of 2002, little data were available regarding occurrence in drinking water. This is perhaps simply a reflection of drinking water concentrations being below the current method detection limits. Better delineation is needed of the types, concentration, frequency, spatial/temporal variability, and geographic extent and distribution in sewage (aqueous phase and biosolids and aquatic systems need to be better defined on a national level with more monitoring – surface, ground, drinking). Important to recognise that while *all* municipal sewage, regardless of location, will contain PPCPs (i.e. the issue is not unique to any particular municipal area), each geographic area will differ with respect to the types, quantities, and relative abundances of individual PPCPs (so the usefulness of generalisations may be limited).
- Delineate the relative significance of PPCP loads in surface waters, groundwaters, and finished drinking waters (as well as in "pristine" areas, for the purpose of benchmarking). This will facilitate the unmasking of newly emerging trends.
- Delineate the relative significance of PPCP loads in waters as opposed to soil, sediment, and suspended particulates.
- Establish status and trends of individual PPCPs.
- Prevalence of PPCP occurrence in marine environments vs. fresh waters.
- Of all the classes of PPCPs, the occurrence of illicit drugs has received by far the least attention (Daughton 2001d).
- Are there exponentially more types of PPCPs occurring at exponentially lower concentrations? Does the distribution of chemical types versus their concentrations follow a power law (see Daughton 2003d)?
- Current state of monitoring using discrete (e.g. grab) samples provides only a momentary picture of an ongoing process whose dynamic qualities are unknown but perhaps highly variable – where concentrations can fluctuate widely over time (short and long term). Discrete samples may be providing a distorted view. Assess need for performing monitoring using temporally and spatially integrative sampling (e.g. see Jones-Lepp et al. 2001).

- Literature is silent regarding the occurrence of perhaps the vast majority of PPCPs (both entire classes and individual members). Is this because of an absence of data or a failure to report "data of absence"? This points to the need for actively populating databases with those data falling below method detection limits, as well as the need for new analytical methodologies and non-target monitoring.
- What fraction of total PPCPs that occur in the environment is represented by those that have been monitored for?
- What fraction of the overall environmental chemical stressor universe do PPCPs comprise?
- Data needed not just for parent compounds, but also for transformation products (especially, significant bioactive metabolites); use understanding ADME to guide study of transformation. The limited few studies that have been conducted on transformation products can be used to guide others (e.g. DellaGreca et al. 2003).
- Occurrence data for PPCPs that share similar MOAs are particularly important, especially for obtaining a better indication of cumulative exposure profiles that contribute to risk.
- Do dissolved concentrations reflect actual environmental loads? Does partitioning to solid phases (e.g. suspended particulate, sediments, biofilms) lead to environmental load estimates that are biased low when calculated from monitoring data derived from dissolved concentrations (Daughton 2002b, 2003a)?
- Significance of regional prescribing customs and usage fads.
- Significance of various sewage and drinking water treatment technology capabilities.
- Occurrence of PPCPs in plants (especially food crops), resulting from their uptake following application of biosolids and animal manure to land, the use of treated sewage waters for irrigation, or the direct application of pharmaceuticals such as antibiotics to certain crops.
- Prevalence of drugs in (or released from) biopharmed food crops (Daughton 2003b).

### 33.12.4

#### Fate and Transport

- Potential for formation of bioactive metabolites and other transformation products (e.g. DellaGreca et al. 2003; Latcha et al. 2003).
- Relative significance of the major environmental transformation mechanisms (biological and physicochemical) for each chemical class of PPCP known to occur in the environment; for example, what is the relative significance of photochemical transformation in the diminution of parent compound and formation of persistent photolysis products versus the analogous pathways effected by native microbiota.
- Fate of PPCPs in sewage biosolids requires particular attention (e.g. NRC 2002; US EPA 2003a).
- Distribution of PPCPs to sewage sludge (and ultimately "biosolids") and manure is poorly understood and cannot be predicted by lipophilicity alone (because of alternate partitioning mechanisms such as precipitation and occlusion; Daughton 2002b, 2003a). Furthermore, PPCPs possessing multiple functional groups offer multiple mechanisms for complex intermolecular interaction; therefore, predicting the distribution of PPCPs between environmental compartments is not necessarily possible by conventional computational approaches.
- Contribution of PPCPs to groundwater (and eventually surface water) via septic systems (and unpermitted privies) as well as their significance is unknown.
- Current environmental monitoring data targeted at PPCP concentrations dissolved in water could possibly underestimate environmental loads by unknown magnitudes for a variety of reasons (this is particularly relevant at least to antibiotic occurrence data; Daughton 2002b, 2003a).
- Is bioconcentration in non-target species indeed not a concern? In general, the higher polarity of most PPCPs (exceptions include, for example, the synthetic musks and certain parenteral drugs) coupled with their designed pharmacokinetic elimination would preclude their

bioconcentration in non-target species (except by active transport). But advancement in drug delivery systems could increase the lipophilicity of future drugs and make them more amenable to bioconcentration.

- Significance of incompletely dissolved but excreted PPCP particulate forms (resulting from incomplete dissolution of the formulated product; Daughton 2003a).
- Significance of PPCPs in landfills (from disposal of unwanted product). Drugs discarded to municipal landfills pose not just future environmental risks but also ongoing risks with regard to re-use by those who scavenge them (e.g. "gleaners").

### 33.12.5

#### Hydrology

- Better understanding of transport to, and degradation in, groundwater.
- Potential significance for groundwater recharge regarding recycling to drinking water of "hidden" contaminants (e.g. PPCPs not previously identified).
- Need for consistent, national guidance (tailored to local geology) regarding the target composition of recharge waters. What level of treatment should be required?
- Distribution of vertical concentrations (and temperature effects) of PPCPs in surface water columns (e.g. see Tixier et al. 2003).

#### 33.12.5.1

##### Exposure

- Chemical analysis tools are required not just for establishing occurrence of PPCPs but also for measuring exposure to PPCPs (e.g. not just residues, but also adducts and biochemical markers).
- Given the greater water solubility of PPCPs in general compared with conventional pollutants, the major ultimate environmental distribution compartment is probably the aquatic environment. This highlights the importance of understanding continual, multigenerational exposure to complex mixtures of low-level toxicants.
- Do chemical monitoring data based on dissolved concentrations reflect exposure reality? Dissolved concentrations (or even total solids loadings) may not represent actual exposure concentrations, especially for microorganisms and detritus/filter feeders (Daughton 2002b, 2003a). In microbial settings, much happens in the complex microenvironment of interfaces. Interface chemistry does not necessarily reflect dissolved chemistry. "Effective concentrations" of stressors can be substantially higher at an interface (e.g. at the surface of a biofilm). Consequences of heterogeneous distribution could be profound. For example, bacteria could be exposed to higher concentrations of antibiotics than projections derived from water concentrations, perhaps high enough to select for resistance or elicit change to community species structure.
- One of the major arguments against any reason for concern regarding PPCPs in the environment is that they occur at concentrations orders of magnitude lower than levels required for intended pharmacologic "therapeutic" effects. But with regard to exposure of microorganisms, levels of PPCPs could be orders of magnitude higher in locations such as septic systems and sewage trunk lines (especially for hospitals) close to their points of origin (where there has been less dilution) and in manure. Are these concentrations higher for PPCPs in general? If so, could these special locations serve as microbial reactors or "cauldrons" where microbial diversity and biomass coupled with higher (undiluted) antibiotic concentrations exist, thereby promoting the development of and horizontal transfer of resistance among bacteria (Daughton 2002b)?
- Most antibiotic resistance-gene transfer studies focus on suspended bacteria (e.g. in wastewaters). Little attention has been devoted to possibly more important niches where the probability of gene transfer could be maximised (e.g. where both bacteria and antibiotics might

be more concentrated), such as biofilms (esp. in drinking water distribution lines and bank filtration areas) (Daughton 2002b). These niches may enhance horizontal transfer of resistance genes (both intrinsic and acquired) between autochthonous-allochthonous consortia (or between commensals and pathogens). Biofilms have two inherent features favourable to horizontal transfer lacking in suspended niches: (i) higher diversity of microbial genera and species, and (ii) much greater biomass. The many questions associated with antibiotic resistance and the occurrence of antibiotics in the environment are summarised by Kümmerer (2003) and Thiele-Bruhn (2003).

- Bioavailability; for example, sorbed or ligand species vs. dissolved material.
- Unknown role played by sorbed materials concentrated at interfaces. For example, can bacteria in microenvironments and niches such as biofilms (or organisms exposed to sediments) be exposed to effectively higher "concentrations" of compounds that partition from the dissolved aqueous phase to the solid phase of liquid-water interfaces. While this question is relevant to any PPCP that can concentrate at these interface surfaces, this question is particularly germane to antibiotics, some of which are known to sorb to (or precipitate with) solids, leading to the hypothesis that the higher concentrations at these interfaces (if bioavailable) could enhance resistance gene selection and horizontal transfer of resistance genes (even though the dissolved concentrations might be too low to pose a selective pressure). The two major concerns in this regard are (i) whether dissolved concentrations of PPCPs reflect exposure reality and (ii) whether dissolved concentrations can be used alone to predict total environmental loads.
- Determine significance of chronic, long-term human exposure via drinking water and foods (fin/shell fish) to multiple chemicals (at low,  $\text{ng l}^{-1}$  concentrations).
- Define the potential toxicological significance of each individual therapeutic/use class – not just for humans, but also for non-target organisms, for which much less is known. Currently most is known only regarding antibiotics and oestrogenic steroids.
- Critical need for determining human exposure via drinking water (nearly all monitoring data derives from source waters, which commonly undergo further treatment prior to potable use).
- What is the significance of the background levels of naturally occurring analogs for various therapeutics (e.g. anti-inflammatories, antibiotics); this points to the importance of "exposure totality".
- What is the significance of PPCPs in landfills (from disposal of unwanted product)? Short-term concerns could be acute exposure to foraging wildlife or to those who scavenge (e.g. "gleaners"). Long-term concerns could involve contaminated leachates or alteration of microbial degradative processes.

### 33.12.6

#### Toxicology

- Need for synthesising the normally separated (parallel) medical and environmental literatures regarding toxicological data for PPCPs (especially the literatures regarding "low-dose" effects; an example is that of hormesis; see BELLE 2003; Calabrese 2002); this is not a straightforward literature to access.
- Critical need for developing complementary data sets for both exposure and occurrence. In general, the PPCP data sets that have been developed as of 2002 for occurrence and for effects are non-intersecting. For those PPCPs with occurrence data, little relevant effects data exist, and for those PPCPs with at least some known or postulated effects data, the corresponding occurrence data are usually lacking.
- Are therapeutic endpoints and therapeutic doses of any relevance for extrapolating to non-target organisms? The analogous question applies also to known adverse effects. Most drugs are developed expressly for human therapeutic endpoints. Nontarget- species receptor repertoires, however, are not well characterised. Variations in receptor repertoires across



species are confounded by unknown overlap with those of humans, leading to countless questions regarding the potential for unforeseen effects. MOAs are not fully understood even for humans (witness the only recently hypothesised MOA for acetaminophen [inhibition of COX-3 in the brain, but not COX-1 or -2], a drug with a long and frequent usage history). Moreover, most drugs can each have a multitude of effects, many yet remaining to be discovered. Even the minimum therapeutic doses for drugs are not fully appreciated (Daughton 2003a).

- Is it possible to predict the most susceptible non-target species or assemblages (for a given PPCP), or do the possibilities for unforeseeable effects negate such an approach and instead point to the need for empirical observations and data? The latter may well be true with regard to ecotoxicity given the complexities of interconnectedness of community structure (importance of a systems-level understanding versus reductionist approaches).
- Need for approaches to prioritise PPCPs with regard to toxicological significance (depending on whether concern is for human or ecological exposure). Three major approaches could be considered: (1) conventional "chemical-by-chemical" approach (using the pharmacokinetic principles of ADME for predicting those parent compounds and metabolites most likely to be present, and selecting those with highest potential for adverse effects – partly a function of potency), (2) class-by-class basis (based on mechanisms of action or therapeutic endpoint) using prime surrogates for each class, (3) on the basis of MOA (especially for critical, evolutionarily conserved biochemical processes).
- Critical need for thoroughly mining the data already published in the environmental and medical literatures that are relevant to: (1) human effects at low exposure levels, and (2) non-target effects (microbes, invertebrates, vertebrates, plants, etc.) regardless of exposure level. For effects on non-target organisms, effects endpoints of interest include not just effects perceived from an anthropocentric point of view as being "adverse", but rather *any* type of effect (including those that are subtle and those deemed anthropocentrically as "positive," such as enhanced growth). Central here is the critical mass of literature that has been synthesised by Calabrese and coworkers on the historically controversial dose-response phenomenon known as "hormesis" (e.g. Calabrese 2002).
- Better elucidate effects issues associated with multiple exposures: additive effects, interactions (synergism/antagonism), exposure duration (e.g. multigenerational), windows of exposure vulnerability, and aggregate, cumulative, and complementary exposures; these are all accommodated in the concept of the "4Ts" – Toxicant Totality Tolerance Trajectory.
- Elucidate importance of low-level effects (e.g. fM-pM-nM, sub-pbb/ppt) and "paradoxical" dose response (e.g. U-shaped, hormetic dose-response curves, e.g. Calabrese 2002). As one of many examples of the possible importance of hormetic effects, consider that one of the proposed mechanisms of growth-promotion of domestic animals by sub-therapeutic administration of antibiotics is the alteration of the gut's autochthonous microbiota. Such a mechanism points to the possibility of also altering microbial community structures in ecological niches via hormetic response as opposed to growth suppression.
- What is the relative significance of PPCPs amidst the background of a complementary universe of naturally occurring substances, many of which might share the same MOAs?
- Concern regarding human exposure may devolve to special subpopulations (e.g. those with extraordinary allergies or "multiple chemical sensitivity") and critical windows of vulnerability (e.g. fetal development).
- Elucidate windows of exposure vulnerability in key non-target species.
- Elucidate the importance of long-term, chronic exposure of non-target organisms. The limited existing literature focuses on short-term acute effects as measured by standard ecotoxicological testing protocols. Tests are needed that better reflect realworld exposure and using organisms (and assemblages) that represent the spectrum of trophic levels (and levels of interspecies organisation).

- Determine the significance of PPCPs that have no inherent toxicity of their own, but which can potentiate the toxicity of other stressors (e.g. inhibitors of efflux pumps, and modulators of P450 and the cellular stress response).
- Are concerns regarding selection for pathogen resistance by the use of antibiotics in human and domestic animal medicine focused too narrowly? A wide array of "non-antibiotic" antibiotics (some of which have no inherent toxicity of their own) hypothetically could contribute to the development of both antibiotic resistance as well as susceptibility to low concentrations (Daughton 2002b).
- Determine importance of efflux pumps as first line of defense for aquatic organisms.
- Role of prior exposure (exposure "trajectory" – one of the "4 Ts").
- Expand understanding of non-target effects (especially for non-target organisms); need to push the envelope of understanding beyond that defined by simplistic LD50 and EC50 values based on conventional endpoints. Improve ecotoxicological testing (e.g. accommodate for more subtle effects and endpoints not currently measured; e.g. long-onset, latent damage; subtle shifts in behaviour or intelligence) (Daughton and Ternes 1999; Daughton 2003a).
- Could immediate biological actions on non-target species be sufficiently subtle as to be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time (for example, latent damage, only surfacing later in life)? Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that eventually major outward change cannot be ascribed to the original cause? Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological), e.g. subtle shifts in behaviour or intelligence. The temporal connection between cause and effect has the potential for being of such long duration that the linkage between cause and effect could escape detection or understanding. Continual exposure that causes but a gradual and ongoing diminution of a certain function or ability for a portion of individuals across multiple generations (in such a way that the effects at the population level are of no immediate consequence) may not be detected as connected with eventual population effects (Daughton and Ternes 1999; Daughton 2003a).
- Reductionism vs. Systems-Level, Holistic approaches: Current ecological assessment approaches (e.g. using conventional aquatic toxicity tests) are performed in isolation – out of context of a larger (and more relevant) ecological structure. They therefore represent a reductionist approach that is only slowly yielding to the recognition of the importance of a holistic, "systems level" approach (Daughton 2003a). Need better understanding of effects on community structure and function (e.g. Wilson et al. 2003).
- Expand ecotoxicological considerations for accommodating ecologically conserved (and key) mechanisms or modes of action (e.g. angiogenesis inhibitors, efflux pump inhibitors, cellular stress response).
- Concern with regard to altering microbial community structure (with ramifications for trophic-level dynamics, e.g. via predator-prey interactions and species communication). This is especially true for antimicrobials, where there are two perspectives: (i) selection *for* resistant pathogens and (ii) discrimination *against* sensitive commensal microbes (creating vacant niches) (Daughton 2002b).
- With regard to antimicrobials, what is the environmental prevalence of loss of antibiotic resistance from bacterial populations after removal of selective pressure of antibiotic exposure? A variety of possible mechanisms exist for maintaining selective pressure once antimicrobials usage is discontinued. For example, over-expression of broad-spectrum efflux pumps, "plasmid-addiction" systems, and exposure to naturally produced antibiotics may conserve resistance in the absence of continued "anthropogenic" selective pressure.
- Need to determine the ability of broad-spectrum biocides/disinfectants (e.g. triclosan, triclocarban, and quaternary ammonium compounds) to select for resistance to narrow-spectrum antibiotics.

- Explore the utility of computational toxicology (especially at the "systems" level of biological organisation) for predicting adverse effects on non-target organisms.

### 33.12.7

#### Analytical Chemistry

- Need for enrichment and detection methodologies for compounds more polar than the conventional pollutants with which environmental chemists are historically versed, and for lowering method detection limits (e.g. see Jones-Lepp et al. 2001).
- Need for efficient extraction methods suitable for heterogeneous non-aqueous samples (sludges, sediments, biosolids, suspended particulates, soils, tissues, etc.).
- Need for standardised methods (for PPCPs and for their significant transformation products) so that data of comparable quality can be generated nationally (or harmonised worldwide).
- Facilitate more widespread and efficient implementation of non-target monitoring approaches (e.g. for emerging pollutants – those that were not anticipated or expected; e.g. see Daughton 2001b and Grange/EPA 2002). Target-based environmental monitoring necessarily yields a filtered view of environmental occurrence by neglecting an unknown portion of unidentified constituents.
- Does the high water solubility of most drugs lead to a biased focus on analysis of the water column (i.e. dissolved concentrations)? Does measurement of dissolved water concentrations of parent chemical mislead by yielding underestimates of environmental loads? Does calculating total environmental loads via aqueous-dissolved quantities possibly yield estimates of total loads or burden perhaps orders of magnitude too low? Several caveats regarding the measurement of dissolved concentrations (Daughton 2002b, 2003a) include: (a) Hidden "Reservoirs" (compartments not accounted for by water analysis) including (i) hydrolysis of excreted conjugates leading to reconversion back to parent forms, (ii) desorption from sediments/suspended particulates, (iii) dissolution of poorly soluble forms (e.g. divalent cations – polyprotic tetracyclines); (b) Unsuspected Environmental Compartments, such as conveyance to land via biosolids or to sediments via particulates; and (c) Bias of Analytical Methodologies (especially sample preparation and extraction), including low, uncorrectable analytical recoveries.
- Importance of developing the "change-detection" methodology required for establishing a nation-wide monitoring network to detect all *newly* present (i.e. truly "emerging") chemicals in waterways (including PPCPs) (e.g. Daughton 2001c).

### 33.12.8

#### Monitoring

- A standardised approach for dynamic chemical monitoring of waters should be developed, one that can be applied to hospital effluents, STW influents and effluents, septic systems, streams, lakes, groundwater, runoff, marine waters, etc. A major consideration is the acquisition of more meaningful time-integrated samples (vs. discrete grab samples of lower temporal information content) (Jones-Lepp et al. 2001).
- Need for definitive approach (one with a defensible scientific rationale) for selecting target analytes for monitoring studies.
- Monitoring based on a target approach should optimise the process used for selecting the target analytes. Prediction of environmental occurrence and prevalence is a very complex function of a number of variables, including: known/potential toxicity, potency, usage rates and frequencies (which in turn is a function of geographic locale), MOAs, ADME, potentially exposed organisms of concern (which is a function of locale), partitioning preferences, environmental half-life, etc. Approaches that rely on limited factors, such as manufactured quantities or estimated total sales may be overly simplistic and result in overlooking key analytes. In addition

to evaluating lists of most frequently prescribed drugs as a basis for selecting target analytes, it is important to also consider a wide range of other factors.

- Need for a real-time GIS database for nation-wide PPCP usage (important for gauging absolute usage and geographic variabilities).
- Place ultimate emphasis on monitoring for *outcomes of exposure* rather than on exposure itself or simply on occurrence. Potential regulations requiring environmental chemical monitoring should, for example, consider basing monitoring programs on evolutionarily conserved biochemical features and MOAs rather than on individual chemical stressor entities (Daughton 2003c). Such an MOA-based approach could include assays measuring inhibition/induction of cellular stress response (e.g. HSP with coupled ubiquitin-proteasome pathway), CYP (cytochrome P450), multi-drug transporters (efflux pumps). This could be the best way to automatically account for (i) a multitude of stressors sharing a common MOA (cumulative exposure) and (ii) stressors newly introduced to commerce. (By way of further explanation, instead of monitoring on a chemical-by-chemical basis, it might make more sense to monitor for stressor indicators that reflect biologically important responses (e.g. efflux pump inhibition activity). A monitored value for a response that approaches a set point would then trigger for chemical characterisation of the chemical constituents responsible for the activity. An analogy from chemical analysis is the measurement of conventional "colligative" properties that reflect, for example: (i) all organic chemicals (with TOC as the colligative measure), (ii) all organohalogens as TOX, (iii) all organonitrogen compounds as organic TKN, (iv) all lipids as "oil and grease/TPH". Each of these colligative measures reflects the overall numbers of countless chemicals, all of which share in a particular property; this type of analytical measure is sometimes called a "method-defined parameter". Such an approach (applied to biochemical processes) would place the emphasis more on effects (and potential outcomes) rather than exposure (which conveys little import for the public). This would also eliminate the need to decide which of an ever-expanding universe of new consumer chemicals to consider for monitoring. One of the many aspects differentiating drugs from conventional regulated pollutants is that current-generation therapeutic agents are quickly superseded by an ever-escalating procession of newer members and classes. It may therefore not continue to prove feasible to focus assessments on individual drugs, other than as examples (surrogates) of larger classes. The actual MOAs (which are shared by many substances) – since they have permanence – may therefore prove to be a more useful way to assess overall hazard.)
- Explore the utility of toxicogenomics and computational toxicology for environmental monitoring. A monitoring approach based on MOAs (see previous bullet) would clearly create a definitive linkage of PPCPs with computational toxicology and toxicogenomics, both of which could play major roles.
- Important to develop chemical monitoring methodologies that are not "targetbased," but rather focus on broader characterisation of unknowns. The resulting data can then be used to better formulate target-based schemes. The chemical entities identified from target-based monitoring studies represent only but a fraction of all those that actually occur. Target-based monitoring is useful only for determining the prevalence of pre-selected pollutants, not for identifying those that might be even more prevalent or of more significance (Daughton 2003a,c).
- Develop an integrated nation-wide early-warning water monitoring system based on "change detection". Such a system would simultaneously serve four key purposes: (1) timely elucidation of newly emerging (previously unrecognised) pollutants; (2) uncover trends in pollutant geographic distribution, prevalence, and loads; (3) provide objective geographic data on emerging trends in drug abuse and illicit drug use; and (4) provide early warning of chemical sabotage agents in source waters.
- "Non-culturable" bacteria impede determining the prevalence of antibiotic resistance. Do they also serve as a significant but unidentifiable reservoir of resistance genes for horizontal transfer to human pathogens (Daughton 2002b)?

- More realistic antimicrobial susceptibility testing methods may be required. For example, intrinsic in vivo antibiotic resistance can be masked by in vitro antibiotic sensitivity (e.g. protection of sensitive variants can be conferred by small numbers of resistant variants, such as by pH alteration of the microenvironment) (Daughton 2002b).

### 33.12.9

#### **Environmental Stewardship**

(The many dimensions of the complex issue of PPCP pollution prevention and a *Green Pharmacy* are covered in Daughton 2003a,b,c; Daughton/EPA 2003b.)

- The historical disconnect between human health and ecological integrity still persists. Important to transition away from a reductionist approach to a holistic understanding. Social, scientific, engineering, and regulatory systems traditionally divide and separate what is really one integral system. The health of humans and the ecology are intimately intertwined. A profound disconnect has long prevented progress in treating human and ecological health as one and the same. Environmental stewardship (e.g. pollution prevention) programs (integrated across the spectrum encompassing manufacturers, distributors, the healthcare community, and consumers) are conspicuously absent for PPCPs. A wide array of pollution prevention efforts is feasible for lessening the overall introduction of PPCPs to the environment. The question must be asked whether a holistic stewardship program aimed at overall reduction in drug usage and disposal while maximising recycling and design of ecologically "benign" PPCPs could yield a larger reduction in potential human and ecological exposure for far less investment in R+D and end-of-pipe control technologies, and at the same time yield collateral benefits for consumer/public health. The options for reducing the discharge of PPCPs to the environment are countless, and each could serve as the basis for further R+D.
- One of many stewardship issues requiring particular attention is that of disposal. Harmonised guidance or regulations are needed, at least in the US, for directing the environmentally sound disposal of unwanted/expired PPCPs (Daughton/EPA 2003b).

### 33.12.10

#### **Engineering**

- Delineate the factors that determine the susceptibility of PPCPs to biological sewage treatment.
- Develop inexpensive alterations to sewage plant treatment technologies to control refractory PPCPs. A major collateral benefit would probably derive from optimising or improving existing wastewater/sludge treatment technologies (primarily for POTWs) or developing or implementing new, cost-effective technologies for further lowering the trace levels of PPCPs. Any improvements in engineering treatment technology targeted for the removal of trace levels of PPCPs from waste and drinking waters will more than likely also serve to remove numerous other unregulated pollutants from water, many which have yet to be identified, and others which will derive from chemicals new to commerce (Daughton 2002a).
- Processes intended for treating sewage destined for groundwater recharge require very close scrutiny – even if the waste is treated to existing drinking water standards. Rigorous, definitive treatment standards are therefore required. Groundwater re-injection of treated sewage is fraught with risks if years later problems are discovered regarding the failure to remove trace levels of previously unrecognised solutes eventually known to pose real – or even perceived – risks. Since science at any point in history often finds itself under scrutiny in the future, and since groundwater is a resource not amenable to simple, inexpensive remediation, any technology used for replenishing groundwater using treated wastewaters must be evaluated against extraordinarily high standards (Daughton 2004). There is a particular need to better understand any oxidation processes that are used in treatment chains.

- Determine the optimal sequence of oxidation and nanofiltration when used in sequence for providing drinking water. Oxidative processes can produce a plethora of end-products from a given parent compound (especially from heterocycles, which include many PPCPs). If the end-products are sufficiently small, they may not be rejected by the filtration membrane. Fewer end-products might be created by placing oxidation steps after filtration.
- Ensure that reverse osmosis (as a rigorous process for treating wastewater intended for direct groundwater recharge or direct re-use) meets standards protective of public health and is reliable. Rigorous quality assurance/control protocols are required for ensuring that the treatment process is controlled in real-time to applicable standards that maintain public confidence (Daughton 2004). At the same time, membrane filtration generates concentrated brine rejection streams, whose enriched contaminants might eventually prove to require special treatment before discharge.

### 33.12.11

#### Risk Assessment/Regulation

- Foster wider-spread discussion of the role (if any) that the Precautionary Principle should play. Current knowledge regarding the melange of so-called "emerging" chemicals gives us the luxury of being watchful (proactive) or more cautious with regard to the future introduction to commerce of chemicals having new mechanisms of action.
- Examination of the usefulness of assessing the risk of individual toxicants in isolation from all others (vs. "exposure totality") and without regard to prior exposure history ("trajectory", one of the "4Ts" – Toxicant Totality Tolerance Trajectory; Daughton 2003a). The current approach for assessing risk due to exposure to chemical stressors is performed out of context – in the absence of other chemical stressors (possessing similar and dissimilar modes of action) and without consideration of the exposure trajectory (e.g. prior exposure history). This limitation is particularly important with respect to (i) cumulative exposure to multiple chemicals sharing a like mechanism of action, and (ii) potentiation or sensitisation by chemicals that are not toxic by themselves (such as efflux pump inhibitors and initiators of the cellular stress response). [The significance of simultaneous exposure of target and non-target organisms to multiple PPCPs is twofold: (1) Many individual drugs (together with some non-drugs) share the same mechanism of action (MOA). This poses the likelihood at least of additive effects from cumulative exposure, as well as the possibility of synergism. (2) MOAs that lead directly to adverse effects are not the only consideration – or, paradoxically, not even necessarily the most important. Many drugs have no inherent toxicity of their own but pose substantial risk when combined with those that do have toxicity. Examples include inhibitors of efflux pumps and of microsomal oxidases. The approach to current risk assessment ignores overarching effects, such as efflux pump inhibition and ion-channel effects, that are susceptible to cumulative exposures from MANY different chemicals (Daughton 2003a).]
- Impart better understanding that traditional assessments accommodate only a small portion of the universe of chemicals to which humans and organisms are exposed. For example, what is the relative importance of the conventional pollutants (e.g. PBTs) in the context of all other chemical stressors? Expand understanding that chemical stability per se is not a prerequisite to establish a "persistence" in the environment. The perpetual perfusion of PPCPs to the environment via continual sewage discharges can impart a "pseudo-persistent" quality (Daughton 2003d) to all constituent pollutants regardless of structural instability (environmental half lives become less important). Any diminution by degradative or transformation processes is offset by their continual replenishment (analogous to a bacterial chemostat).
- Need better appreciation for low-dose effects. Therapeutic doses (which are often many orders of magnitude higher than dissolved water concentrations) may not be relevant benchmarks against which to judge risk. Therapeutic endpoints may not represent effects that are of relevance in the environment (or even for humans).

- Are the approaches currently employed for environmental risk assessment of drugs sufficiently sound? For example, there are a number of factors that the approaches used for calculating predicted environmental concentrations (PECs) ignore (Daughton 2003a). Accommodation for these overlooked factors could lead to PECs that are higher by several fold than those estimated using current guidance. For example, non-uniform, wide variations in geographic usage points to a potential problem with the way in which PECs are calculated. Other ignored factors include foreign sales of PPCPs consumed in the US, cumulative exposures (multiple PPCPs sharing the same MOA), and the importance of simultaneous exposure to PPCPs having no inherent toxicity of their own (e.g. efflux pump inhibitors, modulators of cellular stress response) but which can greatly potentiate the toxicity of others.
- Accumulate drinking water occurrence data for consideration for EPA's *Contaminant Chemical List* (CCL, see US EPA 2003b).
- Emphasis with regard to environmental monitoring should perhaps not be placed on individual chemical stressors, but rather on evolutionarily conserved biological receptors. This would place the emphasis more on effects (and potential outcomes) rather than exposure.
- A major hindrance to establishing mandated monitoring programs that incorporate unregulated pollutants is how to cope with identified unregulated pollutants for which health effects data do not exist. Phrased another way, one can ask whether the absence of toxicological data should prevent requirements for the monitoring of an unregulated pollutant. This quandary results from the difficulties in communicating risk to the public.
- Ensure that new knowledge gained is assimilated in new regulations.

### 33.12.12

#### Communication of Risk

(The following points are covered in detail by Daughton 2001b, 2004.)

- The mere fact that PPCPs occur in waters (regardless of any toxicological concerns they may or may not pose) has served to prompt concern on the part of the public (primarily because of the many unknowns involved). The occurrence of even trace levels of a substance whose origin can be traced to only one source (namely excretion from humans) can conjure strong emotional reflexes. The fact that the public can draw mental images of direct hydraulic connections between sewage and drinking water has perhaps played a large role in the difficulties sometimes encountered in the "selling" of water re-use projects to the public (esp. toilet-to-tap projects); water re-use projects will prove critical for the sustainability of arid parts of the US. The issues involved with PPCPs could therefore play a key role in the communication of risk to the public. Needless to say, new approaches to communicating risk are needed. While much has been published on risk communication, one of the under-appreciated aspects that needs much better development is the integration of social sciences with environmental sciences, as well as a new paradigm for involving cognitive sciences (esp. psychology) as an "intermediary" in the dialog between science and the public. Also needed is an alternate method of communicating the water cycle in a manner that makes more sense to the public.
- Imperative to integrate cognitive sciences (e.g. psychology) in the communication of risk (and improving science literacy for the laity). Effective communication of science is also critically important not just to ensure the continued support of science but also to ensure that science plays its due role in the development of policy and the broader social agenda (as well as to convincingly demonstrate when science is NOT capable of playing a role). It is critical that more resources be devoted to studying and improving the communication of risk to the general public. Need better understanding of the origins of the chasm existing between hazard/risk communication and how the public perceives risk. Especially important with the growing need to recycle water for drinking. This will prove critical in the coming years particularly for the "selling" to the public of "toilet-to-tap" water re-use projects. Maintenance of public trust in water supplies will prove critical. Regardless of the thoroughness and soundness of the science that will

continue to be developed, it could all prove for naught by failing to integrate the cognitive sciences (e.g. psychology) into the environmental sciences to develop a better communications interface between science and the public.

### **33.12.13**

#### **Public Outreach**

- Recognition that conventional pollutants (e.g. POPs and PBTs) represent only a portion of the overall environmental pollutant load.
- Show the health benefits of minimising overuse/misuse of drugs (e.g. antibiotics).
- Capitalise on occurrence/effects issues to increase public understanding and appreciation for environmental science. Tie actions of the individual to environmental consequences.
- Create materials for public education (esp. via the web).
- Use of drug monitoring to raise community awareness of local usage (esp. illicit/abused drugs) (e.g. see Daughton 2001d).
- Use of drug monitoring to raise community awareness of inadvertent financial support to terrorism

### **33.12.14**

#### **Fostering New Research and Research Planning**

- Foster communication and collaboration between scientists and regulators across the disparate and historically separated arenas of environmental sciences and medical/healthcare communities (including forensic chemists). These two disparate professions have much to share with one another. As of 2002, the overall issue of PPCPs as environmental pollutants had been developed and led by environmental scientists (primarily analytical chemists). Much could be contributed from the many fields of medical science and healthcare practice. Cross-communication and collaborations would prove extremely useful. Early attempts to bridge this chasm have included the publication of an overview in a medical journal (e.g. Daughton 2002a) with the sole intent of targeting medical practitioners to begin taking an active interest in the topic, especially in the role their profession is uniquely responsible for – environmental stewardship of pharmaceuticals (Daughton 2003a,b).
- Catalyse and promote further exploration, discussion, and collaboration on PPCPs (and "emerging" pollutants in general) by all stakeholders and "beneficiaries" of the work. The European Union, as an example, has a mechanism in place (EU 2002) that holds great potential for fostering research networks and collaboration that could address many of the needs outlined in this document.
- Foster international communication. One limitation, for example, is the body of literature published in the German and Nordic literatures and which therefore does not receive the recognition that it may deserve. Another limitation is the "grey" literature (i.e. literature not captured by traditional means of archiving, such as web publications, reports, slideshows, posters, etc.).
- Is there need for a formal inter-agency forum to discuss the many issues associated with PPCPs as pollutants? To reach a consensus on the important knowledge gaps and set research priorities?
- Is there a need to develop an overarching National Research Strategy to coordinate research across government, industry, and academe? Or is the current rate and coordination of advancement sufficient?
- Is there a need to develop a National/International Research Strategy and priorities regarding PPCPs as pollutants? Currently, in the US, many federal agencies are playing roles in PPCP research (CDC, USDA, USEPA, USFDA, USGS). Is there need to integrate with efforts underway with non-US entities (such as Health Canada, EMEA, various EU committees, Danish EPA, etc.)?



- Organise national/international conferences devoted to specific issues under the overall topic
- The PPCP industries, perhaps through their trade organisations, should be encouraged to become actively involved in the many facets of this topic. Publishing in the open, peer-reviewed literature new as well as old (but currently proprietary) data and playing an active role at conferences would be helpful.

### 33.12.15

#### Summary – and the Future

This chapter attempted to present a framework for organising the wide spectrum of issues encompassed by PPCPs as environmental pollutants that involve partially or completely unmet needs, gaps, uncertainties, or questions. The enumeration of issues presented is by no means comprehensive, nor does it attempt to present any type of prioritisation (which is a strict function of the desired outcomes driving the research). In this regard, this document serves solely as a guide – one subject to continual revision.

### 33.12.16

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