Daughton CG "**Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure**," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, Oxford: Academic Press; 2008, pp. 66-102; DOI: 10.1016/B978-012373960-5.00403-2.

Please note that this is the pre-galley web version of the above-referenced book chapter. There are content, formatting, and page-numbering differences between this web version and the actual published printed version. A reprint for personal use of the published version can be obtained on request from daughton.christian@epa.gov.

The URLs in the text have been enabled in this web version to permit ready accessibility. Note that Internet URLs (Universal Resource Locators) often cease to function for any number of reasons. To locate information on web pages no longer accessible, an archive service such as the "Internet Archive Wayback Machine" (http://www.archive.org) can be useful.

Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure

by Christian Daughton

Environmental Chemistry Branch, Environmental Sciences Division, National Exposure Research Laboratory, U.S. EPA, 944 East Harmon Avenue, Las Vegas, NV 89119, USA
Tel.: 702-798-2207; fax: 702-798-2142; E-mail address: daughton.christian@epa.gov

In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, Oxford: Academic Press; 2008, pp. 66-102;
DOI: 10.1016/B978-012373960-5.00403-2.

PHARMACEUTICALS AS ENVIRONMENTAL POLLUTANTS: THE RAMIFICATIONS FOR HUMAN EXPOSURE

Acronyms

ADI: acceptable daily intake
API: active pharmaceutical ingredient
CAFO: Confined Animal Feeding Operation
DEA: U.S. Drug Enforcement Administration
MDR: multi-drug resistance
NOEL: no-observed-effect level
PECs: predicted environmental concentrations
POU water: point-of-use water (i.e., from plumbing fixtures)
ppb: parts per billion
ppt: parts per trillion

Abstract

Pharmaceuticals enter the environment as trace pollutants largely by way of their intended use in human and veterinary medical practices, agriculture, and personal care. The primary route is their unintentional and largely unavoidable dissemination via excretion and bathing; a secondary route is the purposeful disposal to sewerage and trash of leftover, unwanted medications. Pharmaceuticals began to receive wide attention as an unregulated and complex source of environmental contaminants in the late 1990s. Comprising a remarkably diverse array of thousands of unique chemical substances, most of these substances by design interact with specific biological receptors. Human pharmaceuticals are distinguished from conventional, regulated pollutants in that measurable environmental residues originate from the combined actions, behaviors, and activities of multitudes of individuals. As consumer items, the minuscule contributions from each end user, while meaningless in isolation from each other, can combine to yield measurable environmental concentrations in aquatic systems and certain terrestrial areas (for example, where sewage sludge is disposed). The complex life-cycle of drugs — their numerous points of entry to the environment and ultimate exposure targets — is illustrated in Figure 1. The major potential routes by which human exposure can occur, which compose but one portion of this complex scheme, are the topic of this chapter.

Humans can be unintentionally exposed to trace residues of pharmaceuticals from the environment by ingesting drinking water (when its origin derives at least in part from municipal or domestic animal waste), consuming plant or animal tissue that has been similarly exposed, and by bathing. These minute exposures, which might be sustained indefinitely throughout life, involve concentrations resulting in bodily doses many orders of magnitude below those recommended for therapy. While this does not preclude the possibility for subtle or unmeasurable biological effects, very conservative estimates that account for additive mixture effects do not reveal the possibility of hazard; nor do the limited epidemiological studies of populations that consume drinking water that was at least partially wastewater derived.

With these points in mind, the absence of any empirical data or indications from predictive models for adverse human effects from extremely low-level exposure to pharmaceuticals cannot rule out the possibility. There are simply too many unknowns still faced by toxicology today; one in particular is exposure of sensitive sub-populations, especially for those whose unintended ingestion of particular pharmaceuticals is not recommended. More importantly is that however small these risks might be, they need to be placed in the context of the totality of cumulative and aggregate exposure to other anthropogenic contaminants and myriads of naturally occurring xenobiotics that have long existed and persist in our foods and water. This document summarizes the major gaps in our knowledge of toxicology and environmental chemistry that prevent definitive assessment of small but unwanted hazard, as the absence of evidence is impossible to prove.

The perception of risk is another factor that could play a critical role. Perception of risk is based in part on whether an exposure is borne by choice. And for ambient environmental residues in water and foods, the choice is not be design. Certain measures, summarized at the conclusion, can be implemented in the absence of additional knowledge to begin reducing or limiting unintended human exposure to ambient environmental residues.

Another major aspect of human exposure to pharmaceuticals involves accidental and purposeful ingestion of pharmaceuticals that have accumulated in the home and are awaiting disposal. Diversion of these drugs for recreational use or abuse, or accidental ingestion (for example by toddlers) results in significant human morbidity and mortality. A complex array of circumstances underlie human poisonings by unwanted, leftover waste medications. In the U.S., measures are just beginning to be put in place to reduce the incidence of acute exposure to leftover medications that need to be disposed.

Introduction

Human exposure to pharmaceuticals other than through actual therapeutic, lifestyle, or recreational usage can occur by two primary but very distinct routes. These two exposure routes have totally different consequences and pose completely different challenges with regard to their control or reduction. The first route is unintended, unexpected through the consumption of water and foods contaminated by pharmaceutical residues that have entered the environment as a result of their intended use, such as by excretion and bathing or upon disposal, and which then become "recycled." This route can theoretically lead to chronic, inadvertent exposure to extremely low levels of complex mixtures of pharmaceuticals (as well as other chemical stressors that are part of the ambient environment). The second route involves both the unintended and purposeful human exposure to leftover, unused drugs being stored as wastes but which then become diverted from eventual disposal. This route is known to result in acute, high-level exposures, generally to single drug entities at a time, and is responsible for significant human morbidity and mortality.

While the risks associated with exposure to environmental pharmaceutical residues are probably most significant with regard to ecological exposure (especially in the aquatic environment — see Figure 1), the public's concern is understandably more focused on human exposure. Most of the published literature, however, addresses the occurrence of pharmaceuticals in sewage effluent and natural waters, information not of immediate use for assessing human exposure, where

consumption of tap water (or bottled water) is the key concern. Other exposures can result, however, from consumption of foods contaminated with ambient residues that have been discharged to the environment. For a number of reasons, the concentrations of pharmaceuticals when they persist in tap water can be orders of magnitude lower than in the aquatic environment. Such low concentrations (parts-per-trillion/billion, ppt/ppb, and lower) pose major challenges even for advanced chemical analysis. For this reason, sparse data are available on the occurrence of pharmaceuticals in point-of-use (POU) drinking waters — that is, tap water dispensed for end use from plumbing fixtures.

Needless to say, it is not currently possible to directly assess human exposure to environmental residues of pharmaceuticals by measuring biomarkers of exposure (as done in biomonitoring programs; see the excellent general discussion on biomonitoring provided by Paustenbach and Galbraith 2006) because such markers would be present at concentrations far below those that are detectable and impossible to distinguish from natural background and variation. For the time being, gross estimates of exposure can only be derived indirectly from empirical environmental occurrence data.

For this discussion, it is important to develop a common understanding of what is meant by "drinking water." The published research literature is often confusing because it uses this term interchangeably when referring to "source" waters (an example being "terminal reservoirs" that serve as drinking water sources), finished or polished distributed water (as it leaves water treatment facilities), and POU water. With regard to human exposure, however, it is really only the latter that is pertinent. Nearly all monitoring data purported to apply to "drinking water" actually derive from source waters, which commonly undergo further treatment prior to potable use, rather than from POU drinking water. These important distinctions are often not made clear in the literature. POU concentration data are extremely limited worldwide, with even fewer data available for the U.S. Note, however, that special cases must be acknowledged, where drinking water can be contaminated with abnormally high levels, such as with well water that might be subjected to only nominal treatment before drinking (for example, depth filtration) and which has been contaminated by leaching from septic systems or abandoned landfills.

The knowledge required for eventually assessing whatever risks might exist for ecological exposure to trace levels of pharmaceuticals is more extensive than for assessing risks posed to humans. Although the first paper to address the issue of human exposure was published nearly a decade ago (Christensen 1998), few risk assessments (or even discussions of risk) have been published with regard to drinking water exposure, and these rather rudimentary studies have been based on extrapolations from the comparatively high doses required for therapeutic effects or "safe" therapeutic doses such as acceptable daily intakes (ADIs), which are orders of magnitude higher than the levels that could possibly impart less obvious, perhaps subtle, non-therapeutic effects (e.g., diminution in learning or behavioral alterations). These initial studies include those of Jones et al. (2004, 2005), Schulman et al. (2002), Schwab et al. (2005), and Webb et al. (2003). These approaches use predicted no-effect concentrations determined for each pharmaceutical under consideration. These values are then compared with measured (or predicted) environmental concentrations. Using this extrapolative approach, risks have generally been ruled out for human exposure via drinking water.

Although advances in analytical chemistry have made possible the detection of many drug residues in the environment at individual concentrations of roughly 1 ng/L, these analytical tools are still insufficient for comprehensively identifying and rigorously quantifying the entire universe of pharmaceuticals that might exist in drinking waters or as unintended residues in foods — residues that the consumer should have no reason to expect. Even more difficult is trace-level determination of the unknown numbers of bioactive transformation or degradation products pre-existing from drug usage (e.g., bioactive metabolites) or newly created in drinking water; disinfection by-products from drugs themselves are one example of the latter. The trace residues of pharmaceuticals that remain after treatment of sewage, for example, are usually further removed during later treatment to create finished potable water. The concentrations in drinking water, therefore, can be one or more orders of magnitude lower yet than in source waters. These concentrations challenge the most advanced detection methods currently used by environmental chemists. The analytical wherewithal to implement routine monitoring of drinking waters simply does not yet exist. The little that is known of the occurrence of pharmaceuticals in drinking water represents an unknown portion of the overall exposure picture. Knowledge of unintentional food residues that are derived from the ambient environment is practically non-existent. A databank on drug occurrence in drinking waters simply does not exist. A first step toward establishing such a database is shown in Appendix A (*Environmental Pharmaceutical Residues Leading to Human Exposure via Ingestion*).

Human Exposure - Its Scope

The scope of the human exposure to pharmaceuticals from the environment is a complex function of the: (i) numbers, types, quantities, and geographic usage patterns of human and veterinary pharmaceuticals; (ii) pharmacokinetics of each human and veterinary drug and how these metabolic processes contribute to drug excretion (together with bioactive metabolites) from humans and animals; (iii) direct disposal of unwanted, unused pharmaceuticals to sewerage and trash; (iv) partitioning of the excreted chemicals to environmental compartments that then serve as reservoirs for recycling back to humans (including recreational and drinking waters – municipal, wells, and bottled – sewage sludge, plants, and animal food sources); (v) structural transformation, including excreted bioactive metabolites (or radiological decay products), those formed in the environment from degradation or natural transformation processes (hydrolysis, photolysis) [the numbers of transformation products can greatly add to the scope of these chemicals in the environment, as some pharmaceuticals yield a plethora of products (carbamazepine is one example; see Miao and Metcalfe 2003)], or those formed during waste or water treatment, such as disinfection by-products (e.g., quinones from the chlorination of water containing acetaminophen; see: Bedner and MacCrehan 2006); and (vi) eventual unintended, unexpected human contact with environmental residues in various compartments (via oral ingestion, inhalation, or dermal contact, such as via potable and recreational waters).

Human exposure is but one part of the much larger, overall issue of pharmaceuticals as environmental contaminants (see Figure 1 for a detailed perspective). Exposure is an extremely complex process, one that yields an effect only when a wide spectrum of processes happen to be suitably coordinated spatially and temporally so as to perturb the homeostasis mechanisms of an organism; this is embodied in the concept of the 4Ts: toxicant, totality, tolerance, and trajectory (Daughton 2005). With respect to "totality," it is important to remember that environmental pharmaceutical residues are but one of many classes of anthropogenic and naturally occurring

stressors. But isolating one stressor class from all others in order to assess risk has long been a necessary step in attempting to simplify an otherwise overwhelmingly complex task.

Human Exposure - the Major Unanswered Questions

Of all the aspects of assessing the significance of pharmaceutical residues in the environment, one aspect has received far less attention than the others — human exposure. The research currently underway in assessing human risk is minimal, probably because it is perceived as minimal at best. The data gaps and uncertainties that are apparent from the very limited data regarding human exposure to the recycling of pharmaceuticals from the environment, and from exposure via leftover drug waste awaiting disposal, involve the following key questions and uncertainties:

(1) Knowledge covering the scope of pharmaceutical occurrence in point-of-use drinking water and in foods is extremely limited. This includes the numbers of distinct active ingredients (and their degradates), their frequency of occurrence, distribution across geographic locales, and their individual or combined concentrations; even the existing, limited POU occurrence data (Appendix A) had never before been compiled in a single, publically accessible database.

(2) Toxicological significance of long-term human exposure (including generational and cross-generational) to multiple pharmaceuticals, simultaneously or sequentially, at concentrations that yield ultimate tissue doses many orders of magnitude below therapeutic doses. Knowledge of drugs having the potential to impart effects at extremely low doses (e.g., nM-pM range and below) is extremely sparse. Also, the significance of dose-dependent transitions in mechanisms of toxicity (resulting in multi-phasic dose-response curves) could prove important. Effects at low concentrations may not be predictable from higher concentrations. Even if detectable, subtle effects may not be distinguishable from natural variations in populations; in which case, one can ask if they are even important. Simultaneous exposure to multiple drugs, each significantly below its individual "safe" level, could result in combined action as a result of additive or interactive effects. Potential for interactions with other chemical stressors adds yet another layer of complexity. Exposure to multiple pharmaceutical residues can occur simultaneously or sequentially, as it can for many other chemical stressors (many of which have yet to be characterized) such as algal toxins, pesticides, disinfection by-products, a broad spectrum of other regulated and unregulated inorganics and organics, and radionuclides. These unknowns challenge the outer envelope of modern toxicology, even for legacy pollutants.

(3) Prevalence of cumulative and aggregate exposure. What portion of overall exposure to pharmaceuticals derives from environmental exposure versus therapeutic exposure? But even though exposure to ambient residues is many orders of magnitude lower than exposure to therapeutic doses, individuals are rarely exposed to the vast majority of pharmaceuticals via intentional therapy.

(4) Sub-populations that could be vulnerable to low-level exposure (e.g., during windows of vulnerability, including susceptible life-stages such as fetuses, infants, and elderly, those who are health-compromised, or those with certain polymorphisms, extraordinary allergies or "multiple chemical sensitivity" — Toxicant-Induced Loss of Tolerance, TILT). This is especially important for sub-populations exposed to drug residues that they would otherwise never

encounter, such as those drugs that are contraindicated for certain life stages or medical conditions.

(5) Approaches for prioritizing individual drug entities (or combinations) with respect to greatest human hazard in order to better target monitoring efforts — "measure only what needs to be measured." This is important since it is not known if those few pharmaceuticals (among the thousands in active use) that have been routinely identified to date during environmental monitoring surveys or research studies truly represent the ones that are most commonly present or that pose the greatest hazard.

(6) Portion of pharmaceutical residues in drinking water and foods that originates from disposal of unwanted medications to the environment versus the portion emanating from excretion and bathing. Data that distinguish between the two sources are needed to justify (on environmental grounds) adoption of a nation-wide approach for dealing with unwanted medications. The fraction contributed by disposal might vary: (i) among individual drugs or classes of drugs, (ii) between OTC and prescription drugs, or (iii) among packaging types (e.g., bulk bottles versus blister packs).

(7) Portion of human poisonings resulting from accidental ingestion and from abuse of diverted drugs that are perpetually stored (and which could potentially be averted by timely and proper disposal of unwanted or over-prescribed medications), awaiting disposal, or that go unused because of poor patient compliance (adherence). Supporting data could point to the need for modified prescribing and dispensing practices as well as improvements in patient compliance (all to minimize the need for drug storage and consequent disposal).

(8) Altering the way in which risk is perceived in order to make it comport with actual hazard. This is critical for fostering widespread public acceptance of water recycling and re-use (see Daughton 2004).

(9) Do trace levels of antimicrobials in the aqueous environment (or the higher levels in biosolids) exert any selective pressure on development of resistant bacteria, viruses, or other microorganisms outside the body, in particular those that can play roles in human disease?

The needs outlined under 2 and 5 above, especially those related to low-dose effects and effects from exposure to multiple stressors, are particularly amenable to addressing through toxicogenomics; see Oberemm et al (2005) for an overview.

Possible Outcomes from Filling Data Gaps

Successfully addressing the unknowns surrounding these key unanswered questions could eventually lead to the following major outcomes:

- Human exposure to pharmaceuticals recycled from the environment (via drinking water and foods) is reduced, minimized, or eliminated.

- Consumer health and safety is improved by reducing the quantities and durations that unused, unwanted, leftover drugs are stored and which would otherwise serve as a source of accidental and purposeful human poisonings.

- Healthcare expenses are reduced, by implementing improvements in prescribing and dispensing practices as well as with education to improve patient compliance — all to minimize drug storage, minimize leftovers, and the consequent need for disposal.

- Widespread public acceptance of water recycling/reuse is facilitated. This is critical, as the need for water reuse continues to escalate.

- More effective approaches (e.g., by involving social scientists) are developed for effectively communicating all types of risk to the public. Even if comprehensive occurrence data for drugs in water and foods could be obtained, in the absence of a sufficient understanding of the toxicological ramifications of such chronic exposure, our ability to evaluate the risks (if any) and to convey these risks to the public will pose major challenges (e.g., see: Paustenbach and Galbraith 2006). Indeed, this is the most significant problem facing the growing implementation of human biomonitoring studies for chemical contaminants (NRC 2006) — namely, what do the data mean?

Human Exposure Routes

There are two primary routes leading to human exposure of non-therapeutic or recreational drugs: (1) ingestion of ambient residues by way of their recycling from the environment (via drinking water and foods), (2) and ingestion of leftover drug waste (accidental and purposeful). When considering these routes, the following factors become important to understand.

Critical aspects of human exposure: Exposure to trace residues of drugs from the environment highlights some of the major challenges facing both environmental and human toxicology today. There are many questions but few answers. These consumer chemicals epitomize the importance of:

(i) assessing cumulative exposure (all chemicals sharing the same mode of action; this is possibly important, for example, with co-exposure to drugs from the same therapeutic class);

(ii) aggregate exposure (combined source contributions; multiple exposure routes for the same drug; such as residues of the same drug occurring in municipal drinking water, bottled water, and in a variety of foods);

(iii) better understanding of the possibility of pharmaceuticals eliciting low-dose effects (nM-pM and lower), and the ramifications of complex mixture interactions (e.g., synergism and antagonism), delayed on-set effects (e.g., epigenetic), idiopathic environmental intolerance (e.g., via immune mediated hypersensitivity or the phenomenon of multiple chemical sensitivity, such as TILT [toxicant-induced loss of tolerance], Winder 2002), and dose-dependent transitions in the mechanism of toxicity. The last refers to shifts in the mechanism (or mode) of action for a chemical stressor over the continuum of dose. This phenomenon has numerous causes (comprehensively summarized by Slikker et al. 2004a,b). Its significance is that the endpoint of interest at a high dose might mask,

obscure, or prevent a completely different endpoint for a lower dose. This means that the therapeutic endpoint may be irrelevant with regard to low doses such as those incurred from the environment; an exception is for those drugs where the therapeutic dose exists beyond a toxic dose, such as for some of the chemotherapeutics and possibly for radiologicals;

(iv) related to item (iii), understanding the potential significance of "paradoxical" dose-response at low levels (e.g., hormesis, or "U"-shaped dose response curves); a particularly germane mass of literature has already been synthesized by Calabrese and coworkers on the historically controversial dose-response phenomenon known as hormesis, e.g., see BELLE 2006]);

(v) identifying sensitive sub-populations (e.g., unexpected effects resulting from individual susceptibilities such as those dictated by polymorphisms specific to ethnicity or gender, or by health status or age). As an example, the endogenous levels of sex steroids in children have possibly been overestimated. Children therefore may be more sensitive than previously believed to exogenous steroid at levels that currently cannot be detected (Aksglaede et al. 2006); pharmaceuticals designed specifically for one sub-population may have effects at much lower concentrations in other non-target sub-populations (e.g., gender- or age-specific pharmaceuticals);

(vi) over-relying on models. Actual incidental exposure concentrations may deviate significantly from those predicted by models. For example, actual concentrations can differ between geographic locales as a result of differences in variables such as local prescribing practices or customs, or unusual/substandard water supply or treatment practices that result in higher-than-usual residues in treated water (Daughton 2003a); and

(vii) developing more effective ways to communicate risk and alter the way in which risk is perceived (critical with respect to consumer acceptance of water re-use projects; Daughton 2004).

An overlooked aspect of prioritizing pharmaceuticals for assessing risk is the toxicological significance of those pharmaceuticals having no inherent toxicity of their own but which can potentiate the toxicity of other stressors. Such indirect toxicants include inhibitors of efflux pumps or multi-drug transporters, and modulators or disruptors of P450 and the cellular stress response (Daughton 2005), or immunosuppressants that lead to increased rates of infection.

Ingestion of trace residues originating in the environment: The first major route of exposure is ingestion of trace residues that have entered the environment and persist as contaminants in drinking water or have been assimilated into foods. While this route holds the potential for chronic, simultaneous exposure (cumulative and aggregate) to very low levels of drugs, its full scope, extent, and significance is poorly understood, mainly because of (i) the analytical difficulties in analyzing polished drinking waters and foods for such low concentrations (ng/L and lower) of a wide spectrum of possible analytes (most of which are relatively polar), and (ii) the toxicology of chronic human exposure to low-level mixtures is poorly understood. It is important to note that part of the scope of this exposure route also includes the environmental degradates and transformation products, as well as excreted human metabolites. Some of these chemicals possess significant biological activity themselves; some are even the actual therapeutic entity or are responsible for adverse effects when used therapeutically. This exacerbates the overall complexity of the problem, especially since transformation products are generally not the current targets of environmental monitoring.

Drinking water as a source of exposure: Appendix A (*Environmental Pharmaceutical Residues Leading to Human Exposure via Ingestion*) compiles the majority of data published (as of January 2007) for the occurrence of pharmaceuticals in actual drinking water – both "raw" and polished (finished). "Raw" drinking water pertains to the water as it enters a treatment regime (if any) at a drinking water facility; note that exposure via drinking water includes not only municipal drinking water but also private well water as well as commercial bottled water (e.g., see: Perret et al. 2006). Necessarily excluded from Appendix A are occurrence data for ambient-environment waters (for example, the source waters as they exist in drinking water reservoirs) that have not yet been drawn into a drinking water treatment system. The rationale is to include only those data that are most closely relevant to actual point-of-use human consumption. **It is important to recognize that extremely few monitoring studies or surveys have ever been attempted for actual point-of-use waters — that is, those waters as they are drawn from a household plumbing fixture**. Data from other countries are included (when appropriate) because the data specific for the U.S. are so limited. A substantial amount of negative occurrence data exist in the literature. While these "data of absence" are valuable for drawing conclusions concerning those drugs that are less likely to occur in drinking water, only a few have been captured in this compilation. Purposefully omitted from this compilation are studies resulting from special instances, for example, where drinking water sources are unusually contaminated by drug residues. An example is ground waters highly contaminated by leachate from defective or abandoned landfills or manufacturing wastes; these types of data do not represent the norm with respect to drinking waters.

The available data (as of early 2007) show that the number of APIs and bioactive metabolites that had been detected above their quantitation limits in finished drinking waters was roughly 45 (see Appendix A). Generally, their concentrations tend to be less than 1-10 ng/L, some in the 10-100 ng/L range, and a few in the range of hundreds of ppt (sub-ppb), such as: carbamazepine (258 ng/L max, Stackelberg et al 2004), ibuprofen (930 ng/L: 120 ng/L mean, Loraine and Pettigrove 2006), ibuprofen methyl ester (4,950 ng/L: 330 mean, Loraine and Pettigrove 2006), and triclosan (734 ng/L: 49 ng/L mean, Loraine and Pettigrove 2006). Note that in order to compare the potential for biological effects between drugs, mass concentrations need to be converted to molar concentrations, especially for drugs of wildly disparate molecular weights. Environmental scientists tend to report concentrations on the basis of mass, whereas pharmacologists and those in the life sciences focus in molarity. Probably a larger number of instances have been reported where certain drugs could not be detected above their quantitation limits — data of absence; some of these data are also shown in Appendix A. Of significance, however, is that even the combined numbers of those targeted by analysis (those above and those below their limits of quantitation) represent but a small fraction of those hundreds of drugs that are used most routinely and an even smaller fraction of the thousands in use commercially. The diversity and magnitude of the commercial market for human pharmaceuticals is provided in a discussion by Daughton (2007); these figures do not include the very large amounts of certain drugs (such as antibiotics) used in agriculture.

Worth noting is that of the chemicals listed in Appendix A, the endogenous steroids (e.g., estradiol, estrone, progesterone, testosterone) are included because they are also used in certain pharmaceutical formulations, for example hormone replacement therapies. The concentrations of these steroids in the environment originate from both natural, endogenous synthesis and from therapeutic administration (oral and dermal). Furthermore, with the steroid biosynthesis pathway

(with all of its branches and interconversions), the administration of a therapeutic steroid drug leads to the synthesis of its pathway metabolites — metabolites that would not have been produced (or would not have reached their new concentrations) had the drug not been administered. This further complicates the issue as to whether sex steroids in the environment result from "natural" processes or from pharmaceutical therapy.

With respect to these empirical occurrence data, it is critical to recognize that published data on drug occurrence can be inherently biased. Bias occurs because new target-based monitoring studies often use the positive occurrence data from prior studies as the basis for selecting their targets (partly in order to increase the chances of collecting positive occurrence data). The data for a given pharmaceutical may also not be representative because of the probability of very high spatial and temporal fluctuations in sewage effluents. The probability is high that samples are taken during transiently high or low concentrations. Discrete samples (e.g., grab samples) will not necessarily represent average concentrations. But the greater mixing achieved during transit from time of uptake until drinking water treatment would possibly serve to smooth these fluctuations, reducing their impact on concentration variability.

A particular group of pharmaceuticals with little monitoring data or assessment of potential risks comprises the low levels of radionuclides used in a growing number of diagnostic procedures, and the higher levels of certain radionuclides used in medical treatments. One example is metastable technetium (Tc-99m). While Tc-99m has a short half-life (6 hours), its progeny, Tc-99, is much longer lived and can accumulate in receiving waters after excretion. Other radionuclides, used in much larger amounts, are iodine 131 and samarium 153.

Alternative approaches for assessing drinking water contamination are possible by using the occurrence of certain drugs as indicators of the likely presence of other drugs. One example is the use of occurrence date for iodinated X-ray contrast media. These diagnostic pharmaceuticals are used in very high quantities and are excreted unchanged. They are also among the most refractory to removal by drinking water treatment technologies (especially including oxidation and sorption by activated carbon). Therefore, if X-ray contrast media are present in the feed for drinking water but absent from the treated (polished) water, this could be an excellent indication that most other pharmaceuticals should also be absent (e.g., Bruchet et al. 2005).

Highly conservative assessments show extremely low risks from incidental mixture exposures: In the inadvertent, incidental exposure of humans to APIs (active pharmaceutical ingredients; also known as pharmacons) via drinking water and food, the risks ordinarily deemed as acceptable for doses needed to achieve therapeutic outcomes do not apply, because the doses resulting from these ambient exposures are orders of magnitude lower. Furthermore, those experiencing incidental exposure (beyond their control or knowledge) are not necessarily presuming that they are receiving any benefit. For these people, the so-called "nocebo" effect might even apply (Daughton 2004). Consequently, the use of benchmark therapeutic doses of APIs for assessing the risks of incidental exposure are not applicable. A more conservative approach is therefore required.

One possible conservative approach for roughly estimating the risk associated with incidental ingestion of environmental API residues recycled back via water and food would be to calculate the numbers of APIs that could be ingested on an ongoing lifetime daily basis without exceeding

a predetermined non-therapeutic acceptable daily intake (ADI). Note that the complicating issue of bioconcentration is not a factor with most pharmaceuticals, as this is a design property purposefully avoided for most human medications; also note that dermal exposure to environmentally recycled APIs is probably not an issue because most APIs have poor dermal transport. The problem is in defining sufficiently conservative ADIs (especially if they must be individually determined for each API). An approach that could be broadly applied across nearly all APIs would be most useful for providing a rough but highly conservative assessment of the potential for human risk due to ongoing exposure to multiple APIs.

Because of a lack of data, it is not possible to assume the worst-case but highly improbable scenario — namely, synergistic interactions among the APIs. But another conservative assumption — namely that of dose additivity — can be easily considered for ALL of the APIs as representing a very adverse scenario. By selecting an adverse endpoint such as genotoxicity, one can estimate the number of APIs to which continual exposure can be sustained and for which the lifetime excess cancer risk is limited to the upper bound of 1 in 10^5 to 10^6; this is the approach used for assessing risk from impurities introduced in drug manufacturing or from the degradates resulting after manufacturing. The Threshold of Toxicological Concern (TTC) for carcinogens, based on lifetime exposure, is accepted to be roughly 1 µg/day (except for very highly potent carcinogens) (see: Dolan et al. 2005; McGovern and Jacobson-Kram 2006; Müller et al. 2006). These levels of exposure are considered "virtually safe" (or to pose "reasonable certainty of no harm") for carcinogens; background on the history behind the TTC is provided by Barlow et al. (2001).

For some perspective on the risk associated with the 1-µg/day TTC, consider one of the best-known naturally occurring toxicants. Aflatoxin B1, a ubiquitous mycotoxin naturally occurring especially in grains, is a potent human carcinogen. The FDA action level in human food is 20 ppb for total aflatoxins, with the exception of milk, where the action level is 0.5 ppb for aflatoxin M1 (an aflatoxin metabolite); a dosage of 1-µg/day for total aflatoxins would be reached upon consuming 50 g of grain that just meets the FDA action level.

Although the possibility exists that the thresholds could be lower for other endpoints such as allergenicity or neurologic, immunologic, endocrine, or developmental toxicity, data show that these TTCs are probably at least one order of magnitude higher (Barlow et al. 2001) than for genotoxicity. **If it were assumed that *ALL* APIs act as genotoxicants, and that the nominal concentration for any given API present in POU drinking water in the U.S. were assumed to be upwards of 10 ng/L (this number would need to be refined after expansion of the limited occurrence data; see Appendix A), and the water intake per day were assumed to be 2 L (Webb and Ternes 2003), then the number of APIs that could be simultaneously present on a perpetual basis but remain below the TTC, would be 50 (TTC 1,000 ng/day × L/10 ng × day/2 L).**

With this relatively worst-case scenario, we see that upwards of 50 APIs could be perpetually present in drinking water while maintaining the lifetime excess cancer risk at less than 10^{-6}. Since only a few APIs have ever been identified as occurring simultaneously in given POU drinking waters, and if the assumption is made that exposure to a multitude of APIs occurs only infrequently (because of their episodic release to the environment), then the TTC increases to 120 µg/day (for exposures less than 1 month; Müller et al. 2006). The number of APIs that

could be safely present at individual concentrations of 10 ng/L increases to 6,000, a number that clearly would never be reached under any condition. Furthermore, the TTC of 1 µg/L is a rough estimate for compounds that are "likely to be carcinogenic". Since this does not broadly apply to APIs (with the exception of some chemotherapeutics), the more relevant TTC would be 10 µg/L for compounds that are "likely to be potent or highly toxic" or 100 µg/L for those that are "not likely to be potent, highly toxic or carcinogenic" (Dolan et al. 2005). This would allow the acceptable exposure concentrations of APIs or their total numbers to increase another 1-2 orders of magnitude. Numbers this high would not even be very sensitive to highly conservative uncertainty factors.

Another factor to consider regarding human exposure to APIs is that the ADI in a therapeutic setting is necessarily a direct function of the therapeutic dose, which in turn is a function of potency. This means that if the amount of an API entering the environment exceeds that of others, it also means that its ADI is very possibly higher (assuming similar pharmacokinetics). Predicted environmental concentrations (PECs) are therefore inversely related to potency. So the risk can be considered "self-leveling". This contrasts sharply with industrial chemicals, for example, whose usage rates have much less connection with potencies.

In general, the finding of low risk to humans posed by pharmaceutical residues in drinking water is corroborated by the published literature, albeit limited. This is also the official position of the Pharmaceutical Research and Manufacturers of America (PhRMA; Buzby 2006).

With these points in mind, however, we cannot conclude that the absence of any evidence for adverse human effects from extremely low-level exposure to pharmaceuticals eliminates cause for concern. There are simply too many unknowns facing toxicology today. This is articulated by Grandjean (2005): "Toxicology has failed the purpose of science in society by striving to reach only the limited goals of solving simplified riddles and in recognizing, rather than exploring uncertainty. By ignoring the larger perspectives of chemical causation of disease, it has failed its responsibility to contribute to the foundation of disease prevention."

Moreover, the possibility for adverse human health effects at the extremely low levels of ambient drug residues hinges in part on the meaning of the so-called "no-observed-effect level" (NOEL), which is the maximum concentration of a chemical stressor known to produce an "observed" adverse effect. The key word is "observed". The endpoint measure for the effect is one that is either anticipated or subsequently observed during testing. Necessarily, the NOEL can change with the revelation of new effects never previously observed at concentrations below the established NOEL. This is especially germane to effects that are sufficiently subtle that they cannot currently be anticipated or revealed using current testing protocols. One example of a phenomenon that can confound the interpretation of low-level effects is hormesis. The possibility that hormesis (non-random biological activity below the NOEL) is a widespread phenomenon is becoming clearer with closer re-examination of classic dose-response studies, where it is seen that a threshold-like model for dose response may not hold (Calabrese et al. 2006).

Knowledge gained from epidemiology: Another source of potential information for assessing human exposure derives from certain previously conducted epidemiological studies. These studies have compared populations consuming water derived at least in part from sewage after

varying degrees of treatment. Those studies designed around water reuse projects are particularly germane. The studies on water reused for drinking are few (less than a dozen) and largely conclude that neither microbiological nor chemical contaminants have led to any overt, adverse health effects, although the incidence of certain health problems has been elevated in some of these studies (DHH\PD 2001; NRC 1998). While no adverse health effects in communities using reclaimed water have been documented to result from non-microbiological contaminants, it is important to note that these studies had to use as controls populations relying on conventional sources of water. This approach is therefore obviously insensitive to detecting potential effects resulting from contaminants shared by both types of water supplies. A recent study, among a number of others preceding, found no evidence for an association between partially wastewater-derived drinking water and breast cancer in a locale with a higher-than-predicted incidence of breast cancer (Brody et al. 2006).

Complexities of low-level multiple exposure — the potential for mixture effects: Studies examining the potential for effects from simultaneous exposure to low individual concentrations of pharmaceuticals are rare, even for non-human targets. Studies designed for revealing human risks have only just begun, the first being published in 2006 (Pomati et al. 2006). This study is the first to examine (using an effects endpoint relevant to humans) the important issue of mixture effects with regard to pharmaceuticals. The study used a mixture comprising "near"-real-world concentrations of drugs from disparate therapeutic classes: atenolol, bezafibrate, carbamazepine, cyclophosphamide, ciprofloxacin, furosemide, hydrochlorothiazide, ibuprofen, lincomycin, ofloxacin, ranitidine, albuterol, and sulfamethoxazole. The concentration of each drug by itself was insufficient to impart measurable effects for the endpoint — several aspects of the growth of human embryonic cells — but the mixture could. Although the concentration of each component was probably somewhat higher than what exists in the environment (but still in the ng/L range, sub-ppb), the actual number of drugs in the mixture (roughly a dozen) may better represent reality. Note, however, that it is not known whether these concentrations in cell culture, while reflective of drinking water concentrations, would mimic the actual concentrations that would be available to cells in a human.

Ingestion of waste medications: The second route to human exposure is intimately related to the accumulation and storage of unused, unwanted medications by consumers and other end-users, as a prelude to disposal. Leftover drugs constitute household waste. Many other sources of stockpiled unwanted drugs also exist and serve as potential sources of acute exposure for humans; these are presented in a comprehensive flow chart prepared by Ruhoy (2007). Once medications accumulate unused and unwanted by the consumer, they become chemical waste and therefore represent an exposure route outside of their intended use in medical therapy. That portion of the leftover drugs which is immediately disposed to sewerage constitutes one of the principal sources for environmental residues — excretion being the other major source. That portion of leftover drugs not immediately disposed, but rather stored in the household or other locations, as well as that portion discarded to domestic trash, is subject to diversion (use by those for whom the medications were not prescribed). Drugs discarded to curbside trash or municipal landfills can be reclaimed and re-used by those who scavenge for them (e.g., human "gleaners"); some landfills also practice manual sorting, where the presence of discarded drugs could be readily revealed. Drug diversion of controlled substances is a major concern of the U.S. Drug Enforcement Administration (DEA) and the White House Office of National Drug Control Policy (White House 2007).

Waste medications serve as a principal source of acute human exposure, leading to substantial morbidity and mortality as a result of their purposeful ingestion by those for whom they were not intended (e.g., recreational drug users, drug abusers) or as a result of unintentional or accidental ingestion, for example by infants, toddlers, children, and the elderly (APCC 2005). The relatively large problem of acute drug poisonings, some of which results directly by inappropriate storage of waste pharmaceuticals, represents an intersection of the domain of human health and safety with that of environmental protection. Measures to protect humans from drug poisonings will also serve to protect the environment. Storage of waste drugs in domiciles (as well as a broad spectrum of other places; Ruhoy 2007) is a major source of drug diversion. The growing prevalence of teen "pharming" is one example of diversion, and scavenging domestic refuse is another.

Another means that consumers sometimes employ for dealing with leftover drugs that would otherwise be destined for waste disposal is the practice of reusing drugs by providing them to another end-user. While not always legal (e.g., for prescription medications) or medically prudent, reuse (also called drug "sharing") is usually accomplished by donation to charitable organizations or by sharing with family and friends. Drug "sharing" probably does not play a significant role as an added source of environmental residues, but it does pose substantial acute risks with regard to human health and safety. Drug sharing is a practice that continues to grow as a result of the public's frustration with not being able to make use of drugs that one person no longer wants or needs but which another person does (e.g., Strom 2005). Both consumers and physicians sometimes practice it as an alternative to disposal. The practice of self-medication is hazardous itself and is responsible for a large percentage of hospitalizations from adverse drug responses (e.g., wrong drug, wrong dosage). With respect to charitable drug donations, it is worth noting that the World Health Organization and other international organizations involved with humanitarian relief now discourage the donation of drugs during relief efforts because of the high prevalence of inappropriate, unuseable, or expired drugs (Daughton 2007, in press). Extremely large quantities of donated drugs accumulate on site and create large financial burdens (for warehousing and disposal) as well as opportunities for diversion.

Currently, the only aspect of pharmaceuticals (outside their intended use) known to directly impact human morbidity and mortality is their substantial contribution to accidental and purposeful poisonings (AAPCC 2005). One of the factors determining or encouraging inappropriate or undesired access to drugs is the prevalence of improper storage or misguided attempts at disposal, which are in turn caused by the accumulation of leftover drugs. Many factors lead to the unnecessary storage of unwanted pharmaceuticals in domestic residences. Poor levels of adherence (compliance) by patients to prescribed medication regimes is one of the major factors leading to the accumulation and eventual expiration of unused drugs in the household. Adherence to prescription regimes is an issue of great importance to healthcare. Its causes are many and complex (e.g., see: Kenreigh and Wagner 2005). A variety of ways to improve compliance, ranging from simple to technologically sophisticated, currently exist or are under development (e.g., see: Ukens 2005).

Once the consumer has accumulated a certain number of unwanted or unuseable medications in the home, the quandary of disposal is confronted. Conflicting needs and motivations make disposal of pharmaceuticals a confusing issue in the U.S., where national take-back programs do not exist. Water treatment facilities increasingly no longer want drugs unnecessarily discharged

via sewers, while at the same time, poison control centers have long-advised against discarding them to trash and have always recommended discarding to sewerage (since this is historically the easiest means available for protecting humans and pets from accidental and purposeful poisonings). Drugs discarded to municipal trash/landfills pose not just potential future environmental exposure risks but also ongoing risks with regard to re-use by those who scavenge for them (e.g., human "gleaners" or animal scavengers). Discarding to sewerage, in contrast, is the surest simple means (currently available) for preventing drug diversion. With these conflicting issues aside, the U.S. issued its first public guidance for drug disposal in February 2007 (The White House 2007): "Unless stated otherwise on the label, proper disposal methods include intermingling drugs with undesirable substances ... and depositing them in the garbage or bringing the drugs to a community pharmaceutical take-back or solid waste program. Unless otherwise directed, prescription drugs should not be flushed down the toilet due to the risk of contaminating water sources."

Ingestion of ambient environmental residues incorporated into foods: Drinking water is not the only source of human exposure to ambient environmental residues of drugs. Another source is food contaminated by uptake of ambient residues from the environment. These residues are not expected by the consumer to be present, in contrast to residues from those drugs approved for use during the commercial production of food. Ambient residues can be concentrated in the tissues of aquatic organisms and taken up by food crops that have been irrigated with reused water or amended with sewage biosolids. A screening study targeting 24 pharmaceuticals in the tissues of fish and clams from an effluent-dominated stream revealed residues of 13 at levels up to 80 ppb in muscle and liver (Chambliss et al. 2006). Residues resulting from aquaculture would not be part of this consideration because they result from the purposeful, approved use of drugs. The occurrence of non-therapeutic biocides not intended for ingestion (e.g., triclosan and triclocarban) in human breast milk (Adolfsson-Erici et al. 2002) points to the possibility of this route occurring for lactating women exposed to environmental residues of drugs.

With regard to human exposure, of potential significance is that veterinary drugs and human drugs comprise sets that have little overlap. Human exposure to residues from veterinary drugs from any inadvertent, unintended consumption (e.g., via foods) may have less predictable consequences than exposure to human drugs.

Potential sources for human exposure to ambient residues include not just drinking water and the well-known but less publicized routes such as domestic livestock and fish treated with veterinary drugs, but also the less-known route of edible plants. Foods can potentially become contaminated with pharmaceuticals not just by the recycling of environmental residues originating from therapeutic use in CAFOs (veterinary drugs such as antibiotics and estrogenic and androgenic steroids, for both therapeutic treatment and growth promotion), agriculture (e.g., use of antibiotics for plant disease control), and aquaculture (antibiotics for disease prevention and treatment), but also from uptake of drug residues by food crops grown on land where sewage biosolids have been applied. When biosolids from municipal sewage treatment facilities or the excrement from domestic animals treated with veterinary medicines are used on arable lands (e.g., as soil amendment or fertilizer), vegetation has the potential to remove the drug residues that partition to the soil pore water. These residues can accumulate in shoots and roots. For a limited number of targeted drugs evaluated under controlled conditions, the residues found to

accumulate in certain plants hold the potential for yielding human intakes that approach 10% of the ADIs (Boxall et al. 2006).

Aquaculture can release drugs directly to open waters (from excess medicated feed and from excreta). Aquaculture also experiences off-label and illegal usage of certain drugs (e.g., see FAO 2002), especially highly toxic antibiotics such as chloramphenicol, furazolidone, and nitrofurazone, all of whose use is banned in many countries but continues nonetheless. These released residues can be taken up by wild fin and shell fish, which can then serve as a direct human exposure route via recreational or subsistence fishing; exposure could be enhanced for those drugs known to bioconcentrate, for example in fish. For thorough background on the environmental aspects of concentrated aquatic animal production (CAAP) and the role of pharmaceuticals, refer to the materials available from EPA (2006), and in particular EPA (2004).

Another exposure route related to foods that could emerge in the future is inadvertent exposure to foods genetically engineered to produce proteinaceous pharmaceuticals — "plant-made pharmaceuticals" (PMPs) produced by "molecular farming" or "biopharming"; see Elbehri (2005) for an overview. Current transgenic biotechnology has the potential for using food crop species (primarily corn, soybeans, rice) for producing hundreds of distinct proteinaceous therapeutics (especially enzymes, hormones, vaccines, monoclonal antibodies). PMPs raise a host of questions regarding risk, primarily centered around allergenicity and toxicity in the form of direct endocrine disruption or other mechanisms — should these crops or genes enter the food supply (such as by cross-pollination of food crops) or their PMPs be released directly to the environment. Although drugs based on peptides and proteins would ordinarily not be expected to persist in the environment because they can be easily degraded or denatured, a possible exception is the cyclic peptides and circular proteins. Natural products of the former include cyclosporin (an immunosuppressant) and gramicidin S (an antibiotic); these are distinguished from the circular proteins in being synthesized by enzymatic pathways as opposed to being synthesized ribosomally. Synthetic versions of these chemicals (which cross over into the domain of self-assembling nanostructures) can be designed with broad-ranging biological activities, especially antimicrobial. The significant aspects of this class of drugs is that they resist chemical, thermal, and enzymatic alteration and therefore have the potential to persist in the environment and participate in later exposure events.

Other routes for exposure: There are several less common or unique routes by which humans can be inadvertently exposed to pharmaceuticals. These routes hold the potential for acute exposures. More than 150 drugs are formally recognized as hazardous in the occupational health care setting (NIOSH 2004); NIOSH plans to add to this list in 2007. In contrast to human therapeutic use, however, agricultural use poses concerns with regard to occupational and bystander exposure, especially by way of handling medicated feeds. One example is the inhalation of pharmaceuticals sorbed to dust particles generated by the handling of medicated feeds (Hamscher et al. 2003). Another exposure concern resulting from the use of medications with domestic animals is airborne antibiotic-resistant bacteria (Gibbs et al. 2006); indeed the genes from antibiotic-resistant bacteria are becoming to be recognized as pollutants themselves (Pruden et al. 2006).

Another example involves various ill-conceived proposals to prevent the reuse of drugs destined for disposal to trash. These proposals all increase the risk of unusual exposures for the consumer.

For example, an often recommended but ill-advised step prior to discard to trash is to render unwanted medications unsuitable for consumption by adding reactive chemicals, by heating, or by disassembly of capsules or crushing tablets and mixing with unpalatable "inerts" such as cat litter. Such procedures could prove hazardous themselves because they promote the unnecessary handling of active ingredients and can lead to dermal or pulmonary exposure (e.g., by hand contact or inhalation of dusts) or the generation of highly hazardous vapors (e.g., if denaturing chemicals, such as bleach, or heat are used). Furthermore, unnecessary handling of individual medications also increases their risk of falling unnoticed onto floors or counters from where infants and children could consume them.

An undocumented exposure route might involve inhalation of the combustion gases from incinerators employed for the ultimate destruction of pharmaceuticals (both licit and illicit) that have been collected or confiscated in large quantities (e.g., by local take-back projects or by law enforcement). Except for incinerators designed and approved for RCRA hazardous wastes, the efficiencies of other incinerators are not fully understood. Improper or insufficient incinerator conditions (especially temperature) or design could lead to the air-borne emission of unaltered parent drug entities or of toxic pyrolysis/oxidation by-products. A scenario where air-borne exposure could be substantial is with small incinerators used in humanitarian relief efforts and for on-site disposal of confiscated drugs by law enforcement; one example is the "Drug Terminator" (Elastec/AmericanMarine, 2006).

A little recognized potential route of exposure is the possibility of bodily exchange of drugs between people. A potential route by which this might occur is from the secretion of systemic drugs through the skin, from where they could possibly be transferred directly to another person by direct contact. As an example that systemic drugs can be excreted through the skin, consider the appearance of loratadine on the skin surface 40 minutes after ingesting a 10-mg oral dose of the antihistamine (Takáts 2004).

Finally, there are two routes by which acute dermal exposure can occur. First, certain medications that can be absorbed by the dermis are applied to the skin as gels or creams by use of the fingers or hand; examples are testosterone and progesterone, which are dermally applied in very high concentrations (parts per hundred). The residuals remaining on the hand are not fully removed by casual washing and can then be transferred from the hand to any surface subsequently contacted (telephones, doors, handles, etc). These residues can then be transferred to others. The second route is by contact with dermal patches that have been disposed after usage or expiry. This is especially dangerous because many of these medications tend to be very potent (e.g., fentanyl and testosterone).

Perception of exposure as a confounding factor in assessing risk: While no evidence yet exists that trace levels of drugs in drinking water pose any risk for humans, their mere presence can create a refractory obstacle to public acceptance of, and trust in, recycled wastewater. This important outcome results from the way risk is perceived, which in turn is often little influenced by factual weight-of-evidence. Traces of drugs in drinking water supplies, regardless of how low their concentrations might be, are essentially considered "out-of-place" chemicals, and as such are sometimes looked upon as "chemical weeds" by the consumer (Daughton 2005). The problem with low-level exposure has more to do with the repercussions from the way in which risk is perceived rather than overt toxicological hazard.

At the least, the occurrence of minute quantities of drugs in drinking water could cause what is known as the nocebo response (Daughton 2005) — nocebo deriving from Latin "I will harm." The nocebo effect (the opposite of the placebo effect) is a real, physiologically adverse outcome caused simply by the suggestion or belief that something (such as a chemical) is harmful, despite the absence of any inherent toxicity; a possible biochemical basis for the nocebo response was recently identified (Benedetti 2006). The nocebo effect could play a key role in the manifestation of adverse health consequences from exposure even to non-toxic trace levels of contaminants — simply by the power of suggestion and belief. Public education and a better understanding of how risk is perceived and how it is best communicated are particularly important for minimizing the incidence of the nocebo response (Daughton 2004).

Particularly germane to the concept of "chemical weeds" is the way in which the public perceives the technical concept of a contaminant's "concentration". Whereas scientists readily distinguish the enormous, orders-of-magnitude differences between ppm, ppb, ppt and other measures of concentration, the public often does not perceive these as measures of quantity, but rather as variant shorthands for the fact that a chemical is merely present — all measures of trace contaminants being essentially the same with regard to risk. For the general public, the dose is often not correlated with the potential for an effect — all doses are essentially equal. Another confusing aspect of concentration terminology can derive from the use of the "parts-per" notation, where the quantity descriptors denote relative amounts that have opposite relative sizes when used by themselves. For example, although "trillion" is 1,000 times larger than "million," it is only one thousandth the size when used with "parts-per". This can represent a million-fold discrepancy from reality for the public. So the lower the concentration of a toxicant reported using “parts-per” notation, the higher the perceived risk might be, because the focus is on the quantifiers, and the “parts-per” are simply ignored; making things even more complicated is the fact that numbers larger than 10^9 do not have the same meanings worldwide; this is why NIST does not condone the parts-per notation (http://physics.nist.gov/Pubs/SP811/sec07.html#7.10.3).

One of the ways in which risk is subconsciously framed or valued during its perception derives from a form of "logic" or valuation explained by what are known as the "common laws of magic" (e.g., see: Rozin and Nemeroff, 1990). One of these laws is the Law of Association, which in turn comprises the sub-laws of Similarity and of Contact or Contagion. The "magical law of contagion" constitutes one of the sympathetic laws of magic as introduced over a century ago by anthropologists (see: Nemeroff and Rozin 1994). Of particular relevance to drinking water as a source of pharmaceuticals, the Law of Contagion holds that once contaminated, always contaminated: "Things that have once been in contact with each other continue to act on each other at a distance even after physical contact has been severed." Once objects come into contact with each other, they will continue to influence each other, even after separation. The presence of pharmaceuticals essentially serves as a reminder that the drinking water or food was at one time in "contact" with human waste. This can lead to rejection by the consumer of recycled water for drinking (Daughton 2004; Kahn and Gerrard 2006).

As an example of the difficulty in communicating risk, consider the following hypothetical scenario. A city's drinking water generally contained about 10 ppt of each of nine different pharmaceuticals from various therapeutic classes. For those consumers drinking 2 L per day, the potential for exposure (assuming 100% absorption from the gut) resulted in doses that were roughly the equivalent of 0.0002% of the safe therapeutic dose for each drug (20-ng residue

versus 100 mg of a normal dose). Even though such an exposure would be considered safe, the extenuating factor is that the mere occurrence of the drug residues verifies that the water was derived from human waste and therefore is still "tainted". Communication of facts does not necessarily influence perception based on beliefs and fears.

Antimicrobial resistance: Of the numerous classes of pharmaceuticals, the two that have attracted the most attention as environmental pollutants are the sex steroids and antibiotics. Attention has been focused on the first because of their endocrine modulating effects on wildlife at extraordinarily low concentrations (e.g., 1 ng/L); ethynylestradiol is one example. The second has attracted concern because of the issue of selection for antibiotic resistance in human pathogens. In fact, selection for antibiotic-resistant pathogens is often highlighted as one of the major drivers for concern over pharmaceutical residues in the environment. Despite this concern, there is little evidence that the trace concentrations of antibiotic residues in most environmental settings is sufficiently high to serve as a selecting force for development of resistance; but this is an unresolved issue. The levels monitored in the dissolved aqueous environment (ppt-ppb) are orders of magnitude below those believed necessary to select for antibiotic resistance. These ambient, trace concentrations of antibiotics are insufficiently high to select for resistance whether this were to occur in the environment or in those who ingest ambient, trace residues from water. The limited data on the concentrations of certain antibiotics in biosolids, however, reveal concentrations that can be orders of magnitude higher than in the aqueous environment (100's of ppb versus ppt; e.g., see: Jones-Lepp and Stevens in press 2007; Kinney et al. 2006). At these greatly enhanced concentrations, it might be possible to select for resistance among the bacteria occurring in the biosolids.

The co-occurrence of antibiotic residues with antibiotic-resistant bacteria in environmental settings is often interpreted as causal. The tendency has been to simply note correlations between the occurrence of trace concentrations of antibiotics and the co-occurrence of resistant bacteria, leading to erroneous conclusions that the former leads to the latter. In reality, these resistant bacteria are partly introduced to the environment by their shedding from humans and animals (together with excreted antibiotics) that have been treated with therapeutic levels of antibiotics. These bacteria probably developed resistance during the therapeutic exposures, not from exposure to trace levels in the environment. Any correlation of occurrence of trace levels of antibiotics with the co-occurrence of resistant bacteria most likely results from the sloughing of resistant bacteria from people and animals receiving antibiotic therapy and from horizontal gene transfer after these enteric bacteria are shed to the environment.

Important to recognize at the same time, however, is that antibiotic resistance is also a widespread natural phenomenon due to the ubiquitous production of natural antibiotics by autochthonous soil bacteria. The phenomenon of multiple antibiotic resistance (spanning all significant therapeutic antibiotics, whether naturally or artificially synthesized) and multiple means of resistance may be widespread in the environment (D'Costa et al. 2006). It leads to questions of (1) the origin(s) of widespread resistance (whether naturally evolved as a result of allelopathic defenses or by gene transfer, or both) and (2) whether the soil domain might serve as a reservoir for the transfer of naturally acquired resistance to pathogens. Exposure to an antibiotic of one class can also select for resistance to those from other classes (multi-drug resistance, MDR) if the mechanism of resistance depends on processes with little ligand specificity (such as over-expression of efflux pumps).

It is also important to recognize that development of transient antibiotic resistance can stem not just from exposure to antibiotics, but also from a wide array of so-called "non-antibiotic" antibiotics, some of which have no inherent toxicity of their own (indirect toxicants). Examples include those pharmaceuticals that induce over-expression of the efflux pumps responsible for MDR (these include many widely used drugs, such as certain SSRIs).

The prevalence of ubiquitous "non-culturable" bacteria (often resulting from antibiotic therapy) also impedes determining the prevalence of antibiotic resistance. The many unknowns presented by the fact that most microbes are not culturable (and therefore resistance cannot be determined) is a major complicating factor. These bacteria may serve as a significant but unidentifiable reservoir of resistance genes for horizontal transfer to human pathogens. Indeed, recent studies have shown that healthy people could be the source of many of the antibiotic resistance genes that have led to the rise of "superbugs" in hospitals. One study has found that more than 90% of the harmless E. coli in the guts of healthy people are multi-drug resistant (Hall 2006). Over-expression of broad-spectrum efflux pumps, plasmid-addiction systems, and exposure to naturally produced antibiotics may conserve resistance in the absence of continued "anthropogenic" selective pressure.

Although antibiotic resistance is a major and growing human health concern, it is probably little connected with the issue of pharmaceutical residues being released to the environment as pollutants, but rather related to the imprudent use of these drugs in medical therapy. As opposed to the purported development of resistance among microorganisms exposed to trace levels of antibiotics in the environment, the more salient concern with respect to human exposure is probably the horizontal transfer of resistance genes to human pathogens. The problem is probably more related to environmental "pollution" with resistance genes rather than by antibiotics themselves.

In contrast to therapeutic antibiotics, the high-production volume, broad-spectrum biocides might pose a separate concern. Two of the major high-volume broad-spectrum biocides are triclosan and triclocarban. Whether these two chemicals select for widespread resistance to themselves (or for cross-resistance to narrow-spectrum antibiotics in the environment) is very controversial. Another concern is the possible widespread employment of antivirals, such as oseltamivir carboxylate, during epidemics (Singer et al. 2007). Excretion of antivirals resistant to sewage treatment might lead to significantly higher ambient water concentrations than for antibiotics, which are used by a much smaller percentage of the populace for everyday healthcare. These concentrations could be sufficiently high as to select for resistant viruses carried by wildlife and later subject to crossing over to humans. This is an example of indirect hazard, where the initial exposure (to a chemical) could lead to future exposure to an infectious agent. So the significance of an exposure cannot be considered outside the context of the larger picture.

Proactive Measures to Reduce Exposure

Certain measures can be implemented in the absence of additional knowledge to begin reducing or limiting human exposure. These include:

Scope of occurrence: Compared with environmental monitoring, significantly less effort has been invested in determining the extent, frequency, and distribution of pharmaceutical residues in finished (POU) drinking waters. More extensive monitoring surveys could be designed and implemented.

Status and trends monitoring: Trends data for drugs in drinking water may be the key for determining monitoring priorities relevant to human exposure. Once routine methods can be established, risk assessments might focus on those target analytes found to be trending upward in occurrence frequencies or in concentrations, or the emergence of newly approved APIs. Likewise, methods for non-target analysis could spot newly emerging drugs, triggering risk assessments. If trends data revealed the occurrence of previously unseen drugs or increasing concentrations of existing pharmaceuticals in the aquatic environment or in biosolids, then we would be positioned to take action ahead of that time when these chemicals and their quantities might prove significant. Occurrence data could also be used simply to establish baseline exposure status ("reference" ranges) instead of linking it with risk. Negative concentration trends could be useful in assessing the effectiveness of waste treatment or pollution prevention controls. Drinking water occurrence data that is representative and reproducible could also be used by the public to compare the effectiveness of water treatment among municipalities; the possible intermittent occurrence of many APIs, however, might render this approach fruitless.

Reducing real or perceived exposure via drinking water: The consumer can be proactive to further ensure that drinking water contaminants are minimized, including trace levels of whatever pharmaceuticals might still be present, by use of "point-of-use" treatment systems that install on individual water fixtures, or with "point-of-entry" systems that treat all the potable water entering a building regardless of whether it is used as drinking water; systems using reverse osmosis and activated carbon sorption are particularly effective.

References

AAPCC "Toxic Exposure Surveillance System," American Association of Poison Control Centers, web page 2005; available: TESS: http://www.aapcc.org/poison1.htm

Adolfsson-Erici M, Pettersson M, Parkkonen J, and Sturve J. "Triclosan, a commonly used bactericide found in human milk and in the aquatic environment in Sweden," Chemosphere 2002, 46 (9-10):1485-1489.

Aksglaede L, Juul A, Leffers H, Skakkebæk NE, and Andersson A-M "The sensitivity of the child to sex steroids: possible impact of exogenous estrogens," Hum. Reprod. Update 2006, 12:341-349.

Barlow SM, Kozianowski G, Würtzen G, and Schlatter J "Threshold of toxicological concern for chemical substances present in the diet," Food Chem. Toxicol. 2001, 39(9):893-905.

Bedner M and MacCrehan WA "Transformation of acetaminophen by chlorination produces the toxicants 1,4-benzoquinone and n-acetyl-p-benzoquinone imine," Environ. Sci. Technol. 2006, 40(2):516-522.

BELLE "Biological Effects of Low Level Exposures" (web site). Northeast Regional Environmental Public Health Center, School of Public Health, University of Massachusetts, Amherst, MA 2006. Available: http://www.belleonline.com

Benedetti F, Amanzio M, Vighetti S, and Asteggiano G "The Biochemical and Neuroendocrine Bases of the Hyperalgesic Nocebo Effect," J. Neurosci. 2006, 26(46):12014-12022.

Boxall ABA, Johnson P, Smith EJ, Sinclair CJ, Stutt E, and Levy LS "Uptake of Veterinary Medicines from Soils into Plants," J. Agric. Food Chem. 2006, 54(6):2288-2297.

Brody JG, Aschengrau A, McKelvey W, Swartz CH, Kennedy T, and Rudel RA "Breast cancer risk and drinking water contaminated by wastewater: a case control study," Environ Health.: A Global Access Science Source 2006, 5(1):record28.

Bruchet A, Hochereau C, Picard C, Decottignies V, Rodrigues JM, and Janex-Habibi ML. "Analysis of drugs and personal care products in French source and drinking waters: the analytical challenge and examples of application," Water Sci. Technol. 2005, 52(8):53-61.

Buzby M "Phamaceuticals in the Environment: PhRMA Initiatives," presentation for PhRMA at Emerging Environmental Issues and Policies, Mid-Atlantic States Section of the Air & Waste Management Association Technical Conference, 6 April 2006; available: http://www.mass-awma.net/files/2006-04_Buzby_Presentation.pdf

Calabrese EJ, Staudenmayer JW, Stanek III EJ, and Hoffmann GR. "Hormesis Outperforms Threshold Model in National Cancer Institute Antitumor Drug Screening Database," Toxicol. Sci. 2006, 94(2):368-378.

Chambliss C, Ramirez AJ, Mottaleb MA, and Brooks BW "Liquid Chromatography-Tandem Mass Spectrometry Screening Analysis of Select Pharmaceuticals in Aquatic Organisms Collected from an Effluent-Dominated Stream," poster 82 presented at SETAC, Montreal, 6 November 2006.

Christensen FM "Pharmaceuticals in the Environment—A Human Risk?" Regul. Toxicol. Pharmacol. 1998, 28(3):212-221.

D'Costa VM, McGrann KM, Hughes DW, and Wright GD "Sampling the Antibiotic Resistome," Science 2006, 311(5759):374-377.

Daughton, CG "Pharmaceuticals in the Environment: Sources and Their Management," In Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle (D. Barcelo and M. Petrovic, Eds.), Wilson & Wilson's Comprehensive Analytical Chemistry series (D. Barcelo, Ed.), Elsevier; in press, 2007.

Daughton CG " 'Emerging' Chemicals as Pollutants in the Environment: a 21st Century Perspective," Renewable Resources J. 2005, 23(4):6-23.

Daughton CG "Groundwater Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds," Ground Water Monitor. Remed. 2004, 24(2):127-138 ; available: http://www.epa.gov/nerlesd1/chemistry/ppcp/images/water-reuse.pdf

Dolan DG, Naumann BD, Sargent EV, Maier A, and Dourson M "Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations," Reg. Toxicol. Pharmacol. 2005, 43(1):1-9.

DHH\PD "Review of health issues associated with potable reuse of wastewater," report No. RFT200/00, Department of Health and Aged Care, Department of Health and Aged Care, Canberra, Commonwealth of Australia, 2001, 324 pp.; available: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubhlth-publicat-document-metadata-env_water.htm/$FILE/env_water.pdf.

Elastec/AmericanMarine "Drug Terminator for Disposal of Confiscated Drugs," web page, accessed November 2006; avaibable: http://www.elastec.com/drugTerminator.html

Elbehri A. "Biopharming and the food system: Examining the potential benefits and risks," AgBioForum, 2005, 8(1):18-25; available: http://www.agbioforum.missouri.edu/v8n1/v8n1a03-elbehri.htm

EPA "Environmental Impacts from Aquaculture Facilities," Chapter 7 (available: http://epa.gov/guide/aquaculture/EEBA/EEBA%20-%20Chapter%207.pdf), in "Economic and Environmental Benefits Analysis of the Final Effluent Limitations Guidelines and New Source Performance Standards for the Concentrated Aquatic Animal Production Industry Point Source Category," U.S. Environmental Protection Agency, Washington, D.C., EPA-821-R-04-013, June 2004 (available: http://epa.gov/guide/aquaculture/EEBA/index.html).

EPA "Aquatic Animal Production Industry Effluent Guidelines," web page, U.S. Environmental Protection Agency, Washington, D.C., 2006; available: http://epa.gov/guide/aquaculture/#rule

FAO "The State of World Fisheries and Aquaculture: Part 2. Selected Issues Facing Fishers and Aquaculture (Antibiotic Residues in Aquaculture Products)," Food and Agriculture Organization of the United Nations, FAO Fisheries Department, 2002; available: http://www.fao.org/documents/show_cdr.asp?url_file=//docrep/005/y7300e/y7300e00.htm

Gibbs SG, Green CF, Tarwater PM, Mota LC, Mena KD, Scarpino PV "Isolation of Antibiotic-Resistant Bacteria from the Air Plume Downwind of a Swine Confined or Concentrated Animal Feeding Operation," Environ Health Perspect, 2006, 114(7):1032–1037.

Grandjean P "Non-precautionary aspects of toxicology," Toxicol. Appl. Pharmacol., 2005, 207(2 suppl. 1:652-657.

Hall R "Antibiotic Resistance Genes on the Move," presented at the Australian Society for Microbiology Annual Conference, 2-6 July 2006, Gold Coast, QLD Australia.

Jones OA, Lester JN, Voulvoulis N "Pharmaceuticals: a threat to drinking water?" Trends in Biotech, 2005, 23(4):163-167.

Jones OA, Voulvoulis N, Lester JN "Potential ecological and human health risks associated with the presence of pharmaceutically active compounds in the aquatic environment," Crit. Rev. Toxicol., 2004, 34(4):335-350.

Jones-Lepp TL, Stevens R "Pharmaceuticals in biosolids - The Interface between analytical chemistry and regulation," Anal. Bioanal. Chem., in press 2007.

Hamscher G, Pawelzick HT, Sczensky S, Nau H, and Hartung J "Antibiotics in dust originating from a pig-fattening farm: A new source of health hazard for farmers?" Environ. Health Perspect. 2003, 111(13):1590-1594.

Kenreigh CA and Wagner LT "Medication Adherence: A Literature Review," Medscape Pharmacists, 2005, 6(2); available: http://www.medscape.com/viewarticle/514164_print

Khan SJ and Gerrard LE "Stakeholder communications for successful water reuse operations," Desalination, 2006, 187(1-3):191-202; available: http://www.desline.com/articoli/6969.pdf

Kinney CA, Furlong ET, Zaugg SD, Burkhardt MR, Werner SL, Cahill JD, Jorgensen GR "Survey of Organic Wastewater Contaminants in Biosolids Destined for Land Application," Environ. Sci. Technol. 2006, 40(23):7207-7215.

McGovern T and Jacobson-Kram D "Regulation of genotoxic and carcinogenic impurities in drug substances and products," TrAC Trends Anal. Chem., In Press, 2006.

Miao X-S and Metcalfe CD "Determination of carbamazepine and its metabolites in aqueous samples using liquid chromatography-electrospray tandem mass spectrometry," Anal Chem 2003, 75(15):3731-3738.

Müller L, Mauthe RJ, Riley CM, Andino MM, De Antonis D, Beels C, et al. "A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity," Reg. Toxicol. Pharmacol. 2006, 44(3):198-211.

Nemeroff C and Rozin P "The Contagion Concept in Adult Thinking in the United States: Transmission of Germs and of Interpersonal Influence," Ethos 1994, 22(2):158-186.

NIOSH "Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings,"September 2004, Publication No. 2004-165, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Atlanta GA; available: http://www.cdc.gov/niosh/docs/2004-165/#r

NRC "Issues in potable reuse: The viability of augmenting drinking water supplies with reclaimed water. Committee to Evaluate the Viability of Augmenting Potable Water Supplies with Reclaimed Water," Water Science and Technology Board, Commission on Geosciences,

Environment, and Resources, National Research Council, National Academy Press report; 1998; available: http://www.nap.edu/books/ 0309064163/html.

NRC "Human Biomonitoring for Environmental Chemicals," Committee on Human Biomonitoring for Environmental Toxicants, National Research Council 2006; available: http://newton.nap.edu/catalog/11700.html

Oberemm A, Onyon L, and Gundert-Remy U "How can toxicogenomics inform risk assessment?" Toxicol. Appl. Pharmacol. 2005, 207(2, suppl 1):592-598.

Paustenbach D and Galbraith D "Biomonitoring: Is body burden relevant to public health?" Reg. Toxicol. Pharmacol. 2006, 44(3):249-261.

Pomati F, Castiglioni S, Zuccato E, Fanelli R, Vigetti D, Rossetti C, and Calamari D "Effects of a Complex Mixture of Therapeutic Drugs at Environmental Levels on Human Embryonic Cells," Environ. Sci. Technol. 2006, 40(7):2442-2447.

Pruden A, Pei R, Storteboom H, Carlson KH "Antibiotic Resistance Genes as Emerging Contaminants: Studies in Northern Colorado," Environ. Sci. Technol. 2006, web release date 15 August 2006.

Rozin P and Nemeroff CJ "The laws of sympathetic magic: A psychological analysis of similarity and contagion," in J. Stigler, G. Herdt, and R.A. Shweder (Editors), Cultural Psychology: Essays on comparative human development, Cambridge, England, 1990, pp. 205-232.

Ruhoy I "Sources of unwanted, leftover drugs," flowchart prepared for Doctoral Dissertation (in preparation 2007), University of Nevada, Las Vegas, Environmental Studies.

Schulman LJ, Sargent EV, Naumann BD, Faria EC, Dolan DG, and Wargo JP "A human health risk assessment of pharmaceuticals in the aquatic environment," Hum. Ecol. Risk Assess. 2002, 8(4):657-680.

Schwab BW, Hayes EP, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, and Anderson PD "Human pharmaceuticals in US surfaces waters: a human health risk assessment," Reg. Toxicol. Pharmacol. 2005, 42:296-312.

Singer AC, Nunn MA, Gould EA, and Johnson AC "Potential risks associated with the proposed widespread use of Tamiflu," Environ. Health. Perspect. 2007, 115:102–106.

Slikker W Jr., Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, et al. "Dose-dependent transitions in mechanisms of toxicity," Toxicol. Appl. Pharmacol. 2004a, 201(3):203-225.

Slikker W Jr., Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, et al. "Dose-dependent transitions in mechanisms of toxicity: case studies," Toxicol. Appl. Pharmacol. 2004b, 201(3):226-294.

Strom S "Old Pills Finding New Medicine Cabinets," New York Times, 18 May 2005; available: http://www.nytimes.com/2005/05/18/health/18reuse.html)

Takáts Z, Wiseman JM, Gologan B, Cooks RG. "Mass Spectrometry Sampling Under Ambient Conditions with Desorption Electrospray Ionization," Science, 2004, 306(5695):471-473.

Ukens C "Staying The Course: New gee-whiz technologies are improving patients' compliance with their drug regimens," Drug Topics, 12 September 2005; available: http://www.drugtopics.com/drugtopics/article/articleDetail.jsp?id=179333

Webb S, Ternes T, Gibert M, and Olejniczak K. "Indirect human exposure to pharmaceuticals via drinking water," Toxicol. Lett. 2003, 142(3):157-167.

The White House "The President's National Drug Control Strategy," Office of National Drug Control Policy, The White House, Washington DC, February 2007 (see page 31); avaialble: http://www.whitehousedrugpolicy.gov/publications/policy/ndcs07/ndcs07.pdf

Winder C "Mechanisms of multiple chemical sensitivity," Toxicol. Lett. 2002, 128(1-3):85-97.

****
==========
****

Acknowledgments:
The assistance of H. Galal-Gorchev (EPA, OW/OST/HECD, Washington, DC) in preparing Appendix A is appreciated.

NOTICE: This document is a preliminary draft. It has not been formally released by the United States Environmental Protection Agency and should not at this stage be construed to represent Agency policy. It is being circulated for comments on its technical merit and policy implications.

NOTICE (to be added once manuscript has been cleared by EPA-ORD):

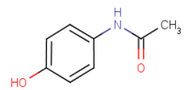
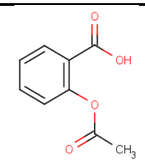
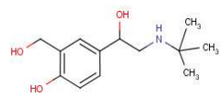
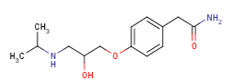
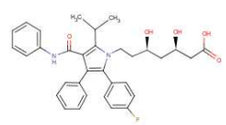
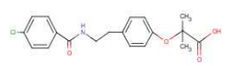
> The United States Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to Agency's administrative review and approved for publication.

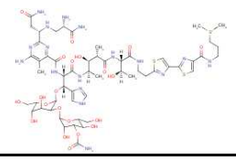
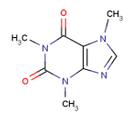
Figure 1. Environmental Life Cycle of Pharmaceuticals
(see next page)

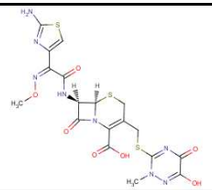
Environmental Life-Cycle of Pharmaceuticals
created by CG Daughton
US EPA, Las Vegas
2 December 2006
transformation/degradation
mineralization
stewardship opportunities
Manufacturer
Commerce distribution
Wholesalers Distributors
Agriculture (e.g., orchards)
runoff
excrement
pets
euthanized carcasses
potential for acute/chronic poisoning of wildlife scavengers
carcasses of medicated animals
physician samples
Physicians
Feedstores
Vet use
domestic animals
airborne dusts (e.g., medicated feed)
occupational human pulmonary exposure
prescribing
CAFOs
Reverse distributors
unsold product
dispensing pharmacies Rx & OTC
Aquaculture
waste residuals pretreatment
humanitarian donations: excess or unusable leftovers
sloughing of antibiotic-resistant bacteria/genes
Waste Treatment (e.g., lagoons)
manure solids
Soil amendment/ disposal
Take-Backs, Mail-Backs, Collection events
atmospheric release (e.g., anaesthetics)
Human consumer use
Gene Exchange multi-drug resistance
naturally occurring bacteria
exposure to resistant bacteria
Incineration
unused/expired leftovers
LTCFs Hospitals Hospice
Leftover medications
Stored awaiting disposal
Diversion Abuse (e.g., pharming)
acute poisonings: accidental & purposeful
diversion by gleaners
Landfill
trash
RCRA Hazardous Waste
release of dermal products from bathing
excretion from oral & parenteral use
Disposal by consumer
trash
Incineration
Waste Treatment
toilet
groundwater (artificial recharge, colloidal transport)
Aquatic exposure
toilet or sewerage
Disposal by Coroner's
research of Runoy 2006
optional
Law enforcement (controlled substances)
Wildlife exposure (scavengers)
straightpiping & overflow events
sediments (sorption)
runoff
leachates
landfill
Plant-Made Pharmaceuticals (PMPs)
finished drinking water treatment
receiving waters
Waste Treatment
Sludge Biosolids
Soil Amendment
groundwater
Molecular Pharming
drug residues & transformation by-products
"toilet-to-tap"
Recreation
Advanced Treatment (recycling)
aqueous effluent
irrigation
PMPs cross-contaminating food supply
Wildlife exposure from grazing foraging
Chronic, Low-Level, Incidental Human Exposure
Oral & Dermal
uptake by plants & crops
uptake by soil-dwelling organisms

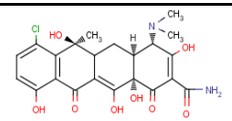
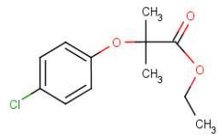
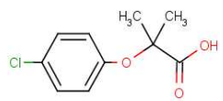
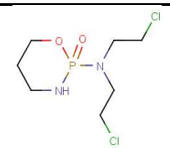
APPENDIX A

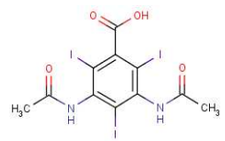
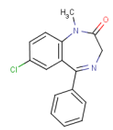
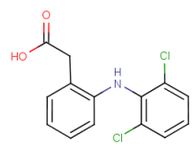
Environmental Pharmaceutical Residues Leading to Human Exposure via Ingestion

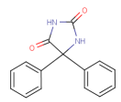
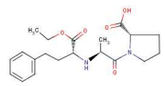
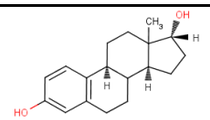
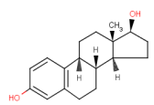
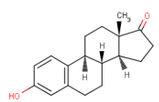
CAS-RN	NAME		SAMPLE TYPE	TYPE OF TREATMENT	OCCURRENCE FREQUENCY	CONCENTRATION, ng/L	COMMENTS	SAMPLING LOCATION	REFERENCE
103-90-2	Acetaminophen (paracetamol)		RDW		6/7	8.3-211	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
			RDW	C-GAC-Cl2	9/12	15 avg (120 max)	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	2/12	0.3 (avg)			
50-78-2	Acetylsalicylic acid		RDW		2/7	0.3-1.4	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
			FDW			>50			Versteegh et al. 2003
18559-94-9	Albuterol (salbutamol)		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
29122-68-7	Atenolol		RDW			6.0 Mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
			FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
134523-00-5	Atorvastatin		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
214217-88-6 (Ca-salt, acid form)	p-hydroxy Atorvastatin		RDW			<0.50		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.50			
41859-67-0	Bezafibrate		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
			FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
			FDW		1/30 > LOQ (=25)	<LOQ-27 (max)		Germany	Ternes 2001a
			FDW			27		Germany	Stumpf et al. 1996

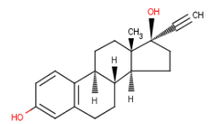
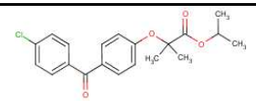
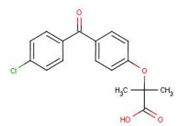
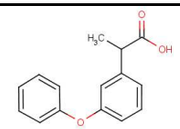
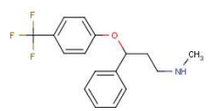
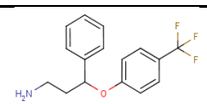
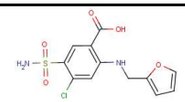
CAS-RN	NAME		SAMPLE TYPE	TYPE OF TREATMENT	OCCURRENCE FREQUENCY	CONCENTRATION, ng/L	COMMENTS	SAMPLING LOCATION	REFERENCE
11056-06-7	Bleomycin		RDW			5-13 mean=8.7		radioimmunoassay	Aherne et al. 1990
58-08-2	Caffeine		RDW			250 Max			Stackelberg et al. 2004
			FDW			119 Max			
			RDW			43		two S Korean cities	Kim et al. in press
			FDW	C-UF-GAC		<10-48			
			FDW		12/20	2.6-83 (25 mean)		20 US drinking water plants	Snyder et al. 2007
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
			RDW	C-GAC-Cl2	5/12	126 avg (190 max)	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0	15 avg			
298-46-4	Carbamazepine		RDW			0.5-2.0			
							over 5-month period	Windsor, Ontario	Hua et al. 2006

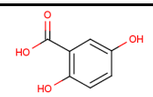
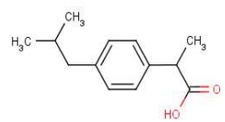
CAS-RN	NAME		SAMPLE TYPE	TYPE OF TREATMENT	OCCURRENCE FREQUENCY	CONCENTRATION, ng/L	COMMENTS	SAMPLING LOCATION	REFERENCE
			FDW	C-S-F		0.5-2.0			
			FDW	C-S-F-O		ND-0.3			
			RDW			400 Max			Stackelberg et al. 2004
			FDW			258 Max			
			RDW			5.8 Mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.50			
			RDW			4.8		two S Korean cities	Kim et al. in press
			FDW	C-UF-GAC		5.3-7.5			
			FDW		3/10	6.5-24		10 Canadian cities	Tauber 2003
			FDW		1/12 > LOQ (=10)	<LOQ-30 (max)		Germany	Ternes 2001a
			FDW	bank filtration, flocculation, disinfection, acidification,	3/3	up to 20 ng/L		Germany	Hummel et al. 2006
			RDW			46		Paris area	Bruchet et al. 2005
			FDW	SF-AC		4		Paris area	Bruchet et al. 2005
			FDW	SF-AC-O		2		Paris area	Bruchet et al. 2005
			RDW		2/7	13.0-43.2	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
			FDW		11/20	1.1-5.7 (2.8 mean)		20 US drinking water plants	Snyder et al. 2007
			RDW	C-GAC-Cl2	11/12	191 avg (600 max)	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	12/12	29 avg (140 max)			
			FDW			23			Versteegh et al. 2003
125-28-0	10,11-dihydroxy-10,11-dihydro-carbamazepine		FDW	bank filtration, flocculation, disinfection, acidification,	3/3	up to 13 ng/L	a primary metabolite of carbamazepine	Germany	Hummel et al. 2006
73384-59-5	Ceftriaxone		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000

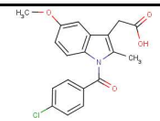
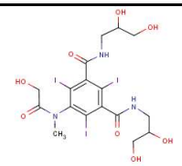
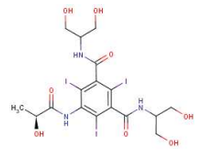
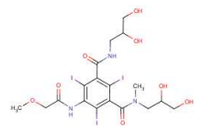
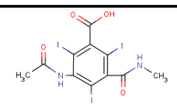
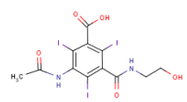
CAS-RN	NAME		SAMPLE TYPE	TYPE OF TREATMENT	OCCURRENCE FREQUENCY	CONCENTRATION, ng/L	COMMENTS	SAMPLING LOCATION	REFERENCE
57-62-5	Chlorotetracycline		FDW		0/10	ND (<50-150)		10 Canadian cities	Tauber 2003
637-07-0	Clofibrate		RDW	C-S-F	2/13	580 Mean of +; 260-900 Range of +; 90 Mean of all	none detected during wet months	San Diego	Loraine and Pettigrove 2006
			FDW			ND		San Diego	Loraine and Pettigrove 2006
882-09-7	Clofibric acid		RDW	C-S-F	1/13	630 mean det. 50 mean of all	none detected during wet months	San Diego	Loraine and Pettigrove 2006
			FDW			ND			
			FDW		12/14	<1.0-170 mean of total =14		14 different Berlin treatment works	Heberer et al. 2001
			RDW		various	ND-7,300	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		2/3	ND-3.2-5.3		3 Italian cities	Zuccato et al. 2000
			FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
			FDW		16/30 > LOQ (=1)	<LOQ-70 (max)		Germany	Ternes 2001a
			FDW			70		Germany	Stumpf et al. 1996
			FDW			270		Germany	Heberer et al. 1997
			FDW			32			Versteegh et al. 2003
50-18-0	Cyclophosphamide		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
67035-22-7	Dehydronifedipine		RDW	C-GAC-Cl2	3/12	1 avg	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	2/12	0.6 avg			
			FDW			4 Max			Stackelberg et al. 2004

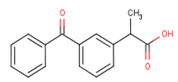
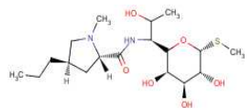
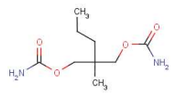
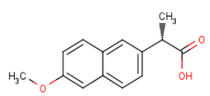
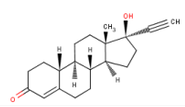
CAS-RN	NAME		SAMPLE TYPE	TYPE OF TREATMENT	OCCURRENCE FREQUENCY	CONCENTRATION, ng/L	COMMENTS	SAMPLING LOCATION	REFERENCE
117-96-4	Diatriazote (diatriazoic acid)		FDW		5/10 > LOQ (=10)	21-85		Germany	Ternes 2001a
			FDW	SF-AC-O		32		Paris area	Bruchet et al. 2005
439-14-5	Diazepam		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
			FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			FDW		1/3	ND-19.3-23.5		3 Italian cities	Zuccato et al. 2000
			FDW			10		UK	Waggot 1981
15307-86-5	Diclofenac		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
			FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			RDW		various	ND-380	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
			FDW		8/30 > LOQ (=1)	<LOQ-6 (max)		Germany	Ternes 2001a
			FDW			6		Germany	Stumpf et al. 1996

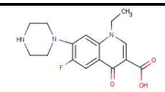
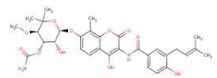
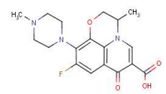
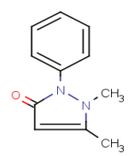
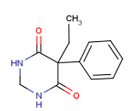
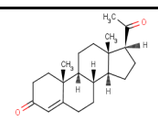
			RDW		6/7	1.4-2.5	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
57-41-0	Dilantin (Phenytoin)		RDW			6.2 mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		1.3 mean			
			FDW			1.2		Nevada	Trenholm et al. 2006
			FDW			1.1		Georgia	
			FDW		14/20	1.6-13 (6.1 mean)		20 US drinking water plants	Snyder et al. 2007
564-25-0	Doxycycline		FDW		0/10	ND (<50-150)		10 Canadian cities	Tauber 2003
75847-73-3	Enalapril		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
114-07-8	Erythromycin		FDW		1/20	1.3		20 US drinking water plants	Snyder et al. 2007
			RDW	C-GAC-Cl2	2/12	40 max	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<10)			
			FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
	Erythromycin-H20		RDW	C-GAC-Cl2	7/12	10 max	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<10)			
57-91-0	17α-estradiol		FDW			0.30-0.30 mean 0.30	LOD=0.10	3 drinking water sites in Southern Germany	Kuch and Ballschmiter 2001
50-28-2	17β-estradiol		FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			FDW			0.20-2.1 mean 0.3	LOD=0.10	3 drinking water sites in Southern Germany	Kuch and Ballschmiter 2001
53-16-7	Estrone		FDW		2/20	1.1-2.3 (1.7 mean)		20 US drinking water plants	Snyder et al. 2007
			FDW			0.2-0.6 mean 0.4	LOD=0.05	3 drinking water sites in Southern Germany	Kuch and Ballschmiter 2001

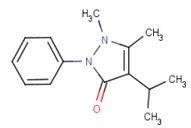
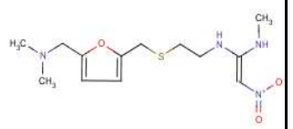
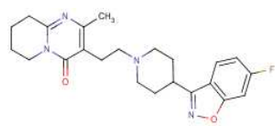
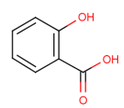
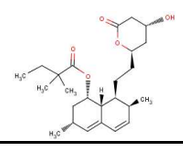
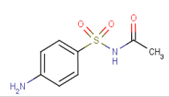
57-63-6	17α-ethynylestradiol		FDW			0.15-0.50 mean 0.35	LOD=0.05	3 drinking water sites in Southern Germany	Kuch and Ballschmiter 2001
			FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			FDW		2/2	<5, <1-4	12 samples in 2 years	SE England	Aherne and Briggs 1989
49562-28-9	Fenofibrate		RDW		various	ND-45	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
42017-89-0	Fenofibric acid		FDW		1/30 > LOQ (=5)	<LOQ-42 (max)		Germany	Ternes 2001a
31879-05-7	Fenoprofen		FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
54910-89-3	Fluoxetine		RDW			<0.50		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.50			
			FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			RDW	C-GAC-Cl2	0/12	ND (<14)	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<14)			
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
56161-73-0	Norfluoxetine		RDW			<0.50		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.50			
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
54-31-9	Furosemide		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
7440-54-2	Gadolinium	Gd	RDW		7/7	1.1-3.0	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
25812-30-0	Gemfibrozil		RDW			0.84 Mean			Vanderford &

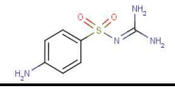
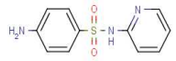
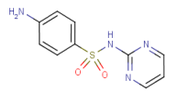
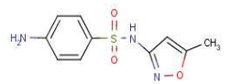
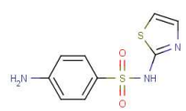
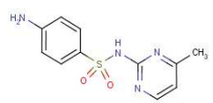
			FDW			<0.25			Snyder 2006
			RDW		various	ND-340	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		15/20	1.3-6.5 (3.9 mean)		20 US drinking water plants	Snyder et al. 2007
			FDW		1/10	ND (<3-90) - 70		10 Canadian cities	Tauber 2003
			FDW			ND		Nevada	Trenholm et al. 2006
			FDW			2.4		Georgia	
490-79-9	Gentisic acid		RDW		various	ND-540	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
15687-27-1	Ibuprofen		RDW		2/15	5850 Mean of +		San Diego	Loraine and Pettigrove 2006
			FDW			930 Mean of +; 510-1350 range of +; 120 Mean of all			
			RDW			15		two S Korean cities	Kim et al. in press
			FDW	C-UF-GAC		18-23			
			RDW		1/1	8.5-17.5 (summer-winter)	seasonal trends study; samples collected in August and March	Drinking water plant in Turku, Finland (32 km downstream from an STP at Aura, Finland)	Vieno et al. 2005
			FDW	C-GAC		<1.0-8.5 (summer-winter)			
			RDW		various	ND-200	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
			FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
			FDW		3/30 > LOQ (=1)	<LOQ-3 (max)		Germany	Ternes 2001a
			FDW			3		Germany	Stumpf et al. 1996
			RDW		3/7	0.2-0.6	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
			FDW			ND		Nevada	Trenholm et al. 2006
			FDW			2.7		Georgia	
			FDW		13/20	1-32 (7.9 mean)		20 US drinking water plants	Snyder et al. 2007
81576-55-8	Ibuprofen methyl ester		RDW			9,220		San Diego	Loraine and

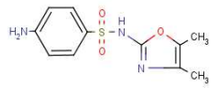
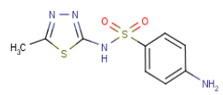
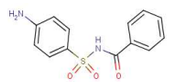
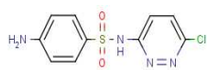
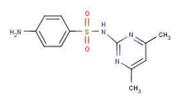
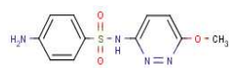
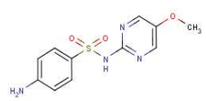
			FDW		1/15	4,950 330 Mean of all			
53-86-1	Indomethacin		FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
78649-41-9	Iomeprol		FDW	SF-AC-O		11		Paris area	Bruchet et al. 2005
60166-93-0 62883-00-5	Iopamidol		FDW		4/10 > LOQ (=10)	<LOQ-79 (max)		Germany	Ternes 2001a
			FDW	SF-AC-O		60		Paris area	Bruchet et al. 2005
73334-07-3	Iopromide		RDW			0-143		two S Korean cities	Kim et al. in press
			FDW	C-UF-GAC		0-177			
			FDW		1/10 > LOQ (=10)	<LOQ-86 (max)		Germany	Ternes 2001a
			FDW	SF-AC-O		<4		Paris area	Bruchet et al. 2005
			FDW		13/20	1.1-31 (8.5 mean)		20 US drinking water plants	Snyder et al. 2007
			FDW			ND		Nevada	Trenholm et al. 2006
			FDW			4.6		Georgia	
2276-90-6	Iothalamic acid		FDW	SF-AC-O		ND		Paris area	Bruchet et al. 2005
28179-44-4	Ioxitalamic acid		FDW	SF-AC-O		12		Paris area	Bruchet et al. 2005

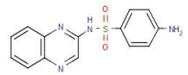
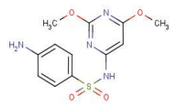
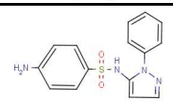
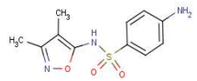
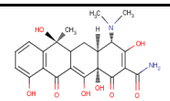
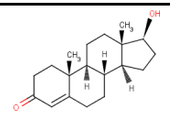
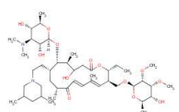
22071-15-4	Ketoprofen		RDW		various	ND-30	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		0/10	ND (<3-90)		10 Canadian cities	Tauber 2003
			RDW		1/1	11.5-7.0 (summer-winter)	seasonal trends study; samples collected in August and March	Drinking water plant in Turku, Finland (32 km downstream from an STP at Aura, Finland)	Vieno et al. 2005
			FDW	C-GAC		<5.0-<8.0 (summer-winter)			
			RDW		3/7	0.31-3.0	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
154-21-2	Lincomycin		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
			RDW	C-GAC-Cl2	2/12	10-50 max	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<10)			
57-53-4	Meprobamate		FDW		15/20	1.6-13 (6.1 mean)		20 US drinking water plants	Snyder et al. 2007
			RDW			18 Mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		5.9 Mean			
			FDW			6.5		Nevada	Trenholm et al. 2006
			FDW			8.0		Georgia	
22204-53-1	Naproxen		RDW			65 Mean			Boyd et al. 2003
			FDW			ND			
			RDW		1/1	7.5-7.5 (summer-winter)	seasonal trends study; samples collected in August and March	Drinking water plant in Turku, Finland (32 km downstream from an STP at Aura, Finland)	Vieno et al. 2005
			FDW	C-GAC		<5.0-<5.0 (summer-winter)			
			RDW			0.54 Mean			Vanderford & Snyder 2006
			FDW	Cl2-O		<0.50			
			RDW			ND		San Diego	Loraine and Pettigrove 2006
			RDW		3/7	0.1-0.2	drinking water wells	Hérault watershed, S. France	Rabiet et al. 2006
			FDW		1/20	8		20 US drinking water plants	Snyder et al. 2007
68-22-4	Noresthisterone		FDW		2/2	<2, <10	12 samples in 2 years	SE England	Aherne and Briggs 1989

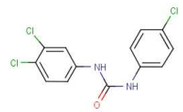
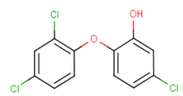
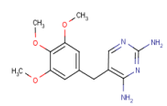
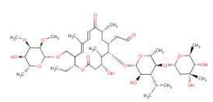
70458-96-7	Norfloxacin		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
303-81-1	Novobiocin		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
82419-36-1	Ofloxacin		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
3922-90-5	Oleadomycin		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
14698-29-4	Oxolinic acid		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
79-57-2	Oxytetracycline		FDW		0/10	ND (<50-150)		10 Canadian cities	Tauber 2003
6493-05-6	Pentoxifylline		FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
60-80-0	Phenazone (Antipyrine)		RDW		various	ND-1,250	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW		1/12 > LOQ (=10)	<LOQ-50 (max)		Germany	Ternes 2001a
			RDW			3,950	groundwater from bank filtration	Berlin	Reddersen et al. 2002
			FDW	aeration, filtration		400	groundwater from bank filtration	Berlin	Reddersen et al. 2002
			FDW			250		Germany	Zuhlke et al. 2004
51940-44-4	Pipemidic acid		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
125-33-7	Primidone (2-Deoxypheno-barbital)		RDW		various	ND-690	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
			FDW	bank filtration, flocculation, disinfection, acidification,	3/3	up to 16 ng/L		Germany	Hummel et al. 2006
57-83-0	Progesterone		FDW		2/20	1.1-1.1 (1.1 mean)		20 US drinking water plants	Snyder et al. 2007
479-92-5	Propyphenazone		RDW		various	ND-1,465	groundwater wells used by	Berlin	Heberer et al.

							treatment works		2001
	(Isopropyl-antipyrine)		RDW	aeration, filtration		1,230	groundwater from bank filtration	Berlin	Reddersen et al. 2002
			FDW	aeration, filtration		120	groundwater from bank filtration	Berlin	Reddersen et al. 2002
			FDW			80		Germany	Zuhlke et al. 2004
66357-35-5	Ranitidine		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
106266-06-2	Risperidone		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
80214-83-1	Roxithromycin		FDW		0/10	ND (<10-150)		10 Canadian cities	Tauber 2003
			RDW			ND	efficiently removed by bank filtration and recharge	Paris area	Bruchet et al. 2005
69-72-7	salicylic acid		RDW		various	ND-1,250	groundwater wells used by treatment works	Berlin	Heberer et al. 2001
79902-63-9	Simvastatin		RDW			<1.0		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<1.0			
12009-77-6 (Na salt)	Simvastatin hydroxy acid		RDW			<0.25		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
8025-81-8	Spiramycin		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000
144-80-9	Sulfacetamine (Sulfacetamide)		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003

57-67-0	Sulfaguanidine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
144-83-2	Sulfapyridine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
68-35-9	Sulfadiazine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
723-46-6	Sulfamethoxazole		RDW			22 Mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
			FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
			BMW	none	2/8	13 and 80		Italian commercial water	Perret et al. 2006
			RDW			9		Paris area	Bruchet et al. 2005
			FDW	SF-AC		2		Paris area	Bruchet et al. 2005
			FDW	SF-AC-O		<1		Paris area	Bruchet et al. 2005
			FDW			14			Versteegh et al. 2003
			FDW		1/20	20		20 US drinking water plants	Snyder et al. 2007
			RDW	C-GAC-Cl2	10/12	60 max	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<10)			
72-14-0	Sulfathiazole		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
127-79-7	Sulfamerazine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003

729-99-7	Sulfamoxole		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
144-82-1	Sulfamethizole		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
			BMW	none	1/8	9		Italian commercial water	Perret et al. 2006
127-71-9	Sulfabenzamide		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
80-32-0	Sulfachloropyridazine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
57-68-1	Sulfamethazine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
80-35-3	Sulfamethoxy-pyridazine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
651-06-9	Sulfameter		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003

59-40-5	Sulfaquinoxaline		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
122-11-2	Sulfadimethoxine		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
			BMW	none	1/8	11		Italian commercial water	Perret et al. 2006
			RDW	C-GAC-Cl2	1/12	10 max	12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007
			FDW	C-GAC-Cl2	0/12	ND (<10)			
526-08-9	Sulfaphenazole		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
127-69-5	Sulfisoxazole		FDW		0/10	ND (<5-75)		10 Canadian cities	Tauber 2003
60-54-8	Tetracycline		FDW		0/10	ND (<50-150)		10 Canadian cities	Tauber 2003
58-22-0	Testosterone		FDW		0/20	ND		20 US drinking water plants	Snyder et al. 2007
108050-54-0	Tilmicosin		FDW		0/3	ND		3 Italian cities	Zuccato et al. 2000

101-20-2	Triclocarban (Trichlorocarbanilide)		RDW		0/3	ND <20	well water	Baltimore County	Halden and Paull 2004
			FDW		0/4	ND <3			
			FDW		0/12	ND<10		12 metropolitan areas in U.S.	TCC Consortium (2002): http://www.epa.gov/chemrtk/pubs/summaries/triclocca/c14186rs.pdf
3380-34-5	Triclosan		RDW			730 Mean of +		San Diego	Loraine and Pettigrove 2006
			FDW			734 Mean of +; 49 Mean of all			
			RDW			<1.0		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<1.0			
			human breast milk		3/5	<20-300 microgram/kg	human breast milk	Sweden	Adolfsson-Erici et al. 2002
			FDW		1/20	43		20 US drinking water plants	Snyder et al. 2007
4640-01-1	Triclosan methyl ester (presumably the authors meant methyl triclosan, or triclosan methyl ether)		RDW			ND		San Diego	Loraine and Pettigrove 2006
738-70-5	Trimethoprim		FDW		1/20	1.3		20 US drinking water plants	Snyder et al. 2007
			RDW			1.2 Mean		Lake Mead, NV	Vanderford & Snyder 2006
			FDW	Cl2-O		<0.25			
			FDW		0/10	ND (<5-60)		10 Canadian cities	Tauber 2003
1401-69-0	Tylosin		FDW		1/3	ND-0.6-1.7		3 Italian cities	Zuccato et al. 2000
Miscellaneous Non-Detects – ca 40 parent APIs and degradates not detected in either raw water or finished water							12 samples at each of 6 locations over 3 weeks	235 ML/day for 850,000 pop.	Stackelberg et al. 2007

Footnotes:

ND= Not detected (<LOD)
FDW= Finished drinking water
RDW= Raw drinking water
BMW: bottled mineral water
AC - GAC - C - S - F - UF - O - Cl2: activated carbon - granular activated carbon - coagulation - sedimentation - membrane filtration - ultrafiltration - ozonation - chlorination

References for Appendix A:

Adolfsson-Erici M, Pettersson M, Parkkonen J, Sturve J. "Triclosan, a commonly used bactericide found in human milk and in the aquatic environment in Sweden," Chemosphere 2002, 46 (9-10):1485-1489.

Aherne GW, Briggs R. "The relevance of the presence of certain synthetic steroids in the aquatic environment," J Pharm Pharmacol 1989, 41(10):735-6.

Aherne GW, Hardcastle A, Nield AH. "Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples," J Pharm Pharmacol 1990, 42(10):741-2.

Boyd RG, Reemtsa H, Grimm DA, Mitra S. "Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada,"Sci Total Environ. 2003, 311(1-3):135-149.

Bruchet A, Hochereau C, Picard C, Decottignies V, Rodrigues JM, Janex-Habibi ML. "Analysis of drugs and personal care products in French source and drinking waters: the analytical challenge and examples of application," Water Sci Technol 2005, 52(8):53-61.

Halden R, Paull D. "Analysis of triclocarban in aquatic samples by liquid chromatography electrospray ionization mass spectrometry," Environ Sci Technol 2004, 38(18):4849-4855.

Heberer Th., Dünnbier U., Reilich Ch., Stan H.-J. "Detection of Drugs and Drug Metabolites in Ground Water Samples of a Drinking Water Treatment Plant," Fresenius Environ Bull 1997, 6:438-443.

Heberer T, Fuhrmann B, Schmidt-Baumier K, Tsipi D, Koutsouba V, Hiskia A. "Occurrence of Pharmaceutical Residues in Sewage, River, Ground, and Drinking Water in Greece and Berlin (Germany)," In Pharmaceuticals and Personal Care Products in the Environment; Scientific and Regulatory Issues; Daughton, C., Jones-Lepp, T., Eds.; American Chemical Society:Washington, DC, 2001; Chapter 4.

Hua W, Bennett ER, Letcher RJ. "Ozone treatment and the depletion of detectable pharmaceuticals and atrazine herbicide in drinking water sourced from the upper Detroit River, Ontario, Canada," Water Res 2006, 40(12):2259-2266.

Hummel D, Löffler D, Fink G, Ternes TA. "Simultaneous Determination of Psychoactive Drugs and Their Metabolites in Aqueous Matrices by Liquid Chromatography Mass Spectrometry," Environ. Sci. Technol. 2006, 40(23):7321 -7328.

Kim SD, Cho J, Kim IS, Vanderford BJ, Snyder SA. "Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters," Water Res, in press; available online 23 August 2006.

Kuch HM, Ballschmiter K. "Determination of Endocrine-Disrupting Phenolic Compounds and Estrogens in Surface and Drinking Water by HRGC-(NCI)-MS in the Picogram per Liter Range," Environ Sci Technol 2001, 35(15):3201-3206.

Loraine GE, Pettigrove ME. "Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in southern California," Environ Sci Technol. 2006, 40:687-695.

Perret D, Gentili A, Marchese S, Greco A, Curini R. "Sulphonamide residues in Italian surface and drinking waters: a small scale reconnaissance," Chromatographia 2006, 63(5-6):225-232.

Rabiet M, Togola A, Brissaud F, Seidel JL, Budzinski H, Elbaz-Poulichet F. "Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized Mediterranean catchment," Environ Sci Technol 2006, 40(17):5282-5288.

Reddersen K, Heberer T, Dünnbier U. "Identification and significance of phenazone drugs and their metabolites in ground- and drinking water," Chemosphere 2002, 49(6):539-544.

Snyder SA, Lei H, Wert EC "Removal of Endocrine Disruptors and Pharmaceuticals during Water Treatment," In: DA Aga (Ed.), Fate of Pharmaceuticals in the Environment and in Water Treatment Systems, CRC Press, Taylor & Francis Books, FL, USA, in press (targeted for November 2007).

Stackelberg PE, Furlong ET, Meyer MT, Zaugg SD, Henderson AK, Reissman DB "Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant," Sci Total Environ 2004, 329 (1-3):99-113.

Stackelberg PE, Gibs J, Furlong ET, Meyer MT, Zaugg SD, Lippincott RL “Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds,” Sci Total Environ 2007, 377(2-3):255-272.

Stumpf M, Ternes TA, Haberer K, Seel P, Baumann W. "Nachweis von Arzneimittelrückständen in Kläranlagen und Fließgewässern" (Determination of drugs in sewage treatment plants and river water). Vom Wasser 1996, 86:291-303.

Tauber R. "Quantitative Analysis of Pharmaceuticals in Drinking Water from Ten Canadian Cities," report prepared for Mark Stevenson (CTV News, Canada), Enviro-Test Laboratories/Xenos Division, Ontario, Canada, 20 January 2003; available: http://popups.ctv.ca/content/publish/popups/PDFs/DrugReportFinal030202.pdf

Ternes TA. "Pharmaceuticals and metabolites as contaminants of the aquatic environment," In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, ACS Symposium Series 791. American Chemical Society, Washington DC, USA, pp. 39-54, 2001a.

Ternes TA. "Analytical methods for the determination of pharmaceuticals in aqueous environmental samples," Trends Anal Chem 2001b, 20(8):419-434 [provides data on a wide array of pharmaceucails that were below the limits of quantitation]

Trenholm RA, Vanderford BJ, Holady JC, Rexing DJ, Snyder SA. "Broad range analysis of endocrine disruptors and pharmaceuticals using gas chromatography and liquid chromatography tandem mass spectrometry," Chemosphere 2006, 65(11):1990-1998.

Vanderford BJ, Snyder SA. "Analysis of pharmaceuticals in water by isotope dilution liquid chromatography/tandem mass spectrometry," Environ Sci Technol, 2006, 40(23):7312-7320.

Versteegh JFM, Stolker AAM, Niesing W, Muller JJA. "Geneesmiddelen in drinkwater en drinkwaterbronnen" [Pharmaceuticals in drinking water and sources for drinking water], RIVM rapport 703719004, 2003, 45pp, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; available: http://www.rivm.nl/bibliotheek/rapporten/703719004.pdf

Vieno NM, Tuhkanen T, Kronberg L. "Seasonal Variation in the Occurrence of Pharmaceuticals in Effluents from a Sewage Treatment Plant and in the Recipient Water," Environ Sci Technol, 2005, 39(21):8220-8226.

Waggott A. "Trace organic substances in the River Lee (Great Britain)," Chemistry in Water Reuse Ed. W.J. Cooper, Vol. 2 (1981) pp. 55-99. Ann Arbor Sci., Ann Arbor, MI.

Zuccato E, Calamari D, Natangelo M, Fanelli R. "Presence of therapeutic drugs in the environment," The Lancet 2000, 355:1789-1790.

Zuhlke S, Dunnbier U, Heberer T. "Detection and identification of phenazone-type drugs and their microbial metabolites in ground and drinking water applying solid-phase extraction and gas chromatography with mass spectrometric detection," J Chromatogr A 2004, 1050(2):201-209.