Chemicals from the Practice of Healthcare: Challenges and Unknowns Posed by Residues in the Environment

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The practice of healthcare often relies heavily on the use of a bewildering array of chemicals for diagnostics, therapy, prophylaxis, and lifestyle/cosmetic modification. Excretion, bathing, manufacturing, and disposal of pharmaceuticals and personal care products (PPCPs) serve as conduits to the environment for complex mixtures of parent chemicals and transformation products, primarily via sewage and domestic refuse. As members of a much larger universe of natural products and other anthropogenic chemicals that already pervade the environment, PPCPs enter the environment primarily from multitudes of individually miniscule sources. Each source by itself contributes relatively insignificant quantities but the combined inputs can yield measureable levels in waters and other environmental compartments, with the general exception of air. Scenarios abound for chronic, low-level ambient exposure of wildlife, microbiota, and humans but special situations can lead to higher-level, acute exposures. Whatever the existing risks, they can span a wide spectrum of modalities and can be difficult to decipher because of the complexities posed by simultaneous exposures to numerous chemical stressors - perhaps each present individually below any level known to alter biological processes - and some leading to difficult-to-detect or delayed-onset subtle effects.

The study of PPCPs in the environment (PiE) has proved challenging over the course of the last 15-20 years of international research. Significantly, the ultimate aims of PiE research are sometimes unclear. Overall priorities need to be established to achieve outcomes that still remain to be articulated. While the published scientific literature has grown to thousands of papers - targeted primarily at deciphering the shape, scale, intensity, and spatiotemporal aspects of the environmental footprint and exposure envelope of PPCPs - many aspects of PiE remain obscure. Given the possible reality of continually diminishing resources for research, a concerted effort is needed to: identify those select aspects capable of removing the most uncertainty in assessing whatever risks might be posed by PiE; target those aspects having the highest potential to broadly benefit human health and the environment; and better coordinate and focus future research.

The study of PiE is notable in that it requires expertise spanning a remarkably diverse spectrum of disciplines - ranging from hydrology, civil engineering, and chemistry, to pharmacology, toxicology, medicine, and even social psychology and risk communication. PiE has captured the attention of not just scientists, but also policy makers, legislators, regulators, environmental agencies, healthcare communities, public, press, and the pharmaceutical, pharmacy, and health

insurance industries. It has also slowly morphed into the much larger issue of the so-called but loosely defined "emerging contaminants" - a catch-all term for contaminants whose presence or significance was previously unknown, unrecognized, or underappreciated [1].

Why does PiE persist as a topic of interest for so many? A major reason is that despite the accelerating pace of published investigations, new questions continue to be generated while some major ones remain unanswered. Moreover, the fact that PPCPs (coined in 1999 by Daughton and Ternes [2]) occur in waters serves to illustrate the intimate connections between the activities and behaviors of humans and the environment - a continual reminder of the hydraulic connectivity between sewage and “natural” waters. We might wish to ignore their presence but can’t. They remind each of us that we're integral parts of the water cycle. Their seeming ubiquity in waters, especially drinking waters, serves as a constant (and sometimes emotional) reminder that these waters originated at least in part from the excretions of others – from feces, urine, and sweat. The so-called "yuck factor" certainly looms large with the life cycle of PPCPs and can play a critical role in the public acceptance of water reuse.

PPCPs comprise thousands of distinct chemical entities (and tens of thousands of commercially formulated products), possessing an immense range of physicochemical and physiological properties. For drugs, each active pharmaceutical ingredient (API) can be assigned to one of many therapeutic groups, such as those in the tiered Anatomic Therapeutic Chemical (ATC) Classification system or the analogous system for veterinary medicines (e.g., see discussion in: [3]). Because of the extreme diversity of PPCPs (especially their wide range of biochemical activities), generalizations applied across the entire spectrum (or even within defined classes) are prone to misrepresentation and numerous exceptions. Even broad classes sharing the same therapeutic modalities (e.g., lipid regulators [ATC C10] or antidepressants [ATC N06A]) can act via a wide variety of biochemical routes.

Among the citations in the US EPA’s bibliographic database on PPCPs ([4] http://www.epa.gov/ppcp/lit.html), publications with a focus on personal care products compose a much smaller portion than APIs (about 10% of the total) - the major groups being the synthetic musks, triclosan/triclocarban, UV filters/sunscreens, parabens, and siloxanes, in decreasing order of prevalence; phthalates, bisphenol A, and nonylphenols are involved with higher numbers of publications but their usage in personal care is minor compared with other commercial uses. In general, the active agents in the thousands of commercial formulations of personal care products are produced and consumed in much larger quantities than APIs but their biological potencies are much lower.

Nearly all of the aspects of APIs in the environment have parallels for both human and animal pharmaceuticals; indeed many APIs have dual uses. The relative importance, however, of these aspects among human and animal applications can differ greatly because of the dominance of (and special needs imposed by) confined animal feeding operations in the overall use of APIs targeted for animals, where antibiotics and the endogenous and synthetic steroids play dominant roles. The focus of roughly 10% of the articles inventoried in the US EPA bibliographic database on PPCPs is veterinary and aquaculture usage. Perspectives on the roles of veterinary medicines

as environmental contaminants have been covered in a number of excellent reviews, including those published in Crane et al. [5].

Many Challenges – but Which Are Most Important?

PPCPs can serve as a source of nearly endless challenges for environmental scientists and healthcare professionals. But which of these challenges leads to valuable near- and long-term outcomes – where human health and ecological function are protected or improved? An even larger question is how do we determine where the priorities concerning research with PPCPs fall within the growing list of overarching environmental issues? In a world of diminishing resources and continually emerging concerns, where should our attention be directed?

The issues and concerns surrounding PiE involve the interface between humans and the environment – where the everyday actions, activities, and behaviors of multitudes of people intersect with the environment via dynamic transfer and recycling of countless different chemicals, most of which were designed to impart biological effects. To best guide the targeting of research will require a vision that integrates knowledge regarding the presence, fate, and effects of PPCP in the environment with what is known about the countless sources and origins of their release as a direct result of the management and administration of healthcare. A key insight into this challenge is that any number of actions targeted at reducing the transfer of PPCPs to the environment holds the potential for also improving the quality and costs of healthcare [6]. Treating the environment and healthcare as an integral system can greatly clarify where and how to invest resources to achieve optimal outcomes.

Using prioritization tools such as multi-criteria decision analysis (MCDA) and value of information (VOI), an examination of the continuum of steps spanning the risk paradigm - beginning with sources and origins and ending with biological effects and risk management - could be used to establish relative priorities; for an example of this process, see Linkov et al. [7]. Nearly every stakeholder involved with PiE serves not just as an interested party, but also as an actual contributor to some aspect of the overall problem - as well as a potential beneficiary from solutions. Each therefore also can play an active role as problem solver - the physician can alter prescribing habits, the consumer can make more prudent purchases and properly dispose of leftover drugs, the insurer can encourage dispensing of prudent quantities, and so on. To identify the relative importance of each modification needed to improve a system as large and complex as health care - one that literally pervades the lives of everyone - requires establishing clear priorities, which in turn must be based on a foundation of sound science.

A Large but Under-Utilized Base of Knowledge – Where Does it Lead Us?

Of the 7,000 or so references currently captured in the US EPA bibliographic database on PPCPs (over 85% of which are articles from journals or books but which largely omit the non-English literature), over 90% have been published only since 1999 [see graphic **here** <see attached bar-graph>]. The international extent of the topic is evident from the numbers of publications (journal articles, book chapters, and reports) that feature a particular country in the abstract or title. Over 1,600 articles mention 10 different countries (Australia, Britain, Canada, China,

Europe, Germany, Italy, Japan, Spain, and Sweden) and Europe, and over 600 mention the U.S. Of 150 academic dissertations, 60% are from outside the U.S. Of the seven most highly cited papers on PiE, five originated in Europe and two from the U.S.

While this certainly shows an ongoing escalation in publishing activity, it begs the question as to whether these works have targeted the most pressing needs and whether they are being actively used to inform decision making. Moreover, if one were to assume what is most likely an extremely conservative cost of merely US$10,000 to $100,000 per paper, the last 10 years of research targeted toward PPCPs may have consumed minimum resources roughly upwards of US$600M, a very substantial investment. Could these resources have had more productive outcomes or greater impact if they had been invested elsewhere in the field of PPCPs or even elsewhere in environmental sciences at large? Perhaps not surprisingly, the impressive wealth of data published on the topic of PiE has generated a host of new questions, which, paradoxically, can serve to breed yet more uncertainty (especially for the public). At the same time, however, the new knowledge gained for PPCPs is often directly relevant to other types of chemical contaminants, serving to leverage resources throughout the environmental sciences arena.

Two overarching concerns for PiE have centered on human health risk (primarily from drinking water and foods tainted with trace residues of PPCPs acquired and recycled from the environment) and ecological integrity (especially aquatic effects from the perpetual entry of residues via sewage). The ultimate destination for PiE research might be evident only in the larger context - one involving a truly holistic examination of PiE and the complete life cycles of PPCPs. Can healthcare systems and the manufacturing and distribution of PPCPs be designed and optimized to leave a minimal environmental footprint? The argument has been made that by taking actions to reduce and ultimately minimize an ill-defined hazard (i.e., the types and levels of PPCPs in the environment) by modifying the way health care is administered and delivered, substantive collateral benefits might result. As a consequence of minimizing the release of PPCPs to the environment by reinventing healthcare administration, improvements in therapeutic outcomes might follow naturally, together with reductions in some of the costs associated with medical care [6].

Optimal outcomes might come about most efficiently not from a focus on minimizing PPCPs in the environment, but rather from optimizing the way in which health care and personal care are administered, distributed, prescribed, dispensed, and employed, and how PPCPs are designed and produced. Reactive approaches using end-of-chain controls are not as efficient or effective as proactive solutions that optimize source reduction or pollution prevention. By focusing on less sustainable solutions, such as improved ways to dispose of unwanted medications or more efficient treatment of wastewaters, approaches with even better outcomes might escape consideration. As one example, consider that the imprudent usage of PPCPs coupled with the extent of leftover medications can be viewed as direct measures of the inefficiencies and wastefulness that can occur along the entire lifecycle of PPCPs. Leftover medications represent much more than just chemical wastes needing disposal. They represent wasted healthcare resources, inflated and unnecessary consumer expense, and missed opportunities to have achieved optimal therapeutic outcomes. By focusing on controlling the many causes leading to the accumulation of unwanted medications, not only would the need for disposal be reduced, but

excretion and discharge of residues of PPCPs might also be incidentally reduced as a result of optimized usage. Such holistic approaches require the involvement of specialists from fields that may not have foreseen ever playing active roles in the PiE issue.

Goldilocks and "Just-Right Health Care": Key to Reducing PiE's Footprint

In the early 1920s, Henry Ford conceived of a new strategy for inventory maintenance - one designed to improve return on investment. Called Just-in-Time, JIT redefined on-hand inventory as essentially being the equivalent of waste. Optimal performance meant perfect balance between demand and on-hand supply. If a JIT perspective were applied to healthcare, medication waste could be viewed not just as additional chemical contaminant burden for the environment, but more importantly as a prime metric of inefficient, non-optimal health care. Redesign of health care using the JIT perspective and the knowledge and expertise of medical practitioners, healthcare administrators, pharmaceutical manufacturers, and environmental scientists could lead to a holistic system of balanced and optimally targeted delivery of medical care. Such a system (based on the Goldilocks Principle of "just right") could yield improved therapeutic outcomes, lowered costs, and reduced environmental impact - "Just-Right Health Care."

The effectiveness of efforts directed at pollution prevention or source reduction increase as the targeted steps move closer to the source or origin of the chemical. Tracing the ultimate origin back to chemical design, advancements in eco-design (using green chemistry, optimizing materials and energy use, and lessening off-target effects) could prove to have significant outcomes not just in reducing environmental impact, but also in improving healthcare outcomes [6, 8]. Consideration could be given to the design of pilot projects designed around stewardship actions in healthcare (targeted at reducing the occurrence of leftover drugs as well as optimized prescribing and dispensing, which holds the potential for reducing the contribution to the environment of APIs via excretion). Healthcare organizations having control over all aspects of medical care might serve as excellent testing grounds for pilot projects; in the U.S., one example could be the nation's largest integrated healthcare system, the Veterans Health Administration.

Framing a Bigger Picture – Human Health and Ecological Integrity as an Integral Whole

Despite the thousands of publications devoted to the many facets of PiE, unanswered questions remain and continue to proliferate. Many of these questions, however, are also germane to some of the major issues that permeate environmental science as a whole rather than being critical to solving specific problems associated solely with PiE. Significantly, despite the wealth of published data, little has yet proved of use in actual implementation of system redesigns that are more sustainable or even for informing regulatory deliberations regarding PiE. Once the PiE issue is successfully framed in a larger, holistic context having meaning to a broader audience and collaborations are established with those from across disparate disciplines, more productive outcomes can emerge. The requisite framing is to show how health care and personal care can directly lead to environmental contamination and, more importantly, how measures directed at redesigning their administration to minimize the PiE footprint can in turn improve the affordability and desired outcomes from the consumer use of PPCPs. Required actions could become clearer when considering the patient and the environment as an interconnected whole.

Solutions that seem at first to solve a problem can have unintended, and sometimes adverse, consequences. The interconnectedness of our world might seem obvious from our vantage point today - and it is certainly embodied in the new "systems" disciplines. But the realization that "everything is connected to everything else" was first formalized less than 40 years ago (in 1971) by Barry Commoner - as his "First Law of Ecology". Garrett Hardin later reformulated the idea in "we can never do merely one thing" (Hardin's Law). That unanticipated or unforeseeable outcomes can result from a single action was captured by what Crawford Holling later called "environmental surprise," where the ultimate outcome can differ dramatically from what was anticipated.

One example is the desire to eliminate the disposal of unwanted medications by flushing to sewers. The most widely available current alternative in some countries such as the U.S. to sewering unwanted drugs is discarding via the trash. The latter, however, can increase the diversion of drugs to others who should not be consuming them - facilitating drug abuse and exacerbating unintended poisonings (especially for children, pets, and scavengers) [3]; the ultimate fate of APIs in landfills is also unknown. At the same time, the importance of disposal to sewers as a contributor to environmental residues is not known but is likely a function of each individual API - perhaps being important for a limited set of APIs (mainly those that are ordinarily extensively metabolized) but unimportant for most others, especially those that are extensively excreted unchanged. By avoiding the flushing of unwanted drugs into sewers (a decades-old standard practice in the U.S. to minimize poisonings), could human morbidity and mortality be exacerbated? This debate serves to demonstrate that the ultimate objective might not be to determine the relative contributory role of disposal in the occurrence of PPCPs in the environment, but rather to design systems that result in eliminating the need for disposal in the first place - an undertaking requiring the efforts of all sectors of health care.

The analogous situation exists for other aspects of the PiE footprint puzzle. For example, does research to determine whether treatment technologies for wastewater or drinking water are effective for PPCPs and how treatment can be improved need to be justified by whether PiE contamination poses known risks? Could the problem instead be reframed by looking at PPCPs as proxies for portions of the universe of other trace contaminants, whose presence will continue to be revealed at an escalating pace as the limits of analytical detection are driven lower and as the stream of new chemicals and nanomaterials are brought to market? If alterations to treatment technologies can be implemented to improve the removals of certain select PPCPs, is it inevitable that these actions will serve to also reduce the presence of contaminants that have yet to be uncovered?

A major weakness in the application of environmental science to PiE has been the failure to frame the issue in a much larger context - using a "systems" approach that involves experts from fields other than primarily just analytical chemistry and engineering, such as social psychologists and risk communicators, physicians, pharmacologists, pharmacists, drug designers, and health insurers. Doing so would beg the need for a comprehensive, international strategy for tackling PiE using an approach integrated across all disciplines.

Mining the Published PiE Literature for Setting Priorities

Just what are the priorities regarding PiE? MCDA and VOI could serve as the principal means for setting them. A number of areas on face value seem to deserve concerted attention. Many have been delineated in publications and various government reports. But without any further deliberation, a primary need is to capitalize on what is already available - the lowest hanging fruit being the publishing literature. The most significant aspect of the large and growing body of published literature is that it possibly contains a wealth of data not yet examined by others and certainly never thoroughly mined, compiled, summarized, evaluated, and distilled into useful insights and knowledge. Instead it sits dormant - a victim of inattention. This problem is not unique to the PiE literature - it is the primary fate of scientific papers in general, the majority of which are never cited (and possibly not even read) [9]. This is largely because synoptic reviews and compilation of prior data are generally not valued in science as much as the publication of new data. But with insufficient evidence as to whether findings are ever read, questions must be asked as to why publish to begin with, how can the impact of publishing be improved, and how do we encourage the capture and synthesis of this hidden knowledge?

An examination of the US EPA bibliographic database on PPCPs reveals that publishing on the topic of PiE began in earnest around 1996, which saw roughly twice as many articles as in 1995 (80 versus 40). The very first publications devoted specifically to the topic of PiE, however, began to appear in the 1970s. One of the very first significant works came from Tabak and Bunch at the U.S. Department of the Interior [10] followed 6 years later by Coats et al. [11]. The topic began to attract more than a thousand publications per year beginning in 2007. The first 2 months of 2009 showed more publications (256) than in all of 1999 (207). A rapidly inflating literature (but not necessarily expanding in scope) greatly increases the possibility that an ever greater share of these publications will not receive adequate examination, as no longer can a single individual commit the time to being thoroughly familiar with the literature as a whole; specialization in individual aspects of the topic is necessitated, and this slows advancements in the absence of well-targeted cross-disciplinary collaborations. The lack of sufficient synoptic review greatly increases the risk of duplication of prior work and in not focusing new work where the highest priority gaps might be.

While review articles continue to compile selected aspects of published data, exhaustive data mining from the published literature is extremely time consuming. Comprehensive compilations of existing information in a centrally available database would be enormously useful for: synthesizing new knowledge; informing data gaps and better targeting new research or monitoring efforts; improving measurement methodologies; assessing risk; avoiding duplication of effort or known dead ends; leveraging resources; improving the quality of data; and fostering a widespread dialog regarding the issues. Compiled data are needed not just for geographically based occurrence in waters, contaminant treatability, and toxicity, but also for other environmental compartments (e.g., landfills, biosolids, and sediments) and for various aspects of the larger issue, such as aquatic and vegetative bioconcentration and for drug disposal; parallel, negative data for those PPCPs documented to not be present above detection limits would also be useful.

Notable Gaps

Cursory examinations of the studies published to date hint that the majority of data appears to focus on environmental occurrence and monitoring and on treatability efficiencies for wastes and drinking water. At the other end of the spectrum are significant areas that have received surprisingly little attention.

Some notable gaps or liabilities in completed PiE research include: (1) the comparatively slight coverage of extent and scope of PPCPs occurrence in point-of-use, finished drinking water (water as drawn from domestic plumbing fixtures; most drinking water studies have instead focused on source waters, where the prevalence and concentrations of PPCPs would likely be higher) and landfills, (2) an emphasis on targeted monitoring (based on prior results) often preempting efforts to expand the identification of PPCPs in the environment to those not previously targeted, (3) astonishingly light coverage of the occurrence (and bioconcentration/bioaccumulation) of environmentally derived residues of PPCPs in the tissues of aquatic organisms and in plants (e.g., grown on biosolids-amended soil), (4) poor summary of inventories of disposed medications and of the method of disposal (needed to learn about drug wastage and patient non-compliance), (5) attention beginning only in 2007 to API residues that might occur in manufacturing waste streams (long discounted as probably a non-issue, recent monitoring data from manufacturing waste streams in India now raise the question as to whether this could be at least an overlooked localized source of APIs in receiving streams in the US and other countries [12], (6) while considerable evidence exists regarding the potential for low-dose effects (from cellular and whole-organism exposures at pM-nM levels, and lower, in humans and non-target organisms), little work has succeeded in tying this to adverse consequences from real-world environmental exposures, (7) the nearly complete absence of research devoted to the potential for human effects (from trace-level exposures via APIs recycled from the ambient environment in drinking water and foods; regardless of how low the risk potential is currently deemed, can minimum levels for concern be established), especially with respect to sensitive sub-populations (e.g., drugs contraindicated during pregnancy or exposures during critical windows of vulnerability), sensitization (e.g., toxicant-induced loss of tolerance), and immune responses, and (8) standardized approach(es) for prioritizing individual PPCPs for future work. With respect to the last point, access to real-time, geographic PPCP sales/usage data, which is largely proprietary in the U.S. or available only via a subscription service, would greatly help in developing tools for prioritizing PPCPs to target for further studies or for informing the selection of monitoring targets, such as for the US EPA's Contaminant Candidate List ([13] http://www.epa.gov/ogwdw/ccl/index.html) as well as for validating predictive models for environmental fate. Four recent but uncommon examples of valuable data mining and synthesis are the compilations of occurrence and waste treatment data for various PPCPs [14-16] and ecotoxicity data [17].

Data Quality, Biased Targeting, and Future Challenges for Environmental Monitoring

An important aspect of environmental monitoring or site characterization studies rarely discussed is the quality of structural identification of contaminant unknowns. Not known is the frequency with which PPCPs purportedly identified in environmental samples have undergone

rigorous (or even minimal) structural confirmation. What percentage of PPCPs reported as identified in environmental matrices might have incorrect structural assignments? What are the assurances that we have an adequate understanding of what we are measuring? To what degree is the published literature possibly corrupted with incorrect structural assignments from mass spectral data? Are publishing standards needed for ensuring that the structures of unknowns purportedly identified have indeed been appropriately confirmed (based upon standardized quality objectives) or, instead, tagged as tentatively identified?

This problem has a corollary. Monitoring or chemical characterization studies often use a targeted approach that pre-selects analytes. Target analytes are often selected based on the results of prior studies; it is unknown how often the analyte selection process is based on prior work simply because of the availability of a workable analytical method as opposed to any consideration regarding risk. Chemicals previously identified then have a tendency to be targeted for future monitoring - at the expense of targeting other possible analytes, many of which have been ignored for any number of reasons. How often is this pre-selection approach used to maximize the chances of obtaining positive results - not necessarily to gain data of use for reducing uncertainty? Those contaminants not yet reported by monitoring tend to continue to be ignored - whether they were not previously reported because of an absence of data or as data of absence; this points to the importance of populating databases with those API data falling below method detection limits (negative data). The targeted approach to monitoring can spawn biased data sets, which are populated preponderantly by particular, select chemicals - all of which share the one biased commonality that they were simply known to be amenable to analysis. How can we be sure that those PPCPs whose occurrence is repeatedly reported are indeed the most prevalent or most important with respect to risk? Is more emphasis needed on non-targeted analysis (attempts at comprehensive sample characterization), which could greatly expand the universe of PPCPs documented to occur in the environment? An associated question is whether PPCPs identified using discrete grab sampling (versus integrative sampling) adequately represent the types and quantities subject to real-world spatiotemporal variability; likewise, have conjugates of reversible metabolism been accounted for during monitoring as hidden reservoirs of the parent, aglycone APIs?

An emerging trend in API design that could potentially further challenge structural identification is isotopic substitution. Deuterated analogs of APIs (and pesticides) have long been known to have altered pharmacokinetics/pharmacodynamics because of the kinetic isotope effect. Pharmacologic deuteration can yield APIs with greater stability (facilitating longer half-lives and increased duration of action as a result of hindered first-pass metabolism) and fewer side effects because of lower dose, "metabolic switching," and reduced drug-drug interactions. An unknown with deuterated APIs would be whether environmental fate, transport, and effects would be altered (as with enantiomers). But more importantly, would a new analytical challenge emerge if deuterated APIs became established medications? An API having one or multiple deuterated analogs would increase the numbers of potential analytes (multiple isotopic forms of the parent API together with the transformation products from each), hindering the identification of each other if they could not be effectively separated prior to detection.

Challenges for Toxicology

Bringing to bear ever-more advanced measurement methods, analytical chemists allow us to peer into the shadows of chemical space with ever greater magnification and clarity. While this newly discovered chemical landscape might be fascinating to explore and serves to further illuminate the expansive universe of chemical stressor exposure, at the same time it poses ever-greater challenges for risk assessors, especially with regard to one of the greatest problems facing toxicology today - simultaneous/sequential chronic exposure to multiple chemical stressors each present at ever-lower concentrations; while baseline (nonpolar) narcosis is believed to be the most common mode of action at very low stressor concentrations, the possibility of unique, unpredicted mechanisms of action (MOAs) cannot be ruled out, especially since MOAs can change with exposure levels (multi-phasic dose-response) and since receptors can vary across taxa. Ever-lower detection limits will pose increasingly greater challenges for assessing, communicating, and ameliorating ever-diminishing risks. And an inflating known universe of potential chemical stressors will challenge the feasibility or sustainability of regulatory/compliance monitoring on a chemical-by-chemical basis.

At the other extreme, technological prowess in measuring the very small sometimes distracts or over-shadows the potential for unanticipated scenarios for overt toxicity caused by acute exposures and poisonings - not just unintended poisonings of humans and pets from leftover medications, but also poisoning of wildlife via previously unrecognized source/exposure pathways and even unrecognized or unappreciated MOAs. Can the assessment of risk for PPCPs be improved to account for the possibility of unanticipated exposure scenarios or adverse outcomes? What additional knowledge is required to avoid the scale and consequences of acute-exposure incidents such as the mass poisonings of raptors and scavengers by pentobarbital or residues of NSAIDs such as diclofenac (and possibly quinolone antibiotics) remaining in carcasses from medicated domestic animals, or to be able to predict the unexpected acute toxicity of APIs to certain non-target species?

Our environment extends beyond the confines of water, soil, and air. It also encompasses the areas in which we live and even our bodies themselves - where residues of countless chemicals (including the medications we consume) are applied to or excreted from the skin and then transferred to other surfaces where others can then unknowingly be exposed. Other scenarios for acute exposures therefore include inter-human contact (e.g., from high levels of APIs remaining on the skin after dermal application or excreted via the skin) and human contact with excretions from medicated pets; these issues are particularly germane for therapeutic treatments using highly cytotoxic or hormonal drugs.

With respect to prioritizing APIs for in-depth study, little evidence supports an overriding importance of toxicological data derived from therapeutic doses or commercial production volumes or usage rates. Needing also to be factored in are other critical variables involved with the life cycles of APIs, such as pharmacokinetics (e.g., the extent to which an API is extensively excreted unchanged - or as metabolically reversible conjugates - via feces, urine, or sweat), delivery route (e.g., dermally applied drugs are efficiently introduced to sewers via bathing), patient compliance (some therapeutic classes have lower rates of compliance, more effectively generating leftovers and the consequent need for disposal), potency (some APIs - generally those

also having low production volumes - can impart effects at concentrations of pM and lower; ethynylestradiol is an archetype example), usage patterns (e.g., the use of some drugs is focused during certain times of day or year, leading to episodic releases), and an API's propensity for off-target promiscuity.

Tying Effects to Exposure

With respect to exposure, a major problem with studies of low-level ecological exposure is the ever-increasing challenge of deconvoluting the occurrence of what might first appear to be an adverse effect in a certain (sub)population from the effect's frequency of incidence as ambient (natural) background. To what extent do morphological abnormalities in aquatic organisms result from trace-level anthropogenic chemical exposures versus natural incidence? Similarly, to what extent can biological effects be masked or concealed by ambient incidence? Teasing the two apart is problematic - posing a primary barrier to establishing causality. Delayed-onset effects are a confounding factor in ascribing causality. Another important aspect to the risk potential for PPCPs is additive (or interactive) toxicity. This factor is greatly complicated not necessarily by the existence of multiple APIs sharing the same MOA or mode of action (so-called "class effects"), but rather by an MOA being shared with chemicals from other disparate groups unrelated to PPCPs - whether anthropogenic or naturally occurring. Such aggregate or cumulative exposure adds yet further to the complexity in ascribing cause and allocating risk. More attention is needed in design of controlled exposure experiments to ensure that the stressor levels mimic those actually encountered in the environment; sometimes it seems that the need to report positive results (which might drive the need to use unrealistically high exposure levels) overrides the imperative to study exposure conditions that emulate real-world conditions.

With respect to effects, more comprehensive examination and survey is needed of the spectrum of possible subtle effects endpoints (especially aquatic effects that might accumulate across generations, for example via epigenetic changes). Subtle effects, such as behavioral or immunological, have the potential to result from chronic low-level exposures from single or multiple PPCPs, each present below purported no-observed effects levels. Such exposures sometimes involve receptors that differ from those in humans, MOAs can change as the exposure levels are reduced (multi-phasic MOAs and paradoxical [inverted] dose-response), and dose-response linearity can vary greatly among chemicals (e.g., see [18]). Furthermore, the MOAs for many APIs are poorly understood, or the MOAs already established for therapeutic levels may not be relevant to the low levels encountered in the ambient environment. Multiple therapeutic endpoints or off-target effects can result from exposure to a single API because of the intricate interplay and cross-talk between signaling pathways - all of which are a complex function of dose, timing, and duration, among a host of other variables. With respect to ecological exposures, at what point does "adaptive response" give way to "true toxicity" - where disruption of homeostatic controls leads to adverse population-wide effects that cannot be sustained by a population?

Because of the difficulties surrounding low-level mixed-stressor studies, the continued exploration and application of the various omics and computational chemistry/toxicology could be a paradigm shifter. As for environmental monitoring, given the thousands of molecularly

distinct APIs (multiplied further by isomers in racemates and by emerging aspects of drug design such as deuterated analogs), is the ability or capacity to measure them all even necessary? Could carefully selected representative APIs (perhaps based on a suite of calculated properties) serve as surrogate proxies for the presence of many others? Alternatively, could monitoring be better served by switching from chemical targets to biological endpoints (especially those that serve to integrate the response from multitudes of stressors)? Endpoints of particular interest might be those based on mechanisms that are evolutionarily conserved across taxa; efflux pump inhibition and induction of the cellular stress response or apoptosis are but three examples of tests that could comprise a battery of assays - ranging from subcellular to systems-based.

Better Understanding Sources

Other gaps and research needs can be summarized along the continuum of the risk paradigm, spanning the range from chemical stressor sources to biological effects and remediation [19]. Some under-investigated aspects of origins or sources of exposure worth highlighting include: (i) the fate of APIs and creation of by-products during non-optimized incineration (a technology of growing importance if the disposal of drugs to sewers is to be avoided), (ii) the creation and fate of toxicologically significant by-products and transformation products during manufacture, wastewater treatment (e.g., disinfection by-products), metabolism/biotransformation, and physicochemical processes in the environment (e.g., photolysis), (iii) extent of occurrence and fate of PPCPs in biosolids and in recycled water, especially when applied to arable land, (iv) whether the nanomaterials used in the expanding field of nanomedicine/cosmetics (for therapy, regenerative medicine, diagnostics, targeted delivery devices) pose risks once they enter the environment and undergo transformation (nanomaterials based on carbon structures are particularly problematic for chemical characterization because of their structural diversity), (v) to what extent do plant-made pharmaceuticals (biopharming or molecular pharming) pose any hazard if released to the environment, (vi) proactive environmental monitoring for new molecular entities (especially those with new MOAs) at the time they are introduced into commerce, and (vii) apportioning the sources from which APIs gain entry to the environment (disposal, excretion, dermal transfer, bathing). An aspect of sources that is sometimes overlooked is that some endogenous substances (e.g., certain steroidal hormones) are also produced commercially and formulated in medications (17ß-estradiol being one example); unknown, however, is what portions of the ambient levels in the environment originate from commercial APIs versus endogenous synthesis.

Scenarios that might serve to increase existing real-world stressor levels also need to be assessed as integral aspects of the life cycles of PPCPs. Prominent among these are reduced flows of receiving streams (increasing the incidence of effluent-dominated streams) as well as reduced flows of treated sewage (as a result of water conservation and increased sewer-use taxation), both of which would serve to increase API concentrations in receiving streams.

A geographically networked early-warning water surveillance system could prove to be a very useful proactive approach for establishing baselines and detecting the emergence of not just new PPCPs (e.g., new molecular entities in drugs), but *any* newly present pollutant. Such a scheme could be designed around "change detection" or "chemical fingerprint anomalies" - where rapid,

high information-content chemical analysis (such as that based on multidimensional chromatography coupled with time-of-flight mass spectrometry) could be used to establish baseline chromatograms showing the "fingerprint" of a sample in terms of the relative presence of all detectable chemicals. Resources could then be devoted to identifying only those chemicals newly detected in subsequent fingerprints but absent from baseline fingerprints archived from prior monitoring. These newly present chemicals could then be evaluated for potential importance for subsequent targeted tracking. Change-detection could be used to essentially ignore all pre-existing chemicals (unless changes in their relative concentrations happened to be of interest). This approach would be amenable to automation and could also prove to be an efficient means of tracking trends (e.g., to measure the impact or effectiveness of mitigation or stewardship actions).

Dogma Masquerading as Knowledge

As with any field of study, opinions, beliefs, and biases can become codified as dogma. Vigilance is needed to evaluate the veracity of purported facts, especially when misinformation might be unwittingly used to inform decision making. Statements regarding PiE that may be based more on suppositions than facts and which might benefit from more investigation include: (1) drug disposal is a minor (or major) source of APIs in the environment, (2) trace levels of antibiotics in the environment are a driver of selection for antibiotic-resistant human pathogens (similarly, the use of antibiotics in confined animal feeding operations poses a risk with regard to selection of antibiotic-resistant bacteria and genetic transfer of resistance to human pathogens; note that the probable ubiquity of non-culturable bacteria greatly hampers solving this question), (3) malformations and sex alterations in wild aquatic populations are a result of endogenous and synthetic chemicals possessing hormonal activity (possible faulty suppositions regarding causality), (4) manufacturer waste streams are a minor source of APIs in the environment, (5) compared with conventional persistent organic pollutants, APIs are generally not subject to comparable bioconcentration because of their lower lipophilicity and ionizability (perhaps processes other than passive diffusion, such as active transport, can govern API uptake and bioconcentration), and (6) excipients do not need to be considered since they are not "active" ingredients.

The Larger Perspective – Opportunities at the Interface between Health Care and the Environment

A final point involves the key importance in establishing and communicating the full context in which PPCPs exist in the environment as potential stressors for biological systems. Their place in the larger universe of chemical stressors (including those occurring naturally, such as the many toxicants in foods) is essential to appreciate so that: (i) the public can develop a more accurate perspective of chemical exposure in general, (ii) optimally informed regulatory decisions can be formulated, and (iii) diminishing resources for research can be directed to the most significant contributors of environmental risk. Of course, the true picture of the relative toxicological importance of PPCPs (as with any class of chemicals) can only be obtained by considering all hazards, including (in addition to all sources of chemicals) non-chemical forms of stress, such as electromagnetic, radiological, biological, physical, thermal, noise, and emotional,

among many others. This perspective is very important - but not easy - to try and keep at least in the background of discussion and debate.

Despite the voluminous published and gray literatures, a large number of gaps remain that could be investigated with more research [19]. Science is never short on questions. More important to address first, however, is what exactly do we wish to accomplish with more research? What outcomes are we seeking? How would the uncertainty associated with assessing risk be most efficiently minimized? It's important to have the end in sight before beginning the journey. Closer collaboration between researchers and risk assessors would be highly beneficial. Most importantly, however, the concerns, challenges, and solutions regarding PiE need to be framed and examined in the expanded context of the larger systems used for the care of human and animal health.

That PiE exists at all as an environmental concern can be viewed as an opportunity – as a driver for improving the efficiency and efficacy of the responsible systems. By involving the many professional communities engaged in health care, sustainable systems can be designed – ones that could yield substantive savings in healthcare resources, improved patient outcomes, and combined protection of human health and ecological integrity.

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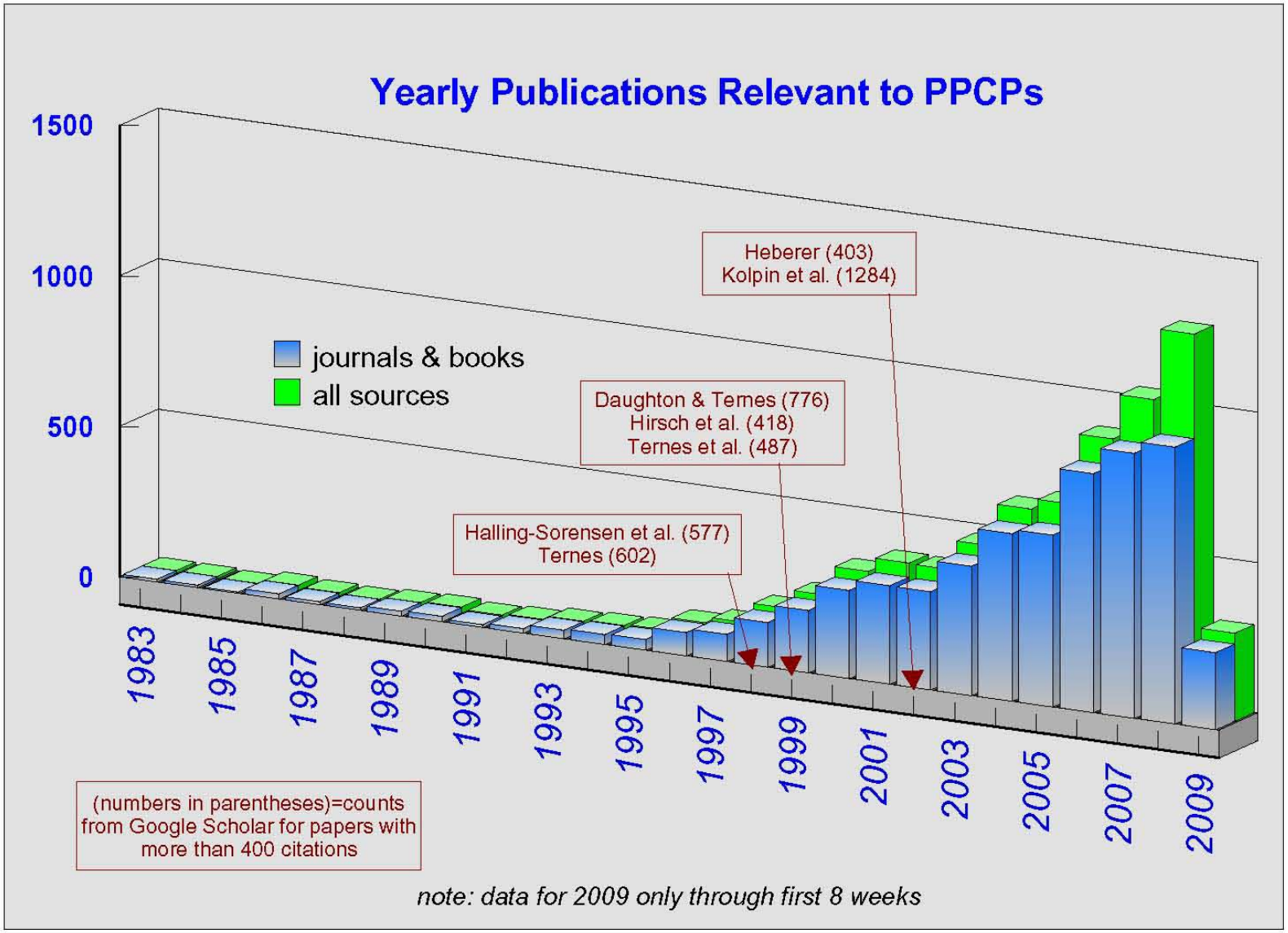
Yearly Publications Relevant to PPCPs
1500
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journals & books
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Heberer (403)
Kolpin et al. (1284)
Daughton & Ternes (776)
Hirsch et al. (418)
Ternes et al. (487)
Halling-Sorensen et al. (577)
Ternes (602)
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(numbers in parentheses)=counts from Google Scholar for papers with more than 400 citations
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