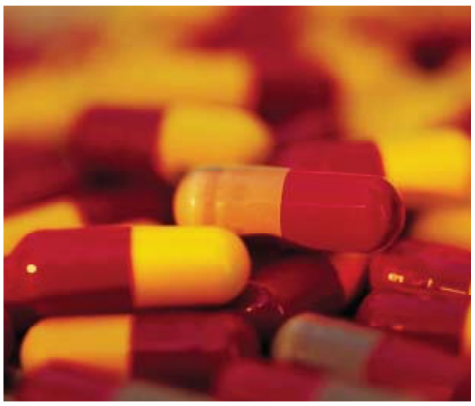

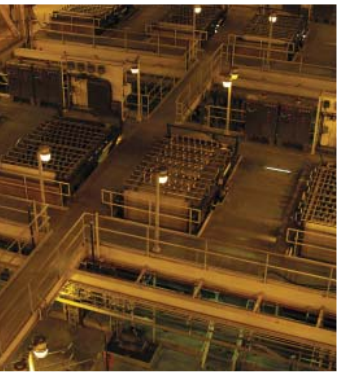

Pharmaceuticals in the Water Environment

NACWA

ASSOCIATION OF METROPOLITAN WATER AGENCIES

This paper is the product of a collaborative effort of a peer review panel consisting of:
Co-Chairs Shane Snyder and Cecil Lue-Hing, together with Joe Cotruvo, Jörg E. Drewes, Andy Eaton, Richard C. Pleus and Dan Schlenk.

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Preface

There are growing public attention and concern about the possibility of ecosystem and human health effects from pharmaceuticals in water. Congressional, federal, and state attention has also increased and several planned or proposed governmental actions are already underway. Public policy initiatives are most successful when science informs government decisions and actions. It is critical that legislators and regulatory agencies proceed with a clear grounding in scientific fact as this will ensure that the public interest is best served and that scarce, public resources are appropriately deployed.

Recognizing the importance of this issue, and with congressional and federal oversight agencies poised to take action, the National Association of Clean Water Agencies (NACWA) and the Association of Metropolitan Water Agencies (AMWA) have convened a panel of experts to review and discuss existing scientific and policy-related information on the issue of pharmaceuticals in the broader water environment.

The goals of the panel are to acquire and integrate information regarding pharmaceuticals in the aquatic environment and to develop a set of strategic recommendations with regard to such, in order to inform and guide the national response to this issue, particularly in the areas of:

- Prevalence;
- Human and ecological health implications;
- Monitoring, source control, and treatment options; and
- Policy and regulatory development strategies.

The purpose of this white paper is to present the panel's work in a clear and concise report summarizing the current state of knowledge on the issues and propounding a series of recommendations to inform NACWA and AMWA members, industry, local and state officials and national policymakers and to help guide development of an appropriate national response.

Executive Summary

Over the past century, evolution in the sciences has led to major breakthroughs that have expanded and vastly improved human life in the area of exploration and development of pharmaceuticals. However, simultaneous advancement in analytical technology now allows the detection and quantification of miniscule amounts of these medicines in natural waters. Pharmaceuticals have been present in our world's waters since humans began experimenting with medicines; however, product proliferation and ready access to pharmaceuticals coupled with burgeoning human population have significantly increased the loading of these compounds into the environment. While reports of pharmaceuticals in US water-ways were published as early as the 1970's, the most salient media coverage came in 2007 when the Associated Press brought this issue to the forefront of international attention.

The enigma of pharmaceutical occurrence in drinking water has especially alarmed the public and regulators despite the fact that relatively few pharmaceuticals have been detected and only at concentrations tens of thousands of times smaller than the therapeutic doses. Fortunately, pharmaceuticals have the most robust database of any environmental contaminant in terms of human health as these compounds undergo rigorous clinical trials during registration and post-registration monitoring. Although adverse human health consequences from the existing trace levels of pharmaceuticals in U.S. drinking water is highly unlikely (at least based on current knowledge), the resulting impacts to aquatic ecosystems are more nebulous. Several studies have demonstrated that fish exposed to wastewater treatment effluents can exhibit reproductive abnormalities. Moreover, fish exposed to trace levels of birth control pharmaceuticals in the range of concentrations found in the environment show dramatic decreases in reproductive success, suggesting population level impacts are plausible.

Treatment processes can and do reduce the concentrations of pharmaceuticals in water, however, the degree of efficacy is often a function of chemical structure, cost, and energy. All treatment processes have some degree of side effects, such as generation of residuals or by-products. Thorough life-cycle analyses should be undertaken to ensure that the solutions for environmental control are not more risky than the problem. Source control of contaminants to wastewater treatment plants should always be considered when unknown or questionable occurrence in effluents is predicted or observed. While pharmaceutical take-back programs may not lead to significant reductions in environmental loading, such activities are helpful in communicating to the public that toilets are not suitable receptacles for a diversity of consumer products.

Although there are currently no federal regulations limiting the levels of pharmaceuticals in wastewater or drinking water, the United States Environmental Protection Agency (U.S. EPA) has added some pharmaceuticals to the most recent contaminant candidate list (CCL 3); however, only four of the compounds on this list are exclusively used as human pharmaceuticals: three birth control substances and one antibiotic (U.S. EPA, 2009a).

The application of ultra-sensitive analytical technologies to detect anthropogenic substances in water at one trillionth of a gram or less per liter will undoubtedly reveal that nearly every compound known to man will be detectable. The question is not whether these compounds occur, as they certainly will, but rather whether they pose a risk of harm to humans and wildlife that are exposed.

Therefore, this committee has provided several recommendations as a path forward that will help fill data gaps, better inform the public and regulators, and lead towards sustainable water resources for future generations. The key recommendations include: development and utilization of standardized analytical methods for monitoring programs, the use of health-based screening values to determine if additional water treatment is warranted, and additional research to evaluate the impact of mixtures and low-level chronic exposure.

Chapter 1
Pharmaceuticals Overview

1.1. Introduction

Pharmaceuticals and endocrine disrupting compounds (EDCs) are a structurally diverse class of emerging contaminants that have been detected throughout the world, especially in wastewater-impacted surface water, groundwater, estuarine water, and drinking water. These compounds include, but are not limited to, prescription pharmaceuticals, over-the-counter medications, naturally-occurring compounds that elicit a physiological effect and compounds used in consumables for the benefit of human health/safety. The most common route by which these compounds enter the environment is via treated and untreated wastewater. Selected pharmaceuticals and EDCs may also enter the environment via other routes, such as urban or agricultural runoff. Once in the environment, pharmaceuticals and EDC concentrations attenuate by processes such as dilution, adsorption to solids, microbial biodegradation, photolysis, or other abiotic transformation. Some compounds that are not easily removed during conventional wastewater treatment, can persist in drinking water supplies and ultimately contaminate consumer tap water.

Although commonly grouped together, pharmaceuticals and personal care products (commonly referred to as PPCPs) are not the same and caution should be taken when using the term PPCP. Similarly, the terms pharmaceuticals and EDCs are not synonymous. Pharmaceuticals include prescription drugs, over the counter medicines and veterinary drugs. Conversely, EDCs encompass a broad range of direct and indirect biological impacts and thus a definitive list of endocrine disruptors is neither available nor plausible. Moreover, the term endocrine disrupter assumes an ability to cause an adverse outcome and it does not consider exposure.

Pharmaceuticals have been measured in water for more than forty years. Within the past decade, the number of papers on analysis of pharmaceuticals in water has increased significantly, concomitant with improvements in analytical instrumentation and isolation procedures, and the increased ability to detect trace levels of pharmaceuticals. Although the initial interest in analysis of water for pharmaceuticals arose as a result of possible ecological impacts that were observed by field biologists, the number of research papers began to increase at the same time that Theo Colbourn's 1996 book, Our Stolen Future, was published. This book is widely attributed with bringing the issue of pharmaceuticals in water to greater visibility by the public

Perhaps the most notorious pharmaceutical in the water environment is ethynylestradiol (EE2), which is widely used as an oral contraceptive. In 1999, the first report documenting EE2 occurrence in U.S. surface waters was published (Snyder et al. 1999). More importantly, the occurrence of both the synthetic estrogen EE2 and the endogenous estrogen 17β-estradiol (E2) in U.S. wastewater effluents were subsequently identified as putative contaminants linked to reproductive ailments in fish (Snyder

et al. 2001). Due to reports of ecological effects, some investigators (Caldwell et al. 2008) have argued that proper environmental measurements of hormones such as EE2 may be required at sub nano gram per liter (ng/L) levels, presenting significant analytical challenges. However, it is important to note that endogenous steroid hormones generally occur at far greater concentrations than synthetic due to the fact that all living creatures excrete hormones as part of their natural cycle. The enigma of EE2 as an environmental contaminant capable of eliciting "feminizing" or "hermaphroditic" impacts in fish created significant concern among the public and scientific communities. While a diversity of anthropogenic and natural substances have been shown to result in endocrine disruptive impacts in animals, unprecedented coverage by major media outlets have exacerbated public fears. In the early 1970s, the U.S. EPA serendipitously discovered and subsequently published the first report specifically addressing pharmaceuticals in wastewater effluents (Garrison 1976). In 2008, the Associated Press released a series of stories related to the discovery of pharmaceuticals in U.S. drinking waters. These reports culminated in a hearing called by the U.S. Senate Subcommittee on Transportation Safety, Infrastructure Security, and Water Quality. Experts from the federal government and the private sector seemed to have paradoxical responses when questioned on the relevance of pharmaceuticals in U.S. drinking water. However, one consistent outcome of the hearing was the clear message that some U.S. politicians and the public were genuinely interested in U.S. drinking water quality and that additional studies to determine prevalence of occurrence and impacts to human health would be necessary.

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1.2. Occurrence

As long as humans have used chemicals for the treatment of ailments, trace levels of these substances have been present in water. What has changed abruptly and dramatically is the increased use and diversity of pharmaceuticals, analytical method sensitivity, and increased discharges of treated wastewater to water bodies. At the present time, more than 3000 prescription pharmaceuticals are registered for use in the U.S. and only an extremely small sub-set of these have been monitored in water.

Only sparse data existed on the occurrence of pharmaceuticals in U.S. drinking water until 2007 when the Water Research Foundation published a report entitled "Removal of EDCs and Pharmaceuticals in Drinking and Reuse Treatment Processes". In this study, 20 municipal drinking water systems were screened for 17 pharmaceuticals. Five pharmaceuticals were detected in at least 50 percent of the drinking water samples evaluated: carbamazepine, ibuprofen, iopromide, meprobamate, and phenytoin. Median concentrations of detected pharmaceuticals in drinking water were consistently less than 10 ng/L (parts per trillion). A more comprehensive follow-on study was published in 2009, which demonstrated the nation-wide occurrence of pharmaceuticals in U.S. drinking waters (Table 1). However, only two pharmaceuticals, meprobamate and phenytoin, were detected in more than 50 percent of drinking water samples. Median concentrations of detected pharmaceuticals in drinking water were again less than 10 ng/L. In both of these studies, the occurrence of pharmaceuticals in

drinking water was governed by the degree of wastewater influence on source water and removal during treatment.

1.3. Pharmaceuticals as a Priority for Drinking Water

The thought of consuming another creature's pharmaceuticals through drinking water is understandably concerning. However, two critical points should be considered when discussing the implications of pharmaceuticals in drinking water. First, the concentrations occurring in drinking water are unfathomably minute, and second, the toxicological information on pharmaceuticals is far greater than for other environmental contaminants. For instance, the minimum therapeutic dose for meprobamate, an anti-anxiety pharmaceutical, is 200 milligrams per day (mg/day). At the maximum concentration ever discovered in drinking water (0.000042 mg/L), a person would need to consume at least 4.7 million liters of water in a single day to ingest the therapeutic dose. For reference, drinking 10 liters of water in an hour can be fatal.

For a more conservative perspective, consider the data from Table 1.

If the maximum concentrations of all detected pharmaceuticals in one sample were summed, the value is approximately 104 ng/L. The most potent of the pharmaceuticals described in Table 1 is atenolol, with a no observable adverse effect level (NOAEL) of 0.80 milligrams per kilogram per day (mg/kg-day) based on human development. Using the U.S. EPA risk assessment paradigm, an acceptable daily intake (ADI) of 0.0027 mg/kg-day has been calculated (Snyder et al. 2008a). If we assume that all of the pharmaceuticals in Table 1 are as potent as atenolol, a child weighing 10 kilograms (kg) would need to consume approximately 26 liters (L) of this water to reach the ADI, which includes a 300 fold safety factor. However, it must be noted that this study only investigated 15 of the more than 3000 pharmaceuticals currently registered in the U.S. (Snyder et al. 2008a).

Human pharmaceuticals are among the only environmental contaminants to have undergone extensive human clinical testing. Although the toxicological databases are rich, exposure data are needed to complete appropriate human-health risk assessments that would provide integral information to determine whether regulations are warranted.

Chapter 2
Ecological Effects of Pharmaceuticals in the Water Environment

Organisms with aquatic life history components may experience continual exposure to aqueous media. In contrast to humans who experience more limited exposure (i.e., oral) to waterborne materials, aquatic organisms could be exposed to aqueous contaminants throughout their entire lifetimes. Consequently, a logical hypothesis would be that aquatic organisms would be highly susceptible to the adverse effects of water-borne contaminants representing the "worst-case" scenario.

Recent concern for the ecological effects of pharmaceuticals or EDCs primarily resulted from studies in the 1990s of surface waters receiving municipal wastewater discharges in the United Kingdom (U.K.) where feral fish were found to have altered reproduction strategies and high incidences of hermaphrodism (Sumpter and Johnson 2008).

Studies included sampling of roach fish throughout several waterways that indicated male fish below wastewater outfalls were undergoing feminization or endocrine disruption. Measurements included the presence of ova within male testes (e.g. intersex) and the occurrence of the egg yolk precursor protein, vitellogenin, in the blood of male or juvenile fish. The field studies were coupled with caged fish studies where fish were exposed upstream and downstream of wastewater treatment outfalls showing induction of vitellogenin in caged fish downstream of wastewater outfalls. Since feminization is largely controlled in fish by estrogens, an estrogen-receptor based bioassay was employed in a chemical fractionation approach similar to a Toxicity Identification Evaluation (TIE). Using these predominantly in vitro approaches, researchers in the U.K. and the U.S. identified natural and synthetic estrogen hormones in active fractions of wastewater effluent. Dose-response studies indicated these compounds (i.e. estrone, estradiol and EE2) were able to induce vitellogenin, intersex and gender shifts to females at ng/L concentrations of varied durations of exposure. Since initial analytical studies detected concentrations of these compounds within this range, it has been proposed that natural and synthetic steroids are predominantly responsible for the estrogenic activities observed in wastewater impacted surface waters (Sumpter and Johnson 2008).

While endocrine disruption was noted in animals exposed to wastewater effluents, the concept was not unique to wastewater. Other sources such as antifouling paints (e.g., tributyltin) and organochlorine pesticides and industrial compounds (e.g., polychlorinated biphenyls) have been previously shown to target endocrine systems. The unique feature of the studies showing feminization from wastewater was that a significant biological response was linked to at least one compound (synthetic estrogen), EE2, consumed and excreted by humans.

Another unique study in Canada indicated that long-term exposure to 5 to 6 ng/L concentrations of EE2 in a lake not only affected individual animals (vitellogenin, intersex) but also led to significant negative population level impacts (Kidd et al. 2007). To date, the Canadian lake study is the only documented case of a population collapse of an aquatic organism due to exposure to a pharmaceutical agent. However, there was some uncertainty with the study with regard to the distribution of EE2, which appeared to be stratified in the upper pelagic areas of the water column in the lake, and significantly exceeded typical concentrations of EE2 observed in surface waters, even in treated U.S. wastewaters.

As advances in analytical chemistry have identified more compounds derived from human usage of pharmaceuticals, questions have arisen as to whether other compounds may have similar impacts. The good news is that few compounds are as biologically active at environmentally relevant concentrations as natural and synthetic hormones. In addition, most compounds are in water-soluble forms that impair rapid accumulation. However, it should be noted that the disposition and fate of many pharmaceutical compounds within fish and wildlife is very much under-studied and therefore uncertain. For example, a compound resistant to degradation or that is continuously present (pseudo persistent) and relatively well-absorbed by biota (Log Kow > 3) may still accumulate to biologically relevant concentrations even when present at low environmental concentrations. This is particularly relevant in wastewater dominated streams and waterways where uptake of pharmaceutical agents have recently been observed in aquatic organisms (Brooks et al. 2005).

An example here are the Selective Serotonin Reuptake Inhibitors (SSRI) where adverse biological effects have been noted in laboratory studies at concentrations (micrograms per liter (µg/L)) that greatly exceed environmental concentrations (e.g., ng/L). However, since these compounds appear to be rapidly absorbed and accumulate within fish, uncertainty surrounds the critical absorbed dose in the target organ (brain; gonad) needed to elicit adverse effects. Examples of other compounds considered to be of concern to aquatic organisms are chemicals designed for cytotoxicity used in cancer chemotherapy. It is also unclear the impact antibiotic agents may have on microbial populations (Fick et al. 2009).

There is tremendous uncertainty regarding the mechanisms/modes of action of many of these compounds in aquatic organisms. Without the knowledge of how compounds act, it is difficult to determine whether acute toxicity tests really provide the best assessment for adverse effects. In addition, understanding the mode of action of these compounds within aquatic organisms may aid assessments of mixtures, which have been highlighted in recent U.S. EPA documents reevaluating methods for setting Aquatic Life Criteria thresholds (EPA 2009b). For example, the average geriatric patient receives seven to ten different medications per day. Assessments made by the pharmacist or physician in these cases use a mode of action approach, which evaluates the safety of using these compounds in mixtures. Clearly, more studies exploring the toxicodynamics (mode of action) and toxicokinetics of pharmaceutical agents and other chemicals of emerging concern in fish and wildlife are necessary to better understand the risk of these compounds to biota.

Chapter 3
Regulatory Activities

The U.S. EPA has authority to regulate contaminants (including pharmaceuticals) in wastewater and drinking water through the Clean Water Act (CWA) and the Safe Drinking Water Act (SDWA), respectively. Under the CWA, the U.S. EPA establishes criteria that may be adopted by the states as enforceable standards through the National Pollutant Discharge Elimination System (NPDES) program. The SDWA provides for the establishment of enforceable primary maximum contaminant levels (MCLs) to regulate the concentration of microbial and chemical substances in drinking water. While initial regulations were set in place to protect consumers from identified chemical and microbial risks with tangible toxicological endpoints, substances known as "emerging contaminants" with less toxicological and occurrence data available are usually left out of regulation until adequate evidence is accumulated. Regardless of federal activity, states have the authority to regulate water quality beyond the national regulatory requirements. For example, California is already discussing requirements for monitoring pharmaceuticals in reuse water.

Although the U.S. EPA has conducted numerous research projects related to the measurement, occurrence and treatment of pharmaceuticals in water, to date, there have been no federal regulations establishing limits for pharmaceuticals. The first major agency policy statement occurred in April 2008 when then Assistant Administrator, Ben Grumbles, testified at a Congressional hearing on pharmaceuticals. The agency then articulated a "four-pronged approach that is aimed at improving the science, communicating risks, identifying partnership and stewardship opportunities, and preparing to take regulatory action when appropriate." (Grumbles 2008). Continuing activities within the U.S. EPA may lead to future recommendations regarding regulation of pharmaceuticals in water.

3.1. Mechanisms for Drinking Water Regulation

There are two mechanisms in place for monitoring potential pollutants of concern. The first such mechanism was created when the U.S. EPA established the candidate contaminant list (CCL) as a means of prioritizing pollutants of concern which should be further evaluated in terms of occurrence and toxicity. The second such mechanism is through the unregulated contaminant monitoring rule (UCMR). The UCMR requires all water supply utilities serving more than 10,000 consumers to monitor a specific list of contaminants (not more than 30 compounds) quarterly or semi-annually for one year. The UCMR results are then coupled with on-going toxicological investigation and risk assessment to determine whether a contaminant should be fully regulated, further investigated in the UCMR program, left on the CCL, or removed entirely. In February 2008, the U.S. EPA included 287 pharmaceuticals in the chemical universe used to develop the draft CCL 3 (http://www.epa.gov/fedrgstr/EPA-WATER/2008/February/Day-21/w3114.htm). In this 2008 list, the only pharmaceutical that met the criteria was nitroglycerin; however, this compound's dominant use has been as an explosive as opposed to medicinal applications. The final CCL 3 was released in

October of 2009 and included nine steroid hormones and an antibiotic (erythromycin) that were not listed in the draft. Interestingly, of the nine steroid hormones, only three are exclusively used as human pharmaceuticals (ethinyl estradiol, mestranol, norethindrone) in oral birth control medications (U.S. EPA, 2009a). While the dominant basis for occurrence of these steroid hormones and for the antibiotic listed in CCL 3 stem from USGS studies (http://www.epa.gov/safewater/ccl/pdfs/ccl3_docs/Final%20PCCL%203%20Contaminant%20Information%20Sheets.pdf), more recent efforts have shown that steroid hormones and erythromycin are generally not detectable in U.S. drinking water, even when extraordinarily sensitive analytical methods are applied (Benotti et al 2009).

3.2. Mechanisms for Waste Water Regulation

In 2008, the U.S. EPA's Office of Water developed a white paper to provide general guidance on how water quality criteria development for Contaminants of Emerging Concern (CECs) could be facilitated through a supplemental interpretation of the 1985 document Guidelines for Deriving Numeric National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses (the Guidelines). In the past, the Guidelines have provided uniformity and transparency in the derivation methodology of aquatic life criteria. Under these Guidelines, EE2 would not have been identified as a contaminant of concern. The purpose of the white paper was to provide general guidance on how criteria development for CECs could be facilitated with a particular attention to pharmaceuticals with an EDC mode of action like EE2.

3.3. Other Activities

The U.S. EPA recently asked the National Academy of Sciences (NAS) to conduct a workshop on pharmaceuticals in water (NAS 2009). The presenters briefly discussed information regarding occurrence, data availability, technology and risks and risk assessment methodology. There were no conclusions from the meeting, but in general, the sense was that levels of pharmaceuticals in water were very low and margins of exposure from therapeutic doses were large; health data on pharmaceuticals are substantial and much more prevalent than most other chemicals, but there are gaps with respect to some populations such as infants and children, and very low level chronic exposure risks; some ecological effects were noted; new risk assessment methodologies are not required; use of the therapeutic dose as a low effect benchmark as a point of departure is appropriate.

The U.S. EPA also provided support to the World Health Organization (WHO) on the issue of risks of pharmaceuticals in drinking water. WHO convened an expert committee in Singapore in June 2009 to review the occurrence, toxicity and potential risks from consumption of drinking water containing pharmaceuticals as understood from the existing occurrence information. The committee produced a draft report for WHO which has not yet been officially released; however, draft conclusions and recommendations were presented with appropriate caveats by a committee member (Sanderson 2009) at a conference following the meeting. In general, the committee concluded that pharmaceuticals are occurring in drinking water at concentrations typically more than 1000 fold less than the therapeutic doses.

Based upon current evidence on margins of exposure to individual compounds, the committee also concluded that the development of global drinking water quality guideline values for pharmaceuticals is not warranted. Additionally, current risk assessment methods do not explicitly address human health effects at low-level chronic exposure to chemical mixtures, including pharmaceuticals. The committee also felt that current evidence does not support a general requirement for additional or specialized drinking water treatment to reduce concentrations of pharmaceuticals from water sources. Finally, enhanced preventive measures including education for prescribers and the public can reduce disposal and discharges to the environment and reduce human exposure from drinking water.

The U.S. government also may be informed by international regulatory initiatives. Australia has taken the first major effort so far with the Australian Guidelines for Water Recycling: Augmentation of Drinking Water Supplies (Australia 2008). They include guidance levels for numerous pharmaceuticals in reclaimed water. These are not mandatory and have no formal legal status, but they were provided to offer nationally consistent guidance for reuse projects. In general, the values are far above concentrations found in drinking water or reclaimed water.

Chapter 4
Issues for Pharmaceutical Analysis

From the 1960s through most of the 1990's, most pharmaceuticals in water analyses were conducted by laborious protocols involving extraction of large volumes of water, followed by derivatization steps and Gas Chromatography (GC) or Gas Chromatography/Mass Spectrometry (GC/MS) analysis. This resulted in analytical sensitivities in the high part per billion (ppb) ranges. As a result of the relatively poor sensitivity of these methods, there were relatively few detections of pharmaceuticals in "clean" waters (e.g., treated effluent or drinking water sources). With respect to assessments of wastewater influents, there was little interest due largely to the analytical challenges of this matrix with large interferences from natural products and more conventional pollutants, such as halocarbons, etc. Initially analyses were done by liquid-liquid extraction followed by GC/MS, but by the mid 1990s there was more use of solid phase extraction as a preparation technique for the GC/MS analysis. GC/MS was used successfully for detection of a limited range of pharmaceuticals, particularly in Europe, but was not a viable technique for analysis of many others that are often polar molecules that are either not extracted well or not detected well by GC/MS.

In the late 1990s, Liquid Chromatography-Mass Spectrometry (LC-MS) began to replace GC/MS as a viable technique for analysis of pharmaceuticals, as sensitivity of LC-MS systems improved to allow detection of a wider range of pharmaceuticals at sub ppb levels.

In the mid 1990s, most of the work on water-bound pharmaceuticals was conducted in Europe and was typically presented at conferences. This engendered more interest among academic researchers, but not much among the public or the regulatory community. In the U.S., the United States Geological Survey (USGS) conducted a series of investigations on the Mississippi River and demonstrated increases in caffeine downstream of many municipalities. This was one of the first stories that captured the interest of the public in showing that pharmaceuticals might potentially impact drinking waters. In 1999, Christian Daughton from U.S. EPA and Thomas Ternes from Germany published a paper that drew significant attention to this issue (Daughton and Ternes 1999). In 2002, the USGS published a seminal paper (Kolpin et al. 2002) illustrating the widespread occurrence of pharmaceuticals in water. This paper captured the attention of the media. However, several critical aspects of this paper, which exposes issues that continue to this day, included the fact that the Kolpin paper had some data that were subsequently withdrawn due to the discovery of analytical interferences, and the aspect that this paper focused not on absolute concentrations, but rather on merely the presence or absence of various constituents. This qualitative versus quantitative approach has continued to characterize most of the USGS work in that the organization provides valuable information regarding frequency of detection, but not necessarily good quantitative data on absolute concentrations.

By the early 2000s, some researchers were using LC-MS or LC-MS-MS techniques for detection, but as yet there was neither standardization of analytical methods nor inter-laboratory studies to validate

the rigor of such methods. Many labs participated in an analytical "arms race", acquiring more and more sensitive instruments, without necessarily looking at the rigor of the analytical methods themselves. So, although this resulted in an increase in the number of papers presented on the analysis of pharmaceuticals, it did not necessarily result in better data. Most analytical methodology was based on peer reviewed journal articles or in-house developed methods. The use of tandem mass spectrometry (MS-MS) significantly reduced the levels of interferences seen, particularly in wastewater type matrices.

One of the key papers on analytical methodology was published in 2003 by Vanderford et al. But subsequent work by the same analytical team (and many others) demonstrated the large potential for false positives and false negatives due to signal suppression and enhancement in LC-MS and LC-MS-MS systems when operated in electrospray positive or negative detection mode (the most common detection methods). Subsequently, Vanderford et al (2006) strongly recommended the use of isotope dilution to correct for this signal variability. With the advent of more sensitive LC-MS-MS systems, it has become possible to detect many of the pharmaceuticals at the ng/L or even sub-ng/L level. This evolution in detection limits is beginning to present significant challenges for sample collection and analysts. For instance, compounds as diverse as caffeine, cotinine, and EE2 may all be present in trace amounts, but sourced to the personal use by field samplers or analysts. The potential for blank contamination and the likelihood of false positives is extreme as the reporting limits continue to be pushed down to ng/L levels. Moreover, recent monitoring data using isotope dilution has demonstrated that steroid hormones rarely occur in U.S. drinking waters even with sub-ng/L analytical sensitivity (Benotti 2009).

As a parenthetical and cautionary observation, many years ago, researchers at California Institute of Technology and Skidaway Institute of Oceanography demonstrated that much of the literature on trace metals in the environment was biased by several orders of magnitude due to "sampling contamination" because of the ubiquitous nature of many metals. This included decades' worth of data published by the USGS on river loads of various metals and much of the environmental literature on lead contamination in water and air. Without being aware of these pitfalls, we run the real risk of repeating these problems for pharmaceuticals. Once data are in the literature, even if withdrawn, they still end up being available to the popular press. This was already the case with some of the steroid hormone data in the USGS 2002 manuscript (Till 2003 and http://toxics.usgs.gov/regional/est_errata.html). Questionable analytical results in this USGS paper may very well have influenced public policy as evidenced by the inclusion of steroid hormones in EPA's CCL 3.

In the last two years we have begun seeing some attempts at standardization of analytical methods for pharmaceuticals to facilitate comparability. The U.S. EPA's Office of Water published Method 1694 in late 2007 (EPA 2007), and already, variations on this method are being used by many water researchers. However, the U.S. EPA now acknowledges that this method should be viewed as a screening method rather than a quantitative technique for water analysis. Consequently, data generated with Method 1694 are best viewed as a presence/absence test, similar to the approach used by the USGS in much of their pharmaceutical literature.

The U.S. EPA's drinking water research organization is currently finalizing a method for steroid hormones at the part per trillion (ppt) level. Under the auspices of the Water Research Foundation (project 4167), a major inter-laboratory study (involving over 20 laboratories worldwide) is underway to evaluate the rigor and comparability of analytical methods for approximately 20 pharmaceuticals in the ppt to sub-ppb range. Preliminary data from this project suggest that many of the reported water measurements of pharmaceuticals and hormones may be subject to significant bias and poor inter-laboratory precision. By 2010, there should be much better knowledge on the reliability of measurements of pharmaceuticals at environmentally relevant concentrations and this new knowledge should provide the basis for method standardization.

Chapter 5
Human Health Consequences of Pharmaceuticals in Water

Although pharmaceutical concentrations reported thus far in U.S. drinking waters are in the parts per trillion range, reported effects in ecosystems (Chapter 2) have raised the question of whether these chemicals could be affecting human health. To address the question of whether pharmaceuticals in drinking water are affecting human health, scientists have been conducting additional studies. One research path is to compare concentrations of pharmaceuticals detected in drinking water to adverse effects noted in the literature (toxicological risk assessment).

Toxicological risk assessment is universally conducted by government agencies world-wide (e.g., the WHO, the Food and Drug Administration (FDA), U.S. EPA, etc.). The process, briefly summarized, consists of 1) gathering and collecting relevant chemicals of concern; 2) analyzing possible exposures (e.g., from drinking water); 3) collecting toxicological information; and 4) characterizing the potential for adverse health effects to occur. The process focuses on preventing effects to the most sensitive populations (e.g., developing fetus). The end result is the development of toxicity guideline values, which are doses (in units of milligram of drug per kilogram of body per day). Toxicity guideline values go by many names, including screening levels, acceptable daily intake values (ADI), reference doses, etc. Often it is easier to convert the ADI into a water concentration, such as the Drinking Water Equivalent Level (DWEL), such that the comparison of chemicals detected in water to the ADI is simpler. The DWEL process the U.S. EPA uses in this conversion assumes a 70 kilogram person drinking 2 liters of water per day, often assuming decades of exposure if not a lifetime. Methods and examples of deriving and calculating ADIs, including DWELs, can be found in Snyder et al 2008a.

For either the screening level or the DWEL, the assumption is made that a person could be exposed to that dose (and more since safety factors are added) on a daily basis without the expectation of adverse effects. These ADI's/screening values are also meant to be used as decision criteria to support selection of an appropriate screening methodology if a chemical is found in source or drinking water. If the pharmaceutical is found in water at or above the screening level determined with this methodology, then more detailed evaluation of the toxicity and occurrence of the compound is considered appropriate. On the other hand, if the concentration of that compound found in water is below the screening level, then there is no expected risk of adverse effect to the public health. Table 2 provides the results of this type of analysis. One way to understand the relationship between the ADI and the water

concentration is to numerically estimate the difference. For example, in Table 2 the ADI/DWEL for Atenolol was calculated to be 70 µg/L. The maximum drinking water concentration was 0.026 µg/L. The water concentration is 2,700-fold lower than the ADI/DWEL (Margin of Exposure), although recall that the ADI/DWEL itself is not a threshold of an adverse effect. Comparing ADI/screening values or DWELs to maximum concentrations of 16 pharmaceuticals in drinking water, the results demonstrate all drinking water concentrations are below their screening values. Thus, no adverse effects would be expected from drinking water with the reported concentrations. This process has continued for another 117 pharmaceuticals and has found, so far, that this is a consistent finding. (Pleus 2009).

A limitation to the research up to now is that only individual pharmaceutical assessments have been considered. Not enough toxicity assessments have been completed to allow evaluation of pharmaceutical mixtures (e.g., summing relevant classes of pharmaceuticals such as beta-blockers). While there is a great deal of conservatism in the process explained above (erring to the side of protecting the most sensitive populations), people are exposed to mixtures of these agents. It is important to evaluate such interactions. Another limitation of the research is that the testing of pharmaceuticals required for FDA approval does not include studies of low doses for long periods of time, which are more representative of these types of exposures. It is clear more research will be conducted along these lines.

Another issue is the amount of time required to conduct a toxicological assessment. The work presented in Table 2 required gathering all relevant studies, examining them carefully for soundness, and carefully analyzing of the data and results/conclusions. This work is resource intensive and costly. This could be a barrier to continuing this research. Moreover, we are expecting more "new" chemicals as chemists work to develop methods for detecting chemicals, particularly at ultra low concentrations. Scientists are examining other methods to expedite the analysis so that information can be provided more quickly. An example of this is the work being conducted based on the Minimum Anticipated Biological Effect Level (MABEL) as the point of departure (Bruce et al. 2009). This method is rapid compared to the approach discussed above.

Regarding the last issue, the focus has been assessing the more classical pharmaceutical agents (e.g., antibiotics, anti-anxiety agents, etc.). These toxicological assessments that have been developed and conducted are satisfactory and appropriate to address possible human health concerns to these medicines. However, new generations of pharmaceutical agents will use different mechanisms of action or use unique aspects of molecules to exert their therapeutic actions. For example, with the use of nanopharmaceticuals (drugs with sizes between 1 and 100nm), are the toxicological assessment complete enough for an sufficient assessment? Current scientific thought assessing the surface area of the nano molecules in addition to the mass are needed in assessing potential adverse effects. The standard toxicological risk assessment framework does not adequately address surface area of molecules. This will need to be considered and addressed for the future of new generation of medicine.

In summary, pharmaceuticals are being detected in drinking water. Scientists have undertaken toxicological assessments to determine if the concentrations for the pharmaceuticals that have been detected exceed their ADI/screening levels. The results so far report that none have exceeded their screening values; in some cases the margins of safety are well over a million fold. However, only a minor percentage of the total population of pharmaceuticals have been evaluated. While the risk to these chemicals in drinking water appears to be small, it is still early in the evaluation and more research needs to be completed.

Chapter 6
Sources and Source Control

Pharmaceutical compounds as developed and marketed for use in human and animal medicine generally have complex chemical structures; some are designed to be toxic; some are antimicrobials; some may be classified as hazardous; some may be radioactive; some may be endocrine modifiers, and unfortunately, there are no reliable data available in the public domain for the total use of these pharmaceuticals (Daughton 2003a and Kümmerer 2008). In addition, once they enter the environment, pharmaceuticals are difficult to remove.

Pharmaceuticals or their active ingredients originate at the manufacturing sites and may leave these sites as finished and packaged products for use in human and animal medicine, as pollutants in process wastewater discharges, or as pollutants in air emissions. Once the pharmaceuticals leave these sites, their distribution to the environment follows a more complex set of potential pathways, which are generally far removed from their sites of origin. Actual data on the discharge of pharmaceuticals and/or their active ingredients from US manufacturing sites are not available, but, predictably, the pharmaceutical industry argues that inputs to the environment from these sources are not significant.

6.1. Sources of Human Pharmaceuticals

The principal sources of human pharmaceuticals include hospitals, extended-care facilities, and private households that discharge into wastewater treatment facilities, which are predominantly publicly owned treatment works (POTWs). All of these sources also contribute via the disposal of unused medicines as trash. Depending on the demographics or occupancy profile of individual households, this source status could be over short periods during any given year, or be continuous for households with senior residents, who are more likely to be on multiple forms of prescription or non-prescription medication.

As every individual, minor and adult, represent a potential discharge point for pharmaceuticals to the environment, it follows that whether they excrete at home, work, church, hospitals or elsewhere, their contributions are temporarily deposited at the POTWs for some treatment or modification on their way to the environment. Even unused or expired medicines, which are discarded in household trash by individuals, ultimately end up in part via landfill leachate at POTWs on their way to the environment. Thus, the individual being medicated, virtually the entire population, represent potential multi-million foci of discharges of non-conventional pollutants (pharmaceuticals) to POTWs, and hence to the environment. Recent studies on the relative contributions of various sources of pharmaceuticals to the water environment, suggest that patient contribution via body excretions is significant, and could be as high as 90 percent (Tischler et al. 2009).

6.2. Sources of Animal Pharmaceuticals

Reliable data on the amount of animal pharmaceuticals including antimicrobials, which enter the environment, are not available in the public domain. However, pharmaceuticals which enter the environment from animal husbandry operations have been estimated to represent a significant source, and they are derived primarily from spills from anaerobic manure storage lagoons, manure fertilization of farm fields, run-off from farm fields, discharge from aquaculture operations, and dust. They follow similar pathways as human pharmaceuticals to reach the same environmental sinks, that is surface waters, ground waters, soil, and air, and they carry their own potential for contaminating these environmental sinks (Boxall et al. 2003 and Boxall 2004).

With respect to antimicrobials, food animal producers in the U.S. administer these medicines at therapeutic, and sub-therapeutic doses, to poultry, swine and cattle. While some of these medicines are administered to treat sick animals, the bulk of them are administered to accelerate growth, and to promote weight gain, a practice approved by the FDA since 1951 (FDA 1977a and b). This FDA approval has since encouraged pharmaceutical companies to begin a race to mass-produce antimicrobials for use in food animal production. The Union of Concerned Scientists has estimated that about 70 percent of antimicrobials used in the U.S. are fed to chickens, pigs, and cattle for non-therapeutic purposes (Mellon et al. 2001), while the Institute of Medicine (1989) estimates this figure to be about 30 percent, with 40 percent to 80 percent considered to be unnecessary (Institute of Medicine 1998). Whichever estimate is correct, the reality translates to the use of tens of millions of pounds of antimicrobials annually in animal husbandry, mostly for non-therapeutic purposes. These estimates cover only antimicrobials, and inclusion of the myriad other pharmaceuticals administered would further emphasize the true extent of the problem of pharmaceuticals which enter the environment from animal medicine.

6.3. Source Control

Complete removal of pharmaceuticals in conventional wastewater treatment plants is not possible; they cannot be relied upon to be the sole mechanism for controlling the entry of pharmaceuticals to the environment. This POTW effluent route represents a major input: by some estimates more than 80 percent of the human input, which can only be expected to grow over time as the pressure for creating newer and more powerful prescription and non-prescription pharmaceuticals increases. This deficiency in treatment capability makes it imperative to control the amount of pharmaceuticals entering these facilities via source control strategies in order to effectively reduce the burden on the environment. Thus, prevention becomes a long-term control imperative (Daughton 2003a).

While there is general concern over the presence of pharmaceuticals in the environment, there is also a consensus that regulatory action to establish CWA criteria are not warranted at this time. However, if and when the need for regulatory action arises, any long term program or strategy for controlling pharmaceuticals to the environment from human medicine must include pollution prevention, be holistic, broadly based, and include a rigorous source control component to complement the limited capability of the POTWs (Daughton 2003b).

With respect to source control of pharmaceuticals from animal medicine, the options are also limited. One option supported by the U.S. human medicine community, including the American Medical

Association, and the Institute of Medicine, is a reduction of the amount of pharmaceuticals used in farm animal production for non-therapeutic purposes (U.S. Senate, Senate Bill S.549). This practice is already in effect in Europe (Wierup 2001). The medical community argues that this action would reduce the increasing incidence of antibiotic resistant infections in the human patient population.

Chapter 7
Treatment Options to Remove Pharmaceuticals

Whether pharmaceuticals and other trace organic chemicals are amenable to treatment will depend on the physicochemical properties of the compound and the key underlying removal mechanisms of a particular treatment process. Given the wide range of properties represented by these chemicals, there is not a single treatment process that provides an absolute barrier to pharmaceuticals. If the objective is to minimize the presence of pharmaceuticals in treated water, research studies have demonstrated that a sequence of diverse treatment processes is needed that is capable of tackling the wide range of physicochemical properties. In most cases, this can be accomplished by combinations of different processes, for example biological processes coupled with chemical oxidation or activated carbon adsorption, physical separation followed by chemical oxidation, or natural processes coupled with chemical oxidation or carbon adsorption. However, pharmaceutics are either transformed, separated or mineralized (oxidized to carbon dioxide) during treatment.

7.1. Conventional Wastewater Treatment

While conventional wastewater treatment plants utilizing activated sludge processes were not primarily designed to remove trace organic chemicals, monitoring efforts in the field as well as controlled experiments in the laboratory have demonstrated that effective attenuation can be achieved for many pharmaceuticals. Important for removal of pharmaceuticals in activated sludge and biological nutrient removal (BNR) processes is maintaining a critical solids retention time (SRT). Maintaining SRT promotes the growth of a more diverse biological community that is probably able to degrade compounds, such as pharmaceuticals, more efficiently. Several studies demonstrated that for a number of pharmaceuticals, SRTs of 5 to 10 days can result in 80 or more percent removal. Well removed compounds are caffeine, ibuprofen, oxybenzone, chloroxylenol, methylparaben, benzyl salicylate, 3-phenylpropionate, butylbenzyl phthalate, and octylmethoxycinnamate (Oppenheimer and Stephenson 2006). Compounds with little removal in biological processes are galaxolide, tris(2-carboxyethyl)phosphine hydrochloride (TCEP), and N,N-diethly-3-methylbenzamide (DEET). It is important to note that "removal" of more hydrophobic and recalcitrant pharmaceuticals commonly means that compounds are removed from the aqueous phase but accumulate in the biosolids. Likewise, oxidative and biological processes often result in transformation products that are structurally altered but are not completely removed.

7.2. Conventional Drinking Water Treatment

The occurrence of pharmaceuticals in drinking water sources highly depends upon the degree of wastewater and non-point source impacts upon the raw water supply. Conventional drinking water treatment consisting of coagulation/flocculation with ferric or alum followed by sedimentation and filtration commonly employed for surface water treatment is not capable of removing pharmaceuticals (Adams et al. 2002, Ternes et al. 2002, Westerhoff et al. 2005).

Removal of some pharmaceuticals, however, can be expected during drinking water disinfection. Chlorine, chlorine dioxide and ozone disinfection are oxidation processes and thus have the potential to transform pharmaceuticals and other trace organic chemicals. Among the three oxidants, ozone is the most reactive. Previous studies reported that compounds with primary or secondary amines (i.e., diclofenac, sulfamethoxazole, trimethoprim) and phenolic compounds (i.e., estrone, 17β-estradiol, 17α-ethinylstradiol, acetaminophen, triclosan, bisphenol A, and nonylphenol) were efficiently removed by chlorine (Alum et al. 2004, Westerhoff et al. 2005). However, chlorine was inefficient at removing ibuprofen, DEET, iopromide, and TCEP (Westerhoff et al. 2005). Chlorine dioxide is generally a stronger oxidant than free chlorine. Huber et al. 2005 observed appreciable removals of sulfamethazine, sulfamethoxazole, estrone, 17β-estradiol, 17α-ethinylstradiol, roxithromycin, erythromycin-H_2O, and diclofenac by chorine dioxide. However, caffeine, clofibric acid, gemfibrozil, ketoprofen, naproxen, iopromide were recalcitrant to chlorine dioxide oxidation. Ozonation is a strong oxidant and very effective in the transformation of many pharmaceuticals (i.e., sulfamethoxazole, roxithroymcin, diclofenac, and naproxen) and steroids (i.e., estrone, 17β-estradiol, 17α-ethinylstradiol) that can be oxidized by more than 90-99 percent for ozone doses $\geq$ 2 mg/L (Ternes et al. 2002, Alum et al. 2004, Westerhoff et al. 2005, Huber et al. 2005). However, X-ray contrast media (i.e., iopromide) were only partially oxidized (Huber et al. 2005). Ultraviolet irradiation at typical disinfection doses of (5-30 mJ/cm^2) is ineffective for destructive treatment of pharmaceuticals.

7.3. Advanced Water Treatment

Activated carbon adsorption can readily remove organic compounds from water, with the exception of some very polar water-soluble compounds, such as iodinated contrast agents and the antibiotic sulfamethoxazole (Adams et al. 2002, Westerhoff et al. 2005). Advanced oxidation processes (AOPs) are very effective treatment processes for oxidizing pharmaceuticals and other trace organic chemicals. However, compared to ozone, AOPs provide only a small increase in removal efficiency (Dickenson et al. 2009). Low-pressure membranes, such as microfiltration (MF) or ultrafiltration (UF), have pore sizes that are insufficient to retain pharmaceuticals based on their size. Some hydrophobic compounds can still adsorb onto MF and UF membrane surfaces providing some short-term attenuation. This also confirms the expectation that MF or UF utilized in a membrane bioreactor (MBR) process do not provide an additional benefit to removal of pharmaceuticals. However, high-

pressure membranes, such as reverse osmosis (RO) and nanofiltration (NF), are very effective in the physical separation of a variety of pharmaceuticals from water (Bellona et al. 2008). Problematic for high-pressure membranes are low-molecular weight organics, such as acetaminophen and the disposal of the concentrate (brine) with elevated levels of pharmaceuticals. Natural processes, such as riverbank filtration (RBF) and soil-aquifer treatment (SAT), can be employed either as an additional treatment step for wastewater reclamation or as a pre-treatment to subsequent drinking water treatment. These natural treatment processes are acting like a slow-sand filter with extended retention times. RBF and SAT are very effective in attenuating a wide range of pharmaceuticals and other trace organic chemicals by sorption and biotransformation processes in the subsurface but are limited in attenuating refractory compounds, such as antiepileptic drugs or chlorinated flame retardants (Drewes et al. 2003).

7.4. Use of Indicator Compounds to Assess Performance of Drinking Water Treatment Processes

Given the large number and chemical diversity of compounds potentially present in water, selecting compounds for occurrence for occurrence monitoring and treatment process performance assessment is challenging. To assess the efficiency of water treatment processes, an approach has been recently proposed that uses a combination of indicator compounds and surrogate parameters to gauge the efficiency of removal of broader classes of pharmaceuticals in the product water (Drewes et al. 2008, Benotti et al. 2009, Dickenson et al. 2009). This approach will require extensive experimental evaluation to determine its efficacy, and is currently proposed only for drinking water systems. If successful, this approach could greatly reduce the analytical cost and complexity of monitoring water treatment systems performance for removal of pharmaceuticals.

Chapter 8
Communication to the Public Regarding Risks and Potential Risks of Pharmaceuticals in Drinking Water

Communicating risks that affect a population or group is rarely easy because the information can be frightening and evoke emotional responses from the audience, thereby further complicating the remainder of the communication. While putting the information into accurate and understandable terms is helpful, there are additional considerations. These emotional responses can be out of proportion with the true risk. It is therefore important for the person or persons charged with imparting this risk information to the public to speak in a clear and straight-forward manner, using terminology appropriate for the particular group (e.g., language, values, context, etc.). The objective is to inform the audience so that they are then able to understand, assess and possibly to minimize or eliminate the risk. It has been observed that natural or voluntary risks are perceived to be less threatening than unnatural or involuntary risks (industrial or manmade) and the public more outraged when it seems to have been caused by government and/or industry (Sandman 1993). But care must be taken; it is an almost instinctive desire to turn an industrial risk into a natural risk, such as pointing out that the sun is a nuclear reactor-type power plant. Poor risk communication can cause greater fear and outrage.

Time and resources available to U.S. government agencies are limited. It is unlikely that agencies will be able to respond to develop reference doses or public health goals for the number of pharmaceuticals that will be detected. This leaves an information vacuum that needs to be filled so that water agencies can address important questions. It is essential to determine whether to pursue additional information or take a proactive position, and convey this to the audience with justification for either stance. If appropriate and feasible, a program with community participation (e.g., water agency public meetings held on a regular basis), may assist the community's understanding of the issues associated with the possible risk from exposures to pharmaceuticals in water.

Chapter 9
Recommendations

Due to uncertainties in occurrence and toxicity databases, more data are needed before meaningful, human and ecological health-based federal criteria and regulations should be considered. The following specific recommendations will address these identified uncertainties:

- A prioritization scheme should be developed to identify pharmaceuticals of greatest concern based upon key influencing factors, including the volume of the pharmaceutical produced, potency, and fate.
- Standardized analytical methods, with sufficient sensitivity and reliability, are needed to generate national occurrence data to fully assess the magnitude and prevalence of prioritized pharmaceuticals in drinking and waste water.
- A national occurrence study that encompasses diverse watersheds (e.g., pristine versus impacted) is needed.
- More studies exploring the toxicodynamics (e.g., mode of action) and toxicokinetics (e.g., accumulation) of pharmaceutical agents in fish and wildlife are necessary to better understand the risk to biota of individual compounds as well as mixtures.
- More population-based studies are necessary at environmentally relevant concentrations to address ecological impacts.
- Since pharmaceuticals undergo mandated clinical trials and are generally subject to follow-on monitoring studies in patients, the body of knowledge of human toxicity and other adverse effects from exposure to pharmaceuticals is far greater than for other environmental contaminants (i.e., pesticides, disinfection byproducts, etc.). However, more data are necessary to properly address the potential for interactions from mixtures of pharmaceuticals and for long-term chronic exposure.
- More research is needed to develop rapid, accurate, cost-effective toxicological screening tools (e.g., risk assessment and/or experimental assays).
- More research is needed to determine how and if new generations of pharmaceuticals can be evaluated using standard toxicological procedures (e.g., nano-pharmaceuticals).
- Studies should be conducted to determine if reductions of pharmaceuticals used in non-therapeutic applications in animal husbandry will significantly reduce environmental loading.
- Source control, such as disposal of unused pharmaceuticals (domestic and industrial), should follow best-management recommendations to minimize environmental exposure.
- Water treatment goals that define levels of pharmaceuticals in final water quality should be based on human and ecological health endpoints, not simply on detection alone.

- Monitoring strategies using surrogates are needed that can assure proper performance of treatment processes selected to remove pharmaceuticals.
- Communication to the public should be open, transparent, accurate and understandable.

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About the Authors

Shane Snyder: R&D Project Manager; Applied R&D Center, Southern Nevada Water Authority; Las Vegas, Nevada. Professor of Chemical and Environmental Engineering, University of Arizona, Tucson, Arizona.

Cecil Lue-Hing: Director of Research and Development (Retired), The Metropolitan Water Reclamation District of Greater Chicago, Chicago, Illinois.

Joe Cotruvo: President, Joseph Cotruvo & Associates LLC, Washington, DC.

Jörg E. Drewes: Professor and Director, Advanced Water Technology Center (AQWATEC), Colorado School of Mines, Golden, Colorado.

Andrew Eaton: Laboratory Technical Director, MWH Laboratories, Monrovia, California.

Richard C. Pleus: Managing Director, Intertox, Inc. Seattle, Washington

Dan Schlenk: Department of Environmental Sciences University of California, Riverside, California.

Tables

Table 1.
Concentrations of Pharmaceuticals in U.S. Drinking Water (Benotti et al. 2009)

		Drinking Water (n=18)		
Compound	MRL(ng/l)	Max. (ng/L)	Med. (ng/L)	#
Meprobamate	0.25	42	5.7	14
Phenytoin	1	19	6.2	10
Atenolol	0.25	18	1.2	8
Carbamazepine	0.5	18	6	8
Gemfibrozil	0.25	2.1	0.48	7
Sulfamethoxazole	0.25	3	0.39	4
Fluoxetine	0.5	0.82	0.71	2
Diazepam	0.25	0.33	0.33	1
Progesterone	0.5	0.57	0.57	1
Estradiol	0.5	<MRL	<MRL	0
Ethynylestradiol	1	<MRL	<MRL	0
Atorvastatin	0.25	<MRL	<MRL	0
Diclofenac	0.25	<MRL	<MRL	0
Estrone	0.2	<MRL	<MRL	0
Naproxen	0.5	<MRL	<MRL	0
Norfluoxetine	0.5	<MRL	<MRL	0
o-Hydroxy atorvastatin	0.5	<MRL	<MRL	0
p-Hydroxy atorvastatin	0.5	<MRL	<MRL	0
Risperidone	2.5	<MRL	<MRL	0
Testosterone	0.5	<MRL	<MRL	0
Trimethoprim	0.25	<MRL	<MRL	0

Table 2
Comparison of Pharmaceutical DWELs with Maximum Drinking Water Concentrations Data (Obtained from Snyder. 2008a)

Drug	Class	ADI (µg/kg-d)	DWEL (µg/L)	Maximum drinking water conc. (µg/L)*	Minimum margin of safety
Atenolol	Beta-blocker	2.0†	70	0.018	3,900
Carbamazepine	Anticonvulsant	0.34†	12	0.018	670
Diazepam	Benzodiazepine tranquilizer	1.0‡	35	0.00033	110,000
Fluoxetine	SSRI antidepressant	0.97‡	34	0.00082	41,000
Norfluoxetine	Metabolite	0.97‡	34	0.00077**	44,000
Gemfibrozil	Antilipidemic	1.3§	45	0.0021	21,000
Meprobamate	Antianxiety agent	7.5‡	260	0.042	6,190
Phenytoin	Anticonvulsant	0.19§	6.8	0.019	360
Risperidone	Antipsychotic	0.014†	0.49	0.0029**	170
Sulfamethoxazole	Anti-infective	510‡	18,000	0.0030	6,000,000
Triclosan	Antibacterial	75‡	2,600	0.0012	2,200,000
Atorvastatin	Antilipidemic	0.54†	19	<0.00025	>76,000
o-hydroxy atorvastatin	Metabolite	0.54†	19	<0.00050	>38,000
p-hydroxy atorvastatin	Metabolite	0.54†	19	<0.00050	>38,000
Diclofenac	NSAID	67‡	2,300	<0.00025	>9,200,000
Enalapril	ACE inhibitor	0.23‡	8.1	<0.00025	>32,000
Naproxen	NSAID	570‡	20,000	<0.00050	>40,000,000
Simvastatin	Antilipidemic	0.54†	19	<0.00025	>76,000
Simvastatin hydroxy acid	Metabolite	0.54†	19	<0.00025	>76,000
Trimethoprim	Antibacterial	190‡	6,700	<0.00025	>27,000,000

*Single highest discrete sample concentration, from finished drinking water unless otherwise noted.
†Derived from a cancer endpoint using the Maximum Tolerated Dose (MTD) method.
‡Derived from a non cancer endpoint.
§Derived from a cancer endpoint using the tumor data and the one-hit model.
**Concentration from distribution drinking water.

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