Pharmaceutical Ingredients in Drinking Water: Overview of Occurrence and Significance of Human Exposure

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Abstract

A comprehensive examination is presented of the data published through 2009 on the active pharmaceutical ingredients (APIs) that have been reported in finished drinking water (FDW). A synoptic review reveals that quantitative occurrence data for FDW exists for 64 APIs and miscellaneous transformation products, reported in 48 publications. Significantly, however, for these 64 substances only 17 have quantitative data from more than two reports each; only 36 have corroborative data from a second study. Almost all of the available data has been published since the year 2000. The occurrence data are organized around the Anatomical Therapeutic Chemical (ATC) classification system. The top four ATC classes for which the most API data have been reported are: N, C, V, and M. APIs have been reported for 7 of the 14 main ATC classes; no API has been reported for ATC classes A, B, H, L, R, or S. Some emphasis is also placed on negative data - those APIs with either data of absence or absence of data. The six most frequently reported APIs in FDW (in descending order) are: carbamazepine, ibuprofen, sulfamethoxazole, clofibric acid, gemfibrozil, and iopromide. The six APIs with roughly the most consistent highest reported concentrations are: ibuprofen, triclosan, carbamazepine, phenazone, clofibric acid, and acetaminophen. With only one exception (ibuprofen and its methyl ester metabolite), no API exceeded a concentration of 1 ppb (1 µg/L). Also covered are some of the reported transformation products and disinfection by-products unique to APIs. Some of the less-discussed aspects of the potential ramifications for human health are also included. A clearer picture is emerging as to the extent and scope of API occurrence in drinking water, some preliminary generalizations can be drawn, and a better sense is emerging of where future research should be directed.

Introduction

Publication of investigations directed at pharmaceuticals as trace environmental contaminants began in earnest in the mid-1990s (1). As of December 2009, the US EPA's citation database of publications on pharmaceuticals as environmental contaminants comprised more than 9,000 documents dealing with the many aspects of this expansive topic (2). Those with a major focus

on pharmaceuticals specifically as contaminants in drinking water totaled roughly only 250. Of these, all but 20 had been published since 2000.

This chapter presents a synoptic overview of the occurrence of active pharmaceutical ingredients (APIs) in finished drinking water and some of the less-discussed aspects of the potential ramifications for human health. The discussion builds on the synopsis published in early 2008 (3); among other overviews are: (4-9) and those in (10,11). Aspects not addressed here include treatment technologies and approaches for reducing API residues in drinking water. Assessment of risk is discussed only briefly with the intent of presenting new insights.

APIs in drinking water continue to attract attention despite a developing consensus that ecological integrity is the major concern regarding APIs as pollutants - because aquatic systems can experience continual exposures to levels of APIs one or more magnitudes higher in concentration than in drinking water. The occurrence of APIs in drinking water is a curious topic in the sense that little empirical data has hinted toward a link with human health - and yet the issue persists as one of great interest. This is because of a wealth of unanswered questions, many of which are key to understanding the more general issue of low-level chronic exposure to multiple chemical stressors.

Attention to the occurrence of APIs in drinking water is driven largely by public concerns. Public concern is disconnected from the actual concentrations of APIs in drinking waters - concentrations so low that they were not routinely measurable a decade ago and for which no toxicological risks have been documented. Rather, a major driver for public concern is the consequence of APIs as micropollutants serving to crystallize an understanding of the water cycle - highlighting the fact that "natural" waters often are derived at least in part from human sewage (and sometimes animal waste). APIs serve to demonstrate that sewage and drinking water are often closely connected hydrologically - APIs being excreted or disposed to sewage and trace amounts surviving long enough to make their way into potable waters. In the course of modern human history, it was comparatively recent that sewage was understood as a major source of infectious disease; chlorination to reduce pathogens was widely adopted only at the beginning of the last century. Such a major determinant of public health contrasts sharply with the current focus on trace levels of chemical contaminants - concentrations that engineered treatment technologies drive ever lower.

APIs have probably long been present in drinking water (often at undetectable low levels) - ever since pharmaceuticals first came into widespread use (12). Their presence in the environment is partly a direct result of their intended use - as therapeutic use inevitably results in certain portions of all APIs to be released in excretions and during bathing. Advancements in analytical chemistry (especially the ability to measure ever-lower concentrations) have served to highlight the topic. Public interest was most recently fostered by the series of news stories published by the Associated Press beginning in 2008 (13), which also helped catalyze several Congressional Hearings in the US. The opening sentence from the first of the AP series (14) served to attract broad attention: "A vast array of pharmaceuticals including antibiotics, anti-convulsants, mood stabilizers and sex hormones have been found in the drinking water supplies of at least 41 million Americans..." But without a comprehensive understanding of the many complexities and

nuances underlying the topic, determining whether APIs in drinking water pose any real concern will not be possible.

In the 2 years since the last synoptic examination of the literature (3), little new information has surfaced regarding the types and concentrations of APIs to which people might be exposed. But even so, a clearer picture is emerging as to the extent and scope of API occurrence in drinking water, some preliminary generalizations can be drawn, and a better sense is emerging of where future focus should be directed. Much less information is available concerning the scope and extent of disinfection by-products (DBPs) or transformation products unique to APIs.

Pathways to Drinking Water

Of the roughly 1,200 small-molecule APIs in common use today in the US (15), only a select few enter the environment in sufficient quantities to survive the gauntlet of hurdles and obstacles to be detectable in drinking water. A broad spectrum of environmental transformation processes and engineered treatment processes continually act to remove APIs - from the time of their release in sewage to their ultimate destination in potable water. Drinking water is the ultimate repository for many of the minute residues of APIs originally discharged primarily to sewage - after having undergone attenuation by a long series of anthropogenic and natural transformation processes.

The types and quantities of those few APIs that enter into finished drinking water are a function of the hydrologic connectivity between human (and animal) waste and the source for the drinking water - as moderated by the spectrum of upgrading treatments used to create tap water. The frequency and levels of API occurrence in drinking waters can decline dramatically as the hydrologic connectivities between waste and source waters are reduced; this includes inputs such as from leaking sewers and landfills. Increasing the spatiotemporal distance between sewage and source water also reduces public perception of risk - regardless of the measured concentrations of chemicals unique to sewage. A balance must be found for optimizing the distance and time from treated sewage to source water.

From the moment of its intended use, the quantity of an API is reduced by absorption and metabolism in the patient, by degradation, transformation, or sorptive processes during sewage treatment followed by the natural processes occurring in the environment, and further yet by treatment for the production of polished (finished) drinking water. The quantities that survive through each of these steps are functions of the route of introduction to sewage (excretion via urine/feces, sweat, bathing), pharmacokinetics (which vary greatly among APIs as well as among individuals), natural physicochemical transformation processes (e.g., photolysis, UV irradiation, oxidation, hydrolysis, sorptive removal such as to sewage sludge or sediments), biodegradation, and the types and sophistication of the array of engineered treatment processes used in waste and water treatment (ranging from advanced oxidation and UV irradiation to reverse osmosis). Those APIs that survive this gauntlet and enter drinking water are characterized generally by their high usage rates or excretion rates (mirrored by low biodegradability), high chemical stability, high water solubility, and reduced propensity for sorption (such as to sewage sludge); the stability of an API is a characteristic important for a drug's efficacy - a half-life in the body sufficiently long to ensure biological action but short enough to avoid bioconcentration. The many factors that

dictate the types and quantities of APIs that might remain in finished drinking waters have been summarized in numerous articles, including: (8,16,17).

A large number of drivers could be involved in future elevations or reductions in the presence of APIs in drinking water. Some prominent ones include: variables associated with the seasons or the weather (e.g., the percentage of source waters derived from STW effluents; sewage treatment efficiencies; local prescribing customs or disease patterns) and consumer disposal practices for unwanted medications (e.g., discarding to trash versus sewers).

Why the Concern?

Some perspective is important regarding the entry of APIs into drinking water sources. There is no such thing as "pure" water (18). Numerous chemicals from nature and from human activities tend to readily contaminate water at trace levels as soon as attempts are made at purification. APIs are among myriad other man-made (and naturally occurring) chemicals that can readily contaminate water - often at levels too low to detect today but undoubtedly will be detectable in the future, with the continual advancements in analytical measurement technologies.

Regardless of the scope of the existing empirical database on APIs detected or measured in drinking water, the major question is "What does it all mean?" Any discussion of APIs in drinking water inevitably segues to the topic of human exposure and risk - an aspect of the larger topic that will be touched upon at the end of this chapter.

As potential contaminants in drinking water, trace constituents in source waters will pose growing concerns as the percentage of the source water originating from either treated or raw sewage (e.g., overflow events) increases. A major driver will be the growing need to reuse water - beginning with indirect water reuse and transitioning eventually to direct reuse (18). In those locales where potable water is becoming scarce and effluent-dominated streams are common, the pressure to implement water reuse or to continually increase the percentage of recycled water will grow. The issues surrounding APIs in water will consequently attract yet more attention.

Another driver that could play a major role in the occurrence of APIs in water is climate change. Several dimensions in the environmental occurrence and distribution of APIs could be directly affected, including not just the increasing incidence of effluent-dominated source water coupled with the need to recycle water, but also the shifting of drug-use patterns and rates as a result of different geographic distribution of diseases and other health factors.

By striving to continually reduce the occurrence of APIs in the environment, the public’s perception of the most visible hydrologic connections between potable water and sewage can be gradually erased. This will make the inevitable need to adopt reused water more acceptable to the public by allowing ever-shorter “loops” to be used between source and point of use - progressing from indirect to direct reuse (e.g., so-called “toilet-to-tap”).

Needed - A Systems Approach

A number of currently unrelated lines of investigation intertwine in the issue of APIs in drinking water. Unfortunately, there is little cross-communication. A systems approach that integrates each of these will be required before definitive answers are possible regarding APIs in drinking water. To understand the ramifications of APIs in drinking water and how to manage the real or perceived risk involves understanding these various aspects of the larger puzzle, few of which currently intersect or inform each other. These include:

- extent and scope of API occurrence in finished drinking water (FDW), especially in point-of-use water (at the tap)
- extent and scope of API occurrence in source waters from which drinking water is derived
- effectiveness of water treatment processes
- possible role of the distribution process (e.g., biofilms in pipes; oxidation by residual chlorine)
- formation of disinfection by-products (DBPs) unique to APIs
- interactive and additive toxicological effects of trace-level APIs ("ultra-low dose" studies [concentrations orders of magnitude lower than those generally accepted to have biological effects]; so-called "micro-dosing" studies; the possible role of hormesis; and the potential role of epigenetics might each play important roles in advancing this major unknown)
- perception of risk and its role in public acceptance of recycled water
- best approach for communicating risk
- approaches for minimizing or preventing the introduction of APIs into the environment.

With regard to the scope and extent of API occurrence in drinking water, municipal utilities in the US and most other countries do not routinely perform any monitoring, as no requirements currently exist. Historically, APIs have not been regulated water pollutants (with the exception of those, such as lindane and pyrethrins, which also are - or used to be - registered as pesticides). The boundaries on the scope and magnitude of API occurrence in drinking water therefore still have much uncertainty. In the US, this may change with implementation of the third EPA Drinking Water Contaminant Candidate List - CCL3 (19). This marks the first time that the CCL has included any API. The list includes nine APIs that are endogenous or synthetic sex hormones and two miscellaneous APIs: equilenin, equilin, 17-α-estradiol, 17-β-estradiol, estriol, estrone, 17-α-ethynylestradiol (EE2), mestranol, 19-norethisterone, erythromycin, and nitroglycerin. At the same time, a joint effort of the USEPA and the U.S. Geological Survey (USGS) ("Emerging Contaminant Sampling Program") plans to monitor up to 50 drinking water treatment plants (DWTPs) for more than 60 APIs and metabolites in both source waters and finished drinking waters (20).

Objectives

The synoptic overview presented here focuses on the current state of knowledge regarding the occurrence of APIs in finished drinking water, referred to hereafter as FDW to distinguish it from source waters or raw drinking water (intake water for DWTPs). This is an important distinction and a source of confusion when examining the published literature (3). Some

attention is also devoted to associated metabolites, transformation products, and DBPs. Some brief perspectives are also provided regarding risk from human exposure via FDW.

Historical Context and Perspective

To give this topic some very basic context and perspective, consider the brief history of societal norms once used in determining whether water was considered safe to drink (21). That focus is now on part-per-trillion residues of so-called micro-contaminants (such as the broad spectrum of APIs) is testament to how far sanitation has evolved. Where only 150 years ago in parts of Britain, a dominant worry was living past age 20 and having to continually ignore the stench of pervasive excrement and raw sewage, we now focus on quantities of chemicals so minute that their presence in drinking water could only have been hypothesized several decades ago.

Interest in APIs as environmental contaminants probably evolved naturally from the earlier interest in identifying and quantifying trace, unregulated chemical contaminants in water. In a landmark 1977 paper, Donaldson (22) formalized the idea that waters contain perhaps countless chemicals; at that time, 2 million organic chemicals had been inventoried by CAS, compared with over 40 million in 2009. Donaldson argued that as analytical detection limits were lowered, the number of detectable chemicals would also increase, eventually leading to an expectation "...to find every known compound at a concentration of 10^{-12} g/L [1 pg/L] or higher in a sample of treated drinking water." This observation was followed in 1981with a corollary by Fielding et al. (23):

> "... a high proportion of the population is exposed, via drinking water (irrespective of its source), to minute quantities of a wide range of organic chemicals. The presence of these compounds at much higher concentrations would undoubtedly be grounds for grave concern in relation to possible carcinogenicity and other toxic effects. However, it is difficult to assess whether the very low levels encountered are significant."

Preceding these two reports was perhaps the first recognition that APIs can enter the environment from human use. Stumm-Zollinger and Fair (24) in a 1965 study of the biodegradation of steroid hormones noted that their paper exemplified:

> "...the kind of inquiry that water engineers and water scientists conceivably will make in increasing number and rising intensity if the available water resource is allowed to become heavily contaminated with the waste products of man and with the expanding complex of chemicals synthesized by him for agricultural and industrial operations as well as for his more immediate personal use. Moreover, ... there must be an awareness of long-range and possibly synergistic effects of low-level amounts of toxic or physiologically active substances among which the steroid hormones are mentioned specifically. That population growth and population aging lie at the base of inquiries of this kind also needs to be emphasized." They went on to say that "it is our responsibility to learn in what amounts steroid hormones may occur in our drinking waters under the most unfavorable conditions,...we must find out to what extent, if any, the steroid hormones are biodegradable in the normal history of wastewaters and receiving bodies of water that may eventually supply drinking water to households."

The first actual reports of non-metabolite APIs in source or drinking waters were minor aspects of larger surveys (in the UK) for chemicals unrelated to APIs. Two of the first were Fielding et al. (23) and Waggott (25) in 1981. In non-targeted monitoring of FDW (from effluent-dominated source waters), Fielding et al. identified pentobarbital in one of 14 samples (and caffeine in another) - among 324 total trace organics. They recognized that analysis by gas chromatography limited the identification of organic matter to probably less than 20% of the compounds present. Also in 1981, Waggott published an extensive characterization of source waters (in the River

Lee, UK), identifying trace levels of a 1,4-benzodiazepine, a clofibrate metabolite, EE2, phenobarbital, and a salicylic acid metabolite, among many other organics.

Perhaps the first investigation to intentionally target an API in drinking water was Stan et al. (26), in 1994. Clofibric acid was quantified in all 64 drinking water samples taken in Berlin, Germany. Concentrations ranged from 10 to 165 ng/L. This study catalyzed a number of follow-up studies in Switzerland and Germany, all published before 2000 by Heberer, Ternes, and others. In 1998, a National Research Council workshop (27) devoted some focus to APIs as meriting attention as drinking water contaminants. One of the earliest evaluations of human risk was by Christensen in 1998 (28). One of the first targeted surveys of APIs in FDW in the US was in 2001 by Frick et al. (29), who detected acetaminophen. Questions regarding APIs in reused water were voiced as early as 2001 (30). Nearly the entire body of literature on APIs in FDW has been published since 2000.

Scope of Examination of APIs in Drinking Water

As used in this discussion, APIs will refer to the active ingredient in any over-the-counter (OTC) or prescription (Rx) medication or diagnostic intended for human or veterinary use but exclude ubiquitous natural products used in large amounts (e.g., natural stimulants such as caffeine and other xanthines, or any nicotine-related chemical or non-hormonal sterols/steroids). APIs covered in this chapter are the "small-molecule drugs" - relatively low-molecular weight, homogeneous chemicals (except for optical isomers) in contrast with the biologics, which include single molecules or multimers that are heterogeneous in composition, especially as a result of subtle amino acid sequence differences and in the degree and types of glycosylation.

Examining data from Overington et al. (31) and Wishart et al. (32) shows over 21,000 formulated drug products (various combinations of ingredients, strengths, and form) utilizing over 1,460 FDA-approved small-molecule APIs (molecularly distinct); the global pharmacopoeia comprises fewer than 1,000 frequently prescribed drugs (15). More than 800 are administered orally, over 420 parenterally, and over 270 topically; there are over 3,200 experimental drugs (only a portion of which are small molecules). Over 16% of the small-molecule drugs are prodrugs, meaning that the therapeutically active agent may not necessarily be the API itself; pro-drug active agents can be formed not just by metabolism during the course of therapy, but also by subsequent biological and abiotic transformation processes in the environment acting on excreted, unaltered prodrug.

There are three major types of FDW data available in the literature:

(1) positive occurrence data (data of presence), which includes quantitative and qualitative data - values above limits of detection (LOD or DL) but below limits of quantitation (LOQ),

(2) data of absence (negative data or non-detects), where an API was specifically targeted but was below its reporting limit or LOD, and

(3) absence of occurrence data, where an API had not been targeted and therefore its presence or absence is not yet known.

The published literature contains a wealth of positive occurrence data for APIs in source waters (including ground waters and wells) and in raw (intake) waters used for generating FDW. In stark contrast, comparatively little positive data exist for actual FDWs themselves, especially waters as distributed to the final point of use (POU) - sometimes referred to in the literature as tap water (although "tap" is sometimes also used in reference to a sampling point within a DWTP). This paucity of FDW data partly reflects the analytical challenges faced by the greatly diminished API levels in FDW, which are often one or more orders of magnitude lower after the various treatment processes used for finishing/polishing. Even fewer data are available for POU drinking water, which are of the greatest relevance for assessing the potential for risk from human exposure (3); less study of POU waters is perhaps partly a result of the heightened prospects of acquiring negative monitoring data (data of absence), which is not as interesting to an investigator.

Summaries of Published Data for APIs in FDW

Various summaries of the data mined from the literature in this study are compiled in Tables I-IV. All four tables use the Anatomical Therapeutic Chemical (ATC) classification system codes (http://www.whocc.no/atcddd/) as a framework for organizing the data; the APIs are sorted according to their ATC codes rather than alphabetically. The in-depth list of positive occurrence data (together with some representative negative data) is shown in Table I. A distillation of just the positive occurrence data is shown in Table II, which presents the numbers of references reporting data for each API (ranked according to total number of references within and among each ATC primary group) along with the upper concentration ranges. Table III shows the top three APIs within each ATC class ranked according to frequency of quantitative data and according to the highest ranges in the published literature. Table IV summarizes the APIs reported (and examples of some not reported) in FDWs, grouped according to the primary ATC classes.

Table I. Compilation of Published Positive Occurrence Data for APIs in Finished Drinking Water (and select data on negative occurrence – indicated by shaded cells).

ATC name[a]	ATC code[a]	API (synonym)	CAS RN	finished drinking water, ng/L [median][b]	distribution water (ng/L)	reference
Alimentary Tract & Metabolism	A01AB21	Chlortetracycline	57-62-5	ND (DL=5-150)		(33)
	A02BA02	Ranitidine	66357-35-5	ND (DL=0.01)		(34)
	A07AB03	Sulfaguanidine	57-67-0	ND (DL=5-75)		(33)
Cardiovascular System: C03 Diuretics; C04 Peripheral Vasodilators; C07 Beta Blocking Agents; C08 Calcium Channel Blockers; C10 Lipid Modifying Agents	C03AA03	Hydrochlorothiazide	58-93-5	0.8-117 [2.8] (RO DWTP)		(35)
				2.6-330 [7.1] (NF DWTP)		(35)
	C03CA01	Furosemide	54-31-9	ND (DL=4.30)		(34)
	C04AD03	Pentoxifylline	6493-05-6	ND (DL=5-60)		(33)
				ND (DL=1)		(36)
	C07AA05	Propranolol	525-66-6		ND (DL=1.9; 3 tap water samples)	(37)
	C07AB02	Metoprolol	37350-58-6	up to 13.5 [2.6] (RO/NF DWTP)		(35)
				14-26 [20] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
	C07AB03	Atenolol	29122-68-7	1.2 [18] (8 of 18 samples)	0.84 [0.47] (8 of 15 samples)	(39)
				[2.8] max=26 (11 of 20 DWTPs)		(40)
				ND (RL=0.25)		(41)
				ND (DL=0.05)		(34)

	C08CA05	Nifedipine	21829-25-4		ND (DL=15.5; 3 tap water samples)	(37)
	C08CA05 metabolite	Dehydronifedipine (metabolite)	67035-22-7	2-6 (2 of 12 samples)		(42)
				4		(43)
	C08DB01	Diltiazem	42399-41-7		ND (DL=13.0; 3 tap water samples)	(37)
	C09AA02	Enalapril	75847-73-3	ND (RL=0.25)		(41)
	C10AA01	Simvastatin	79902-63-9	ND (RL=1.0)		(41)
	C10AA01 metabolite	Simvastatin hydroxy acid	12009-77-6 (Na salt)	ND (RL=0.25)		(41)
	C10AA05	Atorvastatin	134523-03-8	ND (RL=0.25)		(41)
				ND (MRL=0.25) (18 samples)	<MRL (15 samples)	(39)
	C10AA05 metabolite	*o*-Hydroxy atorvastatin	214217-86-6	ND (MRL=0.50) (18 samples)	<MRL (18 samples)	(39)
	C10AA05 metabolite	*p*-Hydroxy atorvastatin	214217-88-6 (Ca-salt, acid form)	ND (RL=0.50)		(41)
				ND (MRL=0.50) (18 samples)	<MRL (18 samples)	(39)
	C10AB01	Clofibrate	637-07-0	ND (DL=55)		(44)
	C10AB01 metabolite	Clofibric acid	882-09-7	up to 170 (12 of 14 DWTPs)		(45)
				3.2-5.3 (1 of 3 DWTPs) (DL=1.50)		(34)
				up to 70 (16 of 30 samples) (DL=1)		(46)
				up to 70 (16 of 25 samples) (DL=1)		(47)
				270		(45)

				32		(48)
				0.9-1.1 (2 of 4 samples)		(49)
				>50, <100 (2 of 22 samples)		(50)
				13-136 [59] (3 of 44 samples; 22 DWTPs over 2 years)		(38)
				10-165 (64 of 64 tap water samples from Berlin)		(26)
				ND (DL=130)		(44)
				ND (DL=3-90)		(33)
	C10AB02	Bezafibrate	41859-67-0	27 (1 of 25 samples) (DL=25)		(47)
				up to 14		(51)
				[0.7] max=1.9		(52)
				13-20 [17] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
				ND (DL=0.05)		(34)
				ND (DL=3-90)		(33)
	C10AB04	Gemfibrozil	25812-30-0	ND (RL=0.25)		(41)
				1.3-6.5		(36)
				70 (1 of 10 DWTPs) (DL=3-90)		(33)
				2.4		(53)
				2.1 [0.48] (7 of 18 samples)	1.2 [0.43] (4 of 15 samples)	(39)
				0.6-10.6 (5 of 5 DWTPs)		(54)

				up to 3.0		(51)
				[0.4] max=0.8		(52)
				[1.0] max=2.0 (6 of 20 DWTPs)		(40)
					>2.4, LOD (mean 3 tap water samples)	(37)
					ND (LOD=0.1; 6 tap water samples)	(55)
	C10AB05	Fenofibrate	49562-28-9	14-21 [18] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
	C10AB05 metabolite	Fenofibric acid	42017-89-0	42 (1 of 30 samples) (DL=5)		(46)
Dermatologicals: D01 Antifungals; D06 Antibiotics & Chemotherapeutics; D08 Antiseptics & Disinfectives	D01AE12 S01BC08	Salicylic acid (also transformation product)	69-72-7	10-122 [39] (13 of 44 samples; 22 DWTPs over 2 years)		(38)
					4.2 (mean 3 tap water samples)	(37)
	D06AX02 (multiple)	Chloramphenicol	56-75-7	12-13 [13] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
	D08AE04	Triclosan	3380-34-5	734 (1 of 15 samples) (DL=125)		(44)
				43 (1 of 20 locales)		(36)
				1.2 (1 of 18 samples)	<MRL (15 samples)	(39)
				[1.1] max=1.2 (2 of 20 DWTPs)		(40)
				ND (DL=1)		(56)
				ND (RL=1.0)		(41)
					ND (DL=2.4; 3 tap water samples)	(37)

	D08 (possible assignment)	Triclocarban (Trichlorocarbanilide)	101-20-2	ND (DL=3)		(57)
					ND (DL= 10; samples from 12 DWTPs)	(58)
Genito Urinary System & Sex Hormones: G03 Sex Hormones & Modulators of the Genital System	G03AC01	Norethisterone (Norethindrone)	68-22-4	ND (DL=10)		(59)
	G03BA03	Testosterone	58-22-0	ND (DL=1)		(36)
				ND (MRL=0.50) (18 samples)	<MRL (15 samples)	(39)
	G03CA01	17α-Ethynylestradiol	57-63-6	0.15-0.50		(60)
				ND (DL=5)		(59)
				ND (DL=1)		(36)
				ND (MRL=1.0) (18 samples)	<MRL (15 samples)	(39)
					<90 (below LOQ; 12 tap water samples over several months)	(61)
					ND (DL=4.8; 3 tap water samples)	(37)
	G03CA03	17α-Estradiol	57-91-0	0.3		(60)
	G03CA03	17β-Estradiol	50-28-2	0.20-2.1		(60)
					>100 (below LOQ; 1 of 12 tap water samples over several months)	(61)
				ND (DL=1)		(36)
				ND (MRL=0.50) (18 samples)	<MRL (15 samples)	(39)
	G03CA07	Estrone	53-16-7	1.1-2.3		(36)
				0.2-0.6		(60)

					1.7 (mean 3 tap water samples)	(37)
				1 (1 of 5 DWTPs; but not in raw water)		(62)
				ND (MRL=0.20) (18 samples)	<MRL (15 samples)	(39)
					<70 (below LOQ; 2 of 12 tap water samples over several months)	(61)
	G03CA07 metabolite	Estrone-3-sulfate	481-97-0	0.22 (post ozonation, but ND after GAC)		(63)
	G03DA04	Progesterone	57-83-0	1.1 (2 of 20 locales)		(36)
				0.57 (1 of 18 samples)	<MRL (15 samples)	(39)
	G03	Estrogens: Estradiol (E2) Estriol (E3) Estrone (E1) Estradiol-17-glucuronide Estrone-3-sulfate Estradiol-17-acetate Ethynylestradiol (EE2) Diethylstilbestrol (DES)		ND (< LOQs): <0.59 <1.02 <0.18 <1.02 <0.02 <0.23 <0.83 <0.21		(63)
Antiinfectives for Systemic Use: J01 Antibacterials	J01AA02	Doxycycline	564-25-0	ND (DL=50-150)		(33)
	J01AA06	Oxytetracycline	79-57-2	ND (DL=50-150)		(33)
	J01AA07 (multiple)	Tetracycline	60-54-8	ND (DL=50-150)		(33)
	J01DD04	Ceftriaxone	73384-59-5	ND (DL=1.80)		(34)
	J01EA01	Trimethoprim	738-70-5	1.3 (1 of 20 locales)		(36)
				ND (RL=0.25)		(41)

				ND (DL=5-60)		(33)
				ND (MRL=0.25) (18 samples)	<MRL (15 samples)	(39)
	J01EB02 (multiple)	Sulfamethizole	144-82-1	9 (1 of 8 bottled waters)		(64)
				ND (DL=5-75)		(33)
	J01EB03	Sulfamethazine (Sulfadimidine)	57-68-1	ND (DL=5-75)		(33)
	J01EB04	Sulfapyridine	144-83-2	ND (DL=5-75)		(33)
	J01EB05 S01AB02	Sulfisoxazole (Sulfafurazole)	127-69-5	ND (DL=5-75)		(33)
	J01EB07 D06BA02	Sulfathiazole	72-14-0	ND (DL=5-75)		(33)
	J01EB	Sulfabenzamide	127-71-9	ND (DL=5-75)		(33)
	J01EC01	Sulfamethoxazole	723-46-6	3.0-3.4 (2 of 3 DWTPs)		(65)
				13-80 (2 of 8 bottled waters)		(64)
				2 (after carbon sorption)		(66)
				14		(48)
				20 (1 of 20 locales)		(36)
				3.0 [0.39] (4 of 18 samples)	0.32 (1 of 15 samples)	(39)
				0.3-0.5 (2 of 4 samples)		(49)
				2.0-5.0 (1 of 5 DWTPs)		(54)
				[0.39] max=3.0 (3 of 20 DWTPs)		(40)
				<25 (2 of 22 samples)		(50)

				19-25 [22] (4 of 44 samples; 22 DWTPs over 2 years)		(38)
				ND (RL=0.25)		(41)
				ND (DL=5-75)		(33)
				ND (DL=10)		(42)
	J01EC02	Sulfadiazine	68-35-9	ND (DL=5-75)		(33)
	J01EC03	Sulfamoxole	729-99-7	ND (DL=5-75)		(33)
	J01ED01	Sulfadimethoxine	122-11-2	11 (1 of 8 bottled waters)		(64)
				7.0 (1 of 5 DWTPs)		(54)
				ND (DL=5-75)		(33)
				ND (DL=10)		(42)
	J01ED04	Sulfameter (Sulfametoxydiazine)	651-06-9	ND (DL=5-75)		(33)
	J01ED05	Sulfamethoxy-pyridazine	80-35-3	ND (DL=5-75)		(33)
	J01ED07 D06BA06	Sulfamerazine	127-79-7	ND (DL=5-75)		(33)
	J01FA01 (multiple)	Erythromycin	114-07-8	1.3		(36)
				4.9 (1 of 3 DWTPs)		(65)
				ND (DL=10)		(42)
				ND (DL=0.03)		(34)
	J01FA01 metabolite	Erythromycin-H20	114-07-8?	ND (DL=10)		(42)
	J01FA02	Spiramycin	8025-81-8	ND (DL=0.75)		(34)

	J01FA05	Oleandomycin	3922-90-5	ND (DL=0.02)		(34)
	J01FA06	Roxithromycin	80214-83-1	1.4 (1 of 3 DWTPs)		(65)
				ND (DL=10-150)		(33)
	J01FF02	Lincomycin	154-21-2	ND (DL=0.02)		(34)
				ND (DL=10)		(42)
	J01MA01	Ofloxacin	82419-36-1	0.7-1.6 (2 of 4 samples)		(49)
				ND (DL=20-100)		(33)
	J01MA06	Norfloxacin	70458-96-7	ND (DL=20-100)		(33)
	J01MB04	Pipemidic acid	51940-44-4	ND (DL=20-100)		(33)
	J01MB05	Oxolinic acid	14698-29-4	2.9-4 (2 of 3 DWTPs)		(65)
				ND (DL=20-100)		(33)
	J01MB07	Flumequine	42835-25-6	1.2-2.5 (3 of 3 DWTPs)		(65)
	J01	Novobiocin	303-81-1	ND (DL=10-150)		(33)
	J01 (misc)	Sulfonamides (misc)[c]: *p*-Toluenesulfonamide *o*-Toluenesulfonamide Benzenesulfonamide	 70-55-3 88-19-7 98-10-2	up to (95-percentile): 240 160 60		(67)
	J01 (misc)	Antibiotics	Absence of 18 of 24 in three DWTPs (with all LODs 3 ng/L or lower, except for minocycline [LOD=6ng/L]).			(65)
			Survey of 28 antibiotics in Australia showed frequent occurrence in all waters (up to 64 µg/L in sewage influent) but absence of all 28 in drinking waters from 20 different sites (with LODs for 21 of the analytes being 20 ng/L or lower).			(68)

L01 Antineoplastic Agents	L01AA01	Cyclophosphamide	50-18-0	ND (DL=0.02)		(34)
				ND (DL=5-60)		(33)
Musculo-skeletal System: M01 Antiinflammatory & Antirheumatic Products	M01AB01	Indometacin (Indomethacin)	53-86-1	ND (DL=3-90)		(33)
	M01AB05 (multiple)	Diclofenac	15307-86-5	up to 6 (8 of 30 samples) (DL=1)		(46)
				up to 6 (8 of 25 samples) (DL=1)		(47)
					up to 2.5 (6 tap water samples)	(55)
				14-18 [16] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
				ND (RL=0.25)		(41)
				ND (MRL=0.25) (18 samples)	ND (MRL=0.25) (15 samples)	(39)
				ND (DL=1)		(36)
				ND (DL=3-90)		(33)
					ND (DL=1.2; 3 tap water samples)	(37)
	M01AE01	Ibuprofen	15687-27-1	510-1,350 [930] (2 of 15 samples) (MDL=280)		(44)
				18-23		(69)
				up to 8.5		(70)
				up to 3 (3 of 30 samples) (DL=1)		(46)

				up to 3 (3 of 25 samples) (DL=1)		(47)
				2.7		(53)
				1-32		(36)
				up to 39		(51)
				up to 112		(56)
				2.2-3.0		(71)
					up to 0.6 (6 tap water samples)	(55)
				28 (1 of 44 samples; 22 DWTPs over 2 years)		(38)
					3.4 (mean 3 tap water samples)	(37)
				ND (DL=0.50)		(34)
				ND (DL=3-90)		(33)
	M01AE01 metabolite	Ibuprofen methyl ester	81576-55-8	4,950 (1 of 15 samples) (MDL=110)		(44)
	M01AE02 M02AA12	Naproxen	22204-53-1	up to 7.5		(70)
				8		(36)
				3.0 (1 of 5 DWTPs)		(54)
				up to 1		(56)
					up to 0.2 (6 tap water samples)	(55)
				ND (DL=0.4)		(72)

				ND (RL=0.50)		(41)
				ND (MRL=0.50) (18 samples)	<MRL (15 samples)	(39)
					ND (DL=2.1; 3 tap water samples)	(37)
	M01AE03	Ketoprofen	22071-15-4		up to 3.0 (6 tap water samples)	(55)
				ND (DL=3-90)		(33)
				ND (DL=8)		(70)
	M01AE04	Fenoprofen	31879-05-7	ND (DL=3-90)		(33)
	M01AG01	Mefenamic acid	61-68-7	up to 19.8 [0.9] (RO DWTP)		(35)
				up to 19.9 [1.9] (NF DWTP)		(35)
Nervous System: N02 Analgesics; N03 Antiepileptics; N05 Psycholeptics; N06 Psychoanaleptics;; N07 Other Nervous System Drugs	N02BA01 A01AD05	Acetylsalicylic acid	50-78-2	>50		(48)
				>50, <100 (2 of 22 samples)		(50)
	N02BB01	Phenazone (Antipyrine)	60-80-0	50 (1 of 12 samples) (DL=10)		(46)
				400		(73)
				250		(74)
				11-29 [21] (8 of 44 samples; 22 DWTPs over 2 years)		(38)
	N02BB04	Propyphenazone (Isopropyl-antipyrine)	479-92-5	120		(73)
				80		(74)
	N02BE01	Acetaminophen (Paracetamol)	103-90-2	0.3-3 (2 of 12 samples)		(42)
				1.1-1.3 [3 of 10 brands of bottled water]		(75)

					up to 210.1 (6 tap water samples)	(55)
				33 (1 of 44 samples; 22 DWTPs over 2 years)		(38)
	N03AA03	Primidone (2-Deoxypheno-barbital)	125-33-7	up to 16		(76)
				0.7-1.3 (4 of 4 samples)		(77)
	N03AB02	Dilantin (Phenytoin)	57-41-0	1.1-1.2		(53)
				[1.3]		(41)
				1.6-13		(36)
				19 [6.2] (10 of 18 samples)	16 [3.6] (10 of 15 samples)	(39)
				[9.4] max=32 (15 of 20 DWTPs)		(40)
				1-2 (3 of 4 samples)		(77)
	N03AF01	Carbamazepine	298-46-4	0.3-2.0		(78)
				258 max		(43)
				5.3-7.5		(69)
				6.5-24 (3 of 10 DWTPs)		(33)
				up to 20 ng/L		(76)
				2 (after ozonation)		(66)
				1.1-5.7		(36)
				[29] max=140 (12 of 12 samples)		(42)

				23		(48)
				18 [6.0] (8 of 18 samples)	10 [6.8] (6 of 15 samples)	(39)
				0.8-135 (2 of 4 samples)		(49)
				2.0-7.0 (3 of 5 DWTPs)		(54)
				2.9-721		(51)
				[5.0] max=9.1		(52)
				up to 1.8 [1.2] (RO DWTP)		(35)
				0.5-5.7 [1.0] (NF DWTP)		(35)
				[5.4] max=18 (12 of 20 DWTPs)		(40)
					up to 43.2 (6 tap water samples)	(55)
				10-25 [17] (4 of 44 samples; 22 DWTPs over 2 years)		(38)
					>0.7, LOD (3 tap water samples)	(37)
				ND (RL=0.50)		(41)
				30 (1 of 12 samples) (DL=10)		(46)
				<25 (1 of 22 samples)		(50)
	N03AF01 metabolite	10,11-Dihydroxy-10,11-dihydro-carbamazepine	125-28-0	up to 13		(76)
	N05AX08	Risperidone	106266-06-2	ND (MRL=2.5) (18 samples)	2.9 (1 of 15 samples)	(39)
				ND (RL=0.25)		(41)

	N05BA01	Diazepam	439-14-5	0.33 [0.33] (1 of 18 samples)	<MRL (15 samples)	(39)
				19.3-23.5 (1 of 3 DWTPs) (DL=0.02)		(34)
				ND (RL=0.25)		(41)
				ND (DL=1)		(36)
					ND (LOD=0.4; 6 tap water samples)	(55)
	N05BA16	Nordazepam	1088-11-5		ND (LOD=0.4; 6 tap water samples)	(55)
	N05BC01	Meprobamate (also a metabolite of the prodrug carisoprodol)	57-53-4	1.6-13		(36)
				[5.9]		(41)
				6.5-8		(53)
				42 [5.7] (14 of 18 samples)	40 [5.2] (11 of 15 samples)	(39)
				[9.2] max=43 (17 of 20 DWTPs)		(40)
				6.3-9.4 (4 of 4 samples)		(77)
	N06AA02	Imipramine	50-49-7		ND (LOD=0.7; 6 tap water samples)	(55)
	N06AA09	Amitriptyline	50-48-6		up to 1.4 (6 tap water samples)	(55)
	N06AA12	Doxepin	1668-19-5		ND (LOD=0.7; 6 tap water samples)	(55)
	N06AB03	Fluoxetine	54910-89-3	0.82 [0.71] (2 of 18 samples)	0.64 (1 of 15 samples)	(39)

				1.0 (1 of 5 DWTPs)		(54)
				10 (1 of 44 samples; 22 DWTPs over 2 years)		(38)
				ND (DL=1)		(36)
				ND (DL=14)		(42)
				ND (DL=5-60)		(33)
				ND (RL=0.50)		(41)
	N06AB03 metabolite	Norfluoxetine	56161-73-0	ND (RL=0.50)		(41)
				ND (DL=5-60)		(33)
				ND (MRL=0.50) (18 samples)	0.77 (1 of 15 samples)	(39)
	N07BC02	Methadone	76-99-3	0.1-2.6		(79)
	N07BC02 metabolite	EDDP (methadone metabolite) [2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine]	30223-73-5	1.7-4.7		(79)
Veterinary: QJ01 Antibacterials for Systemic Use; QP51 Antiprotozoals	QJ01EQ08	Sulfaphenazole	526-08-9	ND (DL=5-75)		(33)
	QJ01EQ12	Sulfachlorpyridazine	80-32-0	ND (DL=5-75)		(33)
	QJ01FA90	Tylosin	1401-69-0	0.6-1.7 (1 of 3 DWTPs) (DL=0.25)		(34)
				4.2 (1 of 3 DWTPs)		(65)
	QJ01FA91	Tilmicosin	108050-54-0	ND (DL=0.75)		(34)
	QP51AG03	Sulfaquinoxaline	59-40-5	ND (DL=5-75)		(33)
	QP51AH03	Monensin	17090-79-8	0.1-2.8 (3 of 5 DWTPs)		(54)

Respiratory System: R03 Obstructive Airway Diseases	R03AC02	Albuterol (Salbutamol)	18559-94-9	ND (DL=0.02)		(34)
					ND (6 tap water samples)	(55)
	R03AC03	Terbutaline	23031-25-6		ND (6 tap water samples)	(55)
	R03AC14 R03AC13	Clenbuterol			ND (LOD=0.6; 6 tap water samples)	(55)
Sensory Organs: S01 Ophthalmol ogicals	S01AB04	Sulfacetamine (Sulfacetamide)	144-80-9	ND (DL=5-75)		(33)
Various: V08 Contrast Media	V08AA01	Diatrizoate (Diatrizoic acid; Amidotrizoic acid)	117-96-4	85 max [21] (5 of 10 samples) (DL=10)		(46)
				32		(66)
				60		(80)
				18-100 (3 of 3 DWTPs)		(62)
				129-149		(81)
	V08AA04	Iotalamic acid (Iothalamic acid)	2276-90-6	10		(80)
				ND (DL=4)		(66)
	V08AA05	Ioxitalamic acid	28179-44-4	12		(66)
				ND (4 of 4 DWTPs) (DL=25)		(62)
	V08AB02	Iohexol	66108-95-0	57 (1 of 44 samples; 22 DWTPs over 2 years)		(38)
				38-40		(81)
			Iohexol transformation product	83		(82)

	V08AB04	Iopamidol	60166-93-0 62883-00-5	244		(82)
				up to 79 (4 of 10 samples) (DL=10)		(46)
				60		(66)
				70		(80)
				180 (1 of 4 DWTPs) (DL=25)		(62)
				72-98		(81)
			Iopamidol transformation product	57		(82)
	V08AB05	Iopromide	73334-07-3	up to 177		(69)
				86 (1 of 10 samples) (DL=10)		(46)
				1.1-31		(36)
				4.6		(53)
				40		(80)
				33-36 [35] (2 of 44 samples; 22 DWTPs over 2 years)		(38)
				29 (1 of 4 DWTPs) (DL=10)		(62)
				69-77		(81)
				ND (DL=4)		(66)
	V08AB10	Iomeprol	78649-41-9	11		(66)
				81-92		(81)
				12 (1 of 4 DWTPs) (DL=10)		(62)
			Iomeprol	18 and 289		(82)

			transformation products			
Schedule I & II Controlled Substances	illicit (also: N01BC01) (multiple)	Cocaine	50-36-2	ND (after ozonation & GAC) (LOD <80 pg/L)		(83)
	illicit (also: N01BC01) (metabolite)	Benzoylecgonine (primary metabolite of cocaine)	519-09-5	[45] with max of 130 (22 of 24 samples		(83)
	illicit	MDMA (ecstasy: 3,4-methylenedioxy-methamphetamine)	69610-10-2	2-10 (after ozonation & GAC) ND (after post-chlorination)		(83)

[a] ATC/DDD Index (Anatomical Therapeutic Chemical) classification system: http://www.whocc.no/atcddd/; AT vet Index: http://www.whocc.no/atcvet/database/index.php

[b] DL: detection limit; GAC: granular activated carbon; LOD: limit of quantitation; max: maximum value in range; NF: nanofiltration; ND: not detected (less than DL or RL); (M)RL: (method) reporting limit; RO: reverse osmosis.

[c] Richter et al. (67) provide an overview of the work done in Germany since the 1990s on a series of sulfonamides [*p*-toluenesulfonamide (*p*-TSA), *o*-toluenesulfonamide (*o*-TSA), and benzenesulfonamide (BSA)], which have had a steady presence in certain areas such as Berlin, which rely on ground waters recharged by rivers; their concentrations in ground waters reach up into the low µg/L range. The sources of these sulfonamides in the environment are not solely from antimicrobials (e.g., *p*-TSA is the primary degradation product of the disinfectant chloramine-T), as they also have a wide variety of other non-pharmaceutical uses. Richter et al. (67) provide some of the only data on finished drinking water for *p*-TSA, *o*-TSA, and BSA, which are detected at ng/L concentrations (95th percentile) up to 240, 160, and 60, respectively.

Table II. Summary of APIs Identified in Finished Drinking Water (ranked according to total number of references providing occurrence data within and among each ATC primary group).

API	ATC code	# references[a]	High range[b] [mean range], ng/L
Nervous System: N02 Analgesics; N03 Antiepileptics; N05 Psycholeptics; N06 Psychoanaleptics; N07 Other Nervous System Drugs			
		TOTAL = **59**	Grand Maximum = **400**
Carbamazepine	N03AF01	20	0.7-721 [1.0-6.0]
Dilantin (Phenytoin)	N03AB02	6	1.2-32 [1.3-9.4]
Meprobamate (also a metabolite of the prodrug carisoprodol)	N05BC01	6	5.9-43 [5.7-9.2]
Acetaminophen (Paracetamol)	N02BE01	4	0.3-210
Phenazone (Antipyrine)	N02BB01	4	29-400
Fluoxetine	N06AB03	3	0.82-10
Risperidone	N05AX08	3	0.3-23.5
Acetylsalicylic acid	N02BA01; A01AD05	2	<100
Primidone (2-Deoxypheno-barbital)	N03AA03	2	1.3-16
Propyphenazone (Isopropyl-antipyrine)	N02BB04	2	80-120
Diazepam	N05BA01	2	0.33-23.5
Amitriptyline	N06AA09	1	1.4
10,11-Dihydroxy-10,11-dihydro-carbamazepine	N03AF01 metabolite	1	13
Norfluoxetine	N06AB03 metabolite	1	0.77
Methadone	N07BC02	1	0.1-2.6
EDDP (methadone metabolite)	N07BC02 metabolite	1	1.7-4.7
Cardiovascular System: C03 Diuretics; C04 Peripheral Vasodilators; C07 Beta Blocking Agents; C08 Calcium Channel Blockers; C10 Lipid Modifying Agents			
		TOTAL = **31**	Grand Maximum = **330**
Clofibric acid	C10AB01 metabolite	10	1.1-270 [59]
Gemfibrozil	C10AB04	9	2.1-70 [0.4-1.0]

Bezafibrate	C10AB02	4	1.9-27 [0.7-17]
Atenolol	C07AB03	2	18-26 [1.2-2.8]
Dehydronifedipine	C08CA05 metabolite	2	0.6-4
Fenofibrate	C10AB05	1	21 [18]
Fenofibric acid	C10AB05 metabolite	1	42
Hydrochlorothiazide	C03AA03	1	117-330 [2.8-71]
Metoprolol	C07AB02	1	13.5-26 [2.6-20]
Various: V08 Contrast Media			
		TOTAL = **26**	Grand Maximum = **244**
Iopromide	V08AB05	8	1-177
Iopamidol	V08AB04	6	60-244
Diatrizoate (Diatrizoic acid; Amidotrizoic acid)	V08AA01	5	32-149
Iomeprol	V08AB10	3	11-92
Iohexol	V08AB02	2	38-57
Iotalamic acid (Iothalamic acid)	V08AA04	1	10
Ioxitalamic acid	V08AA05	1	12
Musculo-skeletal system: M01 Antiinflammatory & Antirheumatic Products			
		TOTAL = **25**	Grand Maximum = **4,950**
Ibuprofen	M01AE01	13	1-1,350 [3.4-930]
Naproxen	M01AE02; M02AA12	5	0.2-8
Diclofenac	M01AB05 (multiple)	4	2.5-18
Ibuprofen methyl ester	M01AE01 metabolite	1	4,950
Ketoprofen	M01AE03	1	3.0
Mefenamic acid	M01AG01	1	19.9 [1.9]
Antiinfectives for Systemic Use: J01 Antibacterials			
		TOTAL = **22**	Grand Maximum = **80 [22]**
Sulfamethoxazole	J01EC01	11	0.3-80 [0.39-22]
Sulfadimethoxine	J01ED01	2	7.0-11
Erythromycin	J01FA01 (multiple)	2	1.3-4.9

Flumequine	J01MB07	1	2.5
Ofloxacin	J01MA01	1	1.6
Oxolinic acid	J01MB05	1	4
Roxithromycin	J01FA06	1	1.4
Sulfamethizole	J01EB02 (multiple)	1	9
Trimethoprim	J01EA01	1	1.3
Sulfonamides (misc): *p*-Toluenesulfonamide *o*-Toluenesulfonamide Benzenesulfonamide	J01 (miscellaneous)	1	60-240
Genito Urinary System & Sex Hormones: G03 Sex Hormones & Modulators of the Genital System			
		TOTAL = **13**	Grand Maximum = **2.3**
Estrone	G03CA07	4	0.2-2.3
Progesterone	G03DA04	2	0.57-1.1
17α-Ethynylestradiol	G03CA01	2	<5
17β-Estradiol	G03CA03	2	<320
17α-Estradiol	G03CA03	1	0.3
Norethisterone (Norethindrone)	G03AC01	1	<10
Estrone-3-sulfate	G03CA07 metabolite	1	0.22
Dermatologicals: D01 Antifungals; D06 Antibiotics & Chemotherapeutics; D08 Antiseptics & Disinfectives			
		TOTAL = **7**	Grand Maximum = **734**
Triclosan	D08AE04	4	1.2-734
Salicylic acid (also transformation product)	D01AE12; S01BC08	2	122 [39]
Chloramphenicol	D06AX02 (multiple)	1	13 [13]
Veterinary: QJ01 Antibacterials for Systemic Use; QP51 Antiprotozoals			
		TOTAL = **3**	Grand Maximum = **4.2**
Tylosin	QJ01FA90	2	1.7-4.2
Monensin	QP51AH03	1	2.8

Schedule I & II Controlled Substances			
		TOTAL = **2**	Grand Maximum = **130**
Benzoylecgonine (primary metabolite of cocaine)	illicit (also: N01BC01) (metabolite)	1	130 [45]
MDMA (ecstasy: 3,4-Methylenedioxy-methamphetamine)	illicit	1	10
TOTAL APIs = 54 (plus 10 metabolites)		TOTAL distinct references presenting FDW data = 48	

[a] The number of references providing quantitative data for each API. TOTAL is the sum of the numbers of individual references within an ATC class providing data.

[b] For each API, the high range is the range of the maximum values [or means] reported by all references for each API. Grand Maximum is the highest value reported within an ATC class.

Table III. Top Three APIs within each ATC Class Ranked According to Frequency of Quantitative Data and According to Highest Ranges in the Published Literature.

APIs most frequently reported[a]	**Number of Reports**	**APIs reported at highest levels within each class**[a]	**High Range**
N: Nervous System	Total APIs = 15		
Carbamazepine*	**20**	**Carbamazepine***	**0.7-721**
Dilantin	6	**Phenazone***	**29-400**
Meprobamate	6	**Acetaminophen***	**0.3-210**
J: Antiinfectives for Systemic Use	Total APIs = 10		
Sulfamethoxazole*	**11**	Sulfamethoxazole	0.5-80
Sulfadimethoxine	2	Sulfadimethoxine	7.0-11
Erythromycin	2	Erythromycin	1.3-4.9
V: Various	Total APIs = 10		
Iopromide*	**8**	Iopamidol	60-244
Iopamidol	6	Iopromide	1-177
Diatrizoate	5	Diatrizoate	32-149
C: Cardiovascular System	Total APIs = 9		
Clofibric acid*	**10**	**Clofibric acid***	**1.1-270**
Gemfibrozil*	**9**	Gemfibrozil	2.1-70
Bezafibrate	4	Bezafibrate	1.9-27
G: Genito Urinary System & Sex Hormones	Total APIs = 7		
Estrone	4	Estrone	0.2-2.3
Progesterone	2	17β-Estradiol	<320
17α-Ethynylestradiol	2	Progesterone	0.57-1.1
M: Musculo-skeletal system	Total APIs = 6		
Ibuprofen*	**13**	**Ibuprofen***	**1-1,350**
Naproxen	5	Diclofenac	2.5-18
Diclofenac	4	Naproxen	0.2-8
D: Dermatologicals	Total APIs = 3		
Triclosan	4	**Triclosan***	**1.2-734**

Salicylic acid	2	Salicylic acid	122
Q: Veterinary	Total APIs = 2		
Tylosin	2	Tylosin	1.7-4.2

[a] ATC classes arranged in descending order of number of reports per class. For each class is included only those APIs reported in more than one paper. The six APIs among all reported with the highest frequencies of reports and the six among those with the highest reported rough concentration ranges are each **bolded with asterisks**.

Table IV. Summary of APIs Reported - and some Not Reported - in Finished Drinking Waters (grouped according to ATC code).

ATC code	ATC main group (1st level)	ATC classes reported in FDW[a]	ATC classes not reported in DW[a]	example of API not reported[b]
A	Alimentary tract and metabolism	none	A01-A10	cimetidine omeprazole
B	Blood and blood forming organs	none	B01-B06	clopidogrel warfarin
C	Cardiovascular system	C03,07,08,10	C01,02,04-06,09	propranolol diltiazem
D	Dermatologicals	D01,06,08	D02-05,07,09-11	triclocarban diphenhydramine
G	Genito urinary system and sex hormones	G03	G01,02,04	testosterone ketoconazole
H	Systemic hormonal preparations (excl. sex hormones and insulins)	none	H01-H05	fludrocortisone methylthiouracil
J	Anti-infectives for systemic use	J01	J02-J07	fluconazole miconazole
L	Antineoplastic and immunomodulating agents	none	L01-L04	fluorouracil methotrexate
M	Musculo-skeletal system	M01	M02-M09	probenecid phenylbutazone
N	Nervous system	N02,03,05-07	N01,04	lidocaine selegiline
P	Antiparasitic products, insecticides and repellents	none	P01-P03	ivermectin metronidazole
Q	*Veterinary (15 classes parallel to ATC)*	QJ01, QP51	all others	many are the same as human APIs
R	Respiratory system	none	R01-R07	albuterol terbutaline
S	Sensory organs	few APIs are specific to this class, having assignments to other classes		
V	Various	V08	V01,03,04,06-10,20	radiologicals physostigmine

[a] 2nd level codes (therapeutic subgroup). Note that some APIs belong to two or more ATC 1st or 2nd level groups.
[b] From 2nd level class having no APIs reported in drinking water.

Limitations of Published Data, and Caveats in Data Interpretation

APIs remaining in FDW (but prior to POU) can undergo further reductions in concentrations. These reductions result from various physicochemical (including oxidation by chlorine residual) and biological (e.g., biofilm) processes occurring in the distribution system leading from the DWTP, as well from whatever treatment processes the consumer might use at the POU water fixture (such as carbon sorption or reverse osmosis). For example, Gibs et al. (84) examined the potential for APIs to persist in FDW (assuming they survived treatment) after exposure to residual chlorine in FDW distribution systems. They evaluated the persistence of roughly 30 APIs/metabolites. The majority of the initial residues for each of 14 APIs remained after 1 day, but only for five APIs (carbamazepine, dehydronifedipine, erythromycin-H2O, gemfibrozil, and ibuprofen) did the majority of their residues remain after 10 days. Note that four of these five refractory APIs are among those reported to occur in FDW (see Table I), corroborating their resistance to removal by chorine oxidation.

It is important to keep in mind that some of the data on FDW is from DWTPs that only use minimal finishing - usually just depth filtration. Sometimes the source waters are exceedingly contaminated with a select few APIs - as a result of spills or seepages from leaking sewer pipes, septic systems, or landfills, or because of artificial recharge or manufacturing facilities; for example, see Fick et al. (85), who documented concentrations in the mg/L range from manufacturing discharges. These data are not representative of the API content of FDW in general, especially that produced by large municipalities.

Also extremely important in evaluating the published data is the great unevenness in study scope and among the individual approaches for sampling, analysis, and application of quality assurance. Comparing data among the various published studies is fraught with a wide array of problems, including an unknown (and possibly very large) amount of quantitative and perhaps even qualitative (structural) error; the accuracy of structural identification of API unknowns in FDW is often not verified. Intercomparisons among studies such as those in this review are certainly very crude without thoroughly examining each study in much greater depth. These limitations must be kept in the foreground when trying to compare data across these disparate studies. **As such, the generalizations derived in this document should be used with at least a mild degree of skepticism. The limitations of this document point to how future overviews of APIs in FDW could be greatly improved.**

No systematic surveys have ever been conducted across countries using standardized methodologies with well-defined LOQs (preferably below 1 ng/L) for a broad range of APIs having the potential to be present (e.g., APIs with well-known occurrence in source waters or at least in wastewaters that contribute to source waters). Many published works report on detectable levels of APIs in FDW but at concentrations below the LOQs. At such low levels, many quality assurance issues arise, not the least of which is the contamination of samples from trace residues of an API (or endogenous steroid) residing on the skin of an analyst (originating from either topical application or excretion via sweat) (86).

Better-Informing the Boundaries of APIs in Finished Drinking Water

Although the focus of this document is solely on the reported levels of APIs in FDWs, data for source and raw waters (and even sewage) could serve an important role in establishing the range of APIs having the potential to occur in FDW, depending on the efficiencies of whatever treatment processes are used.

To obtain perspective on the possible boundaries for API occurrence and concentrations in FDW, the voluminous published data on influent and effluent concentrations from STPs could be evaluated. This will not be done here, but by way of example, a recent study of nine POTWs targeted 58 APIs (87). Of the 58 targeted APIs, 56 were detected in the influent for at least one POTW (34 occurring in the majority of samples) and 31 detected in the effluent from at least one POTW (10 occurring in the majority of samples: carbamazepine, clarithromycin, dehydronifedipine, erythromycin, fluoxetine, gemfibrozil, metformin, sulfamethoxazole, thiabendazole, and triclocarban). Influent levels generally ranged from low ng/L up to several µg/L, with some excursions into 101-250 µg/L (e.g., triclocarban, triclosan, cimetidine, metformin, and ranitidine). Effluent concentrations were generally well below 1 µg/L, with some excursions up to the low µg/L range (e.g., 4-epianhydrochlortetracycline, digoxin, metformin, and norfloxacin).

This type of data is useful for targeting APIs that might have the highest potential to occur in drinking water, as well as for delineating the upper possible bounds for FDW concentrations. For example, of the 15 targeted hormones (87), none were detected in any STP effluent sample, greatly reducing the probability that they could occur in DWTP intakes - much less in FDW. Of the 10 APIs most often present in effluents, little evidence exists for the occurrence of four of them in FDW (clarithromycin, metformin, triclocarban, thiabendazole), while the other six have been reported (carbamazepine, dehydronifedipine, erythromycin, fluoxetine, gemfibrozil, sulfamethoxazole; see Table I). Of the four reported in the highest concentrations in STP effluents, little evidence exists for their presence (or absence) in FDW (4-epianhydrochlortetracycline, digoxin, metformin, norfloxacin; see Table I). For these seven APIs that have not been reported in FDW, the extent of published negative data is not known (that is, how frequently they have been targeted but never found).

Establishing Priority API Targets and the Role of Negative Data

The evaluation presented here focuses on positive occurrence data. The English literature was examined comprehensively (using reference 2), with inclusion of certain major publications in other languages. While the compiled FDW data (Table I) is rather comprehensive for the English literature, it is missing an unknown portion of data published in a variety of non-English journals and reports. It would be expected that a significant body of additional data for APIs in FDW also exists but is unpublished or proprietary. For example, a wide array of APIs are monitored by Dutch DWTPs, particularly at intake points along the Rhine; see van der Aa (88, pages 51-54) and GWRC (89). Some of the data in Dutch databases has been captured by Schriks et al. (90). Some of the additional German and Scandinavia data are compiled in Hembrock-Heger and Bergmann (91).

Only a limited amount of negative data was included in Table I. These data of absence captured in Table I were selected primarily as examples and almost always derived solely from the limited numbers of studies that also provided positive data. Compiling negative data and especially data from the third category (absence of data) would entail major efforts in mining the published literature; exhaustive data compilations from these two categories have not been published. Note that the positive occurrence data for FDW in Table I are presented without notation of the geographic locale or the type of finishing treatment used, which were not deemed necessary for the purposes of this overview.

Reducing the great uncertainty surrounding the absence of data, one of the more promising approaches for expanding the identification of APIs not yet reported but possibly occurring in FDW would be the more widespread application of nontarget analysis (e.g., via accurate mass screening); see Hogenboom et al. (92) for an example. More comprehensive characterization of those APIs not yet identified is critical for ensuring holistic assessment of risk (93).

Given the numbers of APIs that could potentially enter FDW, it is important to formulate a strategy for establishing a limited set of priority targets. Source water data can be used to inform the targeting of APIs in finished DW. Maximum concentrations in source waters or raw waters establish the upward boundaries for concentrations in FDW (assuming that conjugates no longer persist). Such data can inform the prioritization process. An important source of complementary information to mine from the published literature is those APIs that have been targeted in either source waters or in raw or finished drinking waters and verified as not occurring above the LODs (given the specific treatment parameters). These APIs would have an extremely low probability of routine occurrence in FDW. The value of data of absence increases as the LOQs or LODs of the methods are reduced. Low detection limits are critical with respect to highly potent APIs such as hormones, which need LOQs below 1 ng/L. Without the context of the LOQs, negative data cannot be interpreted. Many challenges are faced in ultra-low-level analysis. Some are described by Briciu et al. (94).

For perspective on the types and quantities of APIs that can occur in source waters for FDW, consider the broad surveys of Barnes et al. (95) and Focazio et al. (96). The latter study found that 60% of the 36 targeted APIs were not detected in any source water sample; clearly these particular APIs might be ones that would be rarely detected in FDW in the study areas. On the other hand, this same study found carbamazepine was one of the five most frequently detected APIs in ground waters (being detected in 21% of the samples) with five other APIs being detected over 5% of the time: acetaminophen, diphenhydramine, enrofloxacin, erythromycin-H2O, and trimethoprim. Of these six APIs, carbamazepine is the most frequently reported API in FDW (see Table III), and FDW occurrence data exists for erythromycin and acetaminophen. It is not known if enrofloxacin or diphenhydramine have been targeted in FDW.

For perspective on the types of APIs for which negative data have been reported, consider the studies of: Busetti et al. (97), providing some of the most extensive data obtained in Australia; Fawell et al. (98); Garcia-Ac et al. (99); Jux et al. (100), providing negative FDW data for seven APIs in various locales in Germany (but with LODs around 5 ng/L); Rodriguez-Mozaz et al. (63) and Stavrakakis et al. (101), applying methods with largely sub-ng/L LOQs for a number of estrogens and conjugates; Snyder, Trenholm, Snyder et al. (9); Togola and Budzinski (55),

providing rare tap water data at sub-ng/L; Watkinson et al. (68), applying a method for a broad suite of 28 antibiotics across wastewaters, source waters, and FDW in South-East Queensland, Australia [showing frequent API occurrence in all waters (up to 64 μg/L in sewage influent) but absence of all 28 APIs in FDW from 20 different sites (with the LODs for 21 of the analytes being 20 ng/L or lower)]; Wenzel et al. (62), providing negative data for estrogens; and Ye et al. (65), providing a survey of 24 antibiotics with the absence of 18 of 24 in three DWTPs (but with LODs for 21 of the analytes only being 20 ng/L or lower). Petrovic et al. provide a general overview of the APIs occurring in and removed from wastewaters and surface waters (102).

Contaminants Generated from APIs during Drinking Water Treatment

Possibly as important as the APIs that might be present in FDW (a strict function of those present in respective source waters) are those substances not necessarily present in the source water but rather created from APIs during the finishing steps used for the FDW. These chemicals include disinfection by-products (DBPs) and transformation products that are unique to APIs. Of course, a parallel issue concerns the unique transformation products that can be created from APIs by biological and abiotic processes during their transport in the environment.

Although APIs themselves have been the focus of concern for the public and legislators, a potentially large spectrum of other chemicals that can be generated from APIs during treatment or by natural processes may also be present in FDW. Monitoring studies that verify an API's absence from FDW (i.e., below the LOD) almost always fail to account for reaction products. These potential contaminants include DBPs unique to APIs as well as other unique biotransformation products (such as from bacterial metabolism). API-derived chemicals will also include many of the common lower-molecular weight DBPs that share origins from oxidation of a plethora of other organic constituents. The halogenated products (those containing chlorine, bromine, or iodine) are of particular toxicological concern. As an aside, at least one common DBP - chloral hydrate - is an API itself; choral hydrate is still used in medicine and it is unknown what portion of the trace levels in chlorinated waters originates directly from API residues rather than the disinfection process acting on non-APIs.

There have been few surveys of API-derived chemicals in FDW; most studies have focused on laboratory model systems (103-105) or on samples from DWTPs prior to final polishing. This includes those originally present in the source water (human metabolites and environmental transformation products) as well as those created during drinking water treatment, such as DBPs or other products of conventional or advanced oxidation processes (e.g., ozonation, chlorination via chlorine or chlorine dioxide, TiO2-oxidation, UV/peroxide irradiation, and others). Oxidation mediated by hydroxyl radicals can yield numerous intermediates and end-products from a single reactant, especially from heterocycles. These processes can create a complex array of new chemical structures, most of which are more polar and of lower molecular weight than the parent API (halogenated, hydroxylated, cleaved rings), and many of which are isomeric and more persistent. Although reaction intermediates/end products can sometimes express combined toxicity greater than the parent APIs (106), Reungoat et al. (107) found reduced toxicity after ozonation in a water reclamation plant. Narotsky et al. (108) reported no gross effects in rats fed potable disinfected waters containing hundreds of DBPs from miscellaneous chemical contaminants.

While research has been done on the types of products that could potentially be produced during treatment (e.g., from bench- and pilot-scale controlled studies or via biotransformation), very little field monitoring has been performed to identify and quantify those products that are actually present in FDW, especially POU water. General overviews and some specific studies on API transformation products and DBPs have been published by: Dodd and Huang (109), Huber et al. (110), Kormos et al. (82), Kosjek et al. (111), McDowell et al. (112), Quintana et al. (113), Radjenovic et al. (106), Zwiener (114), and Zühlke et al. (74,115), among others.

Even less is known regarding the potential for transformation (such as by biofilms) within FDW distribution systems. Other factors adding further complexity include the potential for certain reaction products to revert back to the original API, as reported for the N-chlorinated intermediate from sulfamethoxazole when free chlorine is insufficient (109).

Of possible utility in gaining better perspective on the types of API-related chemical unknowns that might occur in FDW is the existing base of knowledge derived from the pharmaceutical industry's testing for degradation-related impurities (DRIs) and the products from "stress testing"; an overview of DRIs is available from Baertschi (116). This base of knowledge has never been evaluated for its possible relevance.

Limitations of Comparisons of Data from Different Studies

The types and quantities of APIs in FDW are intimately tied to variables that vary dramatically across studies - especially studies in different countries. Whether an API survives into FDW obviously depends first on whether it is even an ingredient in medicines used by the local populace and whether it has any potential to survive the many steps and barriers before it reaches source water. Sometimes an API is not detected in FDW because it was never present in the source water - other times because it was efficiently removed by the treatment processes or was below analytical reporting limits.

A plethora of factors dictates whether an API can establish a presence in source waters (such as whether it is excreted or disposed to sewage in sufficient amounts). But some factors depend on the specific geographic location of the DWTP. The major factors among these are the geographic prescribing practices (which dictate the types and quantities of APIs in the subset of medications most prescribed locally), the technologies used for treating raw sewage, the degree of dilution occurring before the treated sewage mixes into the source waters (effluent-dominated streams and those receiving raw sewage, such as from overflow events, will have higher API levels), weather and season (temperature, UV irradiance, and precipitation all play important roles in the efficiency of sewage treatment, the extent of natural transformation processes, and the degree of dilution), the technologies used for treating and finishing the raw drinking water (which vary from minimal to advanced), and whether the consumer employs further treatment at the point of use. The last point greatly lessens the significance of most FDW data, which is usually obtained from sampling done at the DWTP - not at the point of use.

The great number of sequential steps that serve to reduce the probability of any given API entering FDW at a detectable concentration combine to yield concentrations of APIs so low in

FDW that they were not routinely and reliably detectable even 10 years ago. Of all the documents with FDW data on APIs, roughly only a dozen or so were published before 2000, and the vast majority published only since 2006.

Table I presents the data compiled from all published reports evaluated for this study. This is perhaps the most comprehensive compilation to date of data mined from the published literature on the occurrence of APIs (and metabolites) in FDW, expanding on that first presented in 2008 (3). A total of 48 documents have reported occurrence information for APIs in FDW (Tables I and II); this represents a minimum number of studies that have examined FDW. These documents provide both quantitative and qualitative occurrence data. A limited amount of negative occurrence data (data of absence) are also included; these data of absence, however, are probably not representative of the full scope of types of APIs that have been targeted but never detected during monitoring. In many cases of data of absence, parallel positive occurrence data exist for the same API. It is critical to keep in mind, however, that these published data cannot be considered as statistically representative of API occurrence in drinking water from any particular locale. With very few exceptions, each of these studies was extremely limited in scope and employed various methods of analysis and quantitation and quality control measures; no attempt was even made in this examination to determine the veracity of actual identification of a targeted API.

Anatomical Therapeutic Chemical (ATC) Classification System

Given the thousands of distinct APIs used worldwide (formulated into tens of thousands of different medical products), it is critical to use an organizing framework around which to make sense of the reported data. This facilitates intercomparisons of data. The drug classification system of the World Health Organization (WHO) is used in this examination: the Anatomical Therapeutic Chemical (ATC) classification system. The ATC classification attempts to link APIs to their intended therapies. APIs with similar physicochemical properties often exhibit similar biological activity and will therefore group together. Some APIs have numerous trade and generic names; the ATC forces these to be grouped together. The ATC comprises more than 800 hierarchical classes that span five levels within 14 main groups; parallel ATC systems exist for human and veterinary drugs. APIs in the same 5^{th}-level ATC class have higher probabilities of sharing common mechanisms or modes of action. APIs among the same class might therefore be expected to act via combined action; APIs in different classes have potential for interactive effects. Those sharing the same 5^{th}-level ATC class can be readily seen in Table II. One consequence is that the individual concentrations of APIs from the same class might possibly be summed for the purposes of assessing risk. An example of its prior use for APIs as environmental contaminants is provided in Ruhoy and Daughton (117, see Table 5 therein). Note that the challenges posed for environmental monitoring in selecting which of the thousands of molecularly distinct APIs to target are multiplied further not just by isomers composing racemates and further yet by multitudes of products from metabolism and transformation, but also by emerging aspects of drug design such as deuterated analogs and structural analogs; the latter are being increasingly synthesized as unapproved drugs, and their society-wide usage rates are unknown.

Major Findings Distilled from the Published Literature

The summary of positive occurrence data in Table II is distilled from Table I. The negative occurrence data in Table I (including qualitative data when LOQ levels were below 1 ng/L) were removed. For each API, the numbers of references that measured the API in FDW were totaled. Within the appropriate ATC group, the APIs were sorted according to the numbers of references reporting positive occurrence data. These publication numbers are then summed within each ATC group, and the groups sorted according to the summed number of publications.

The APIs reported to occur in FDW belong to the following ATC primary classes, ranked in descending order of prevalence: N (Nervous System) [59 individual reports], C (Cardiovascular System) [31], V (Various) [26], M (Musculo-skeletal system) [25], J (Antiinfectives for Systemic Use) [22], G (Genito Urinary System & Sex Hormones) [13], D (Dermatologicals) [7], Q (Veterinary) [3], and Controlled Substances [2]. **The top four classes with the most APIs (N, C, V, and M) are perhaps the classes that human-health risk assessments could focus on, especially with respect to those APIs that might share a common mechanism or mode of action.** However, since ATC V comprises exclusively iodinated X-ray contrast media, which are established as having extremely low toxicity, the next class to consider would be ATC J (the antiinfectives).

The summary of occurrence data in Table III is distilled from Table II. Published quantitative data for FDW exists for 64 APIs and transformation products (54 APIs and 10 metabolites or transformation products). Significantly, however, for these 64 substances only 17 have corroborating quantitative data from more than two reports each. The numbers of unique APIs reported in each ATC class, ranked in descending order, are: N [15], J [10], V [10], C [9], G [7], M [6], D [3], and Q [2]; illicit controlled substances comprised 2 APIs. The top three APIs within each ATC class are ranked according to frequency of quantitative data in the published literature. As in Table II, the ATC classes are arranged in descending order of number of total measurements per class for all APIs combined. For each class is shown only those APIs reported in more than one paper.

There were 54 APIs/metabolites that had been targeted in a variety of studies but not detected above reporting limits (see Table I). But of these 54, only nine had corroborating negative data from two or more studies. Since these negative data were compiled from only a portion of the studies that reported positive data for other APIs, the number of APIs for which only negative data exist is most likely higher.

From Table I, **of the studies that have surveyed the most APIs at once in FDW, none has identified more than a dozen APIs in any given sample**. The 10 studies that targeted the most APIs in FDW (ranging from 42 to 8 APIs), in decreasing order, are: Tauber (33), Benotti et al. (39), Snyder et al. (36), Vanderford and Snyder (41), Zuccato et al. (34), Togola and Budzinski (55), Ternes (46), Stackelberg et al. (42), Illinois EPA (54), and Bruchet et al. (66).

From Table III, **it is evident that the six most frequently reported APIs in FDW are: carbamazepine [20 reports], ibuprofen [13], sulfamethoxazole [11], clofibric acid [10], gemfibrozil [9], and iopromide [8]. The six APIs with roughly the most consistent highest**

reported concentrations in FDW are: ibuprofen [1,350 ng/L maximum], triclosan [734], carbamazepine [721], phenazone [400], clofibric acid [270], and acetaminophen [210]. Of the 64 APIs/metabolites, none (with only one exception - a single data point for ibuprofen) exceeded a concentration of 1 ppb (1 µg/L).

From Table II, it can also be seen that **of the 64 APIs/metabolites quantified in FDW, nearly half of them (28 APIs) have been reported individually only by a single study**. So for only 36 APIs has positive occurrence data been corroborated in at least a second study.

Of the APIs/metabolites targeted in the planned "Emerging Contaminant Sampling Program" (20), the following additional analytes are also being considered (among possibly others): 17β-estradiol, 17α-ethynylestradiol, clofibric acid, diclofenac, estrone, and naproxen.

For no ATC main group have APIs representing all 2nd-level classes been reported in FDW (Table IV). For six of the 14 ATC main groups, no API has been reported: A, B, H, L, R, or S. Examples for each of the ATC main classes are provided in Table IV. Notably, no antineoplastic or immunomodulating agent has been reported, nor have any radiologicals. Little data exist for any type of drinking water on the occurrence of rare earths or radionuclides used in diagnostics and treatment; one of the few examples is the positive gadolinium anomalies identified in well-water supplies for drinking water in France (118). Finally, note that certain ATC classes have APIs that can originate from other sources, such as pesticides (ATC group P); these have not been included in this survey.

General Observations and Insights

The following are some of the key observations and insights derived from Tables I-III.

API levels reported in FDW rarely ever exceed 1 ppb. The vast majority are probably below 50 ng/L. Many have maximum reported concentrations of only several ng/L. To place these ppt concentrations of APIs into perspective, many halogenated DBPs in FDW occur at concentrations well above 1 µg/L (e.g., see: 119).

Detection limits pose a major challenge in comparing data across studies. LODs can vary by an order of magnitude or more. A positive finding in one study could easily have been a negative finding in another having a higher LOD. At the same time, as LODs are pushed inexorably lower, increasing numbers of APIs (as well as vast numbers of other ultra-trace contaminants) will continue to be revealed.

Veterinary Medicines:

Two APIs used primarily in veterinary medicine (monesin, tylosin) have been identified in FDW. A number of other APIs also share human and veterinary uses, so generalizations as to their origins are not possible.

Possible Outliers:

Some of the individual APIs or instances of seemingly spurious high concentrations occur only in unique and relatively rare situations not translatable to most other locales - such as those using

nominal treatment or where large quantities of APIs have entered source water (e.g., from landfills, manufacturing or hospital waste streams, or groundwater recharge). For this reason, most of the data for these unusual situations was not compiled. This includes data from private wells. This was the case with some of the historic data from Berlin.

X-ray Contrast Media:

X-ray contrast media are established as being among those APIs most difficult to remove in water treatment. Their presence reflects the fact that a water's origin is at least partly contributed by sewage and that other APIs therefore also have the potential to be present. A corollary is that the absence of these iodinated chemicals points to an increased probability that other APIs may not be detectable.

Bottled Water:

Given that bottled water provides a significant source of drinking water for many people (120), the extremely limited data for APIs in bottled water is notable - being limited to the two studies of Perret et al. (64) and Naidenko et al. (75), with positive occurrence data presented for four APIs. A recent examination of bottled water for total estrogenic activity evaluated 20 brands of mineral water commonly available in Germany (121) and provides the first indication that contamination of bottled mineral water by estrogenic chemicals may be widespread. The bottles ranged with values from 2–40 ng/L estradiol equivalents (with a maximum of 75 ng/L estradiol equivalents). Plastic bottles typically had higher values than glass, pointing to an origin associated with the plastic rather than the water's source; APIs, therefore, might not be expected to play a significant role in terms of estrogenicity in bottled water.

Antibiotics:

Antibiotics pose concerns removed from those of other API classes. The potential for selection of antibiotic-resistant pathogens from exposure to low levels in the environment is often cited as a major concern. While the low levels in the environment, which rarely ever exceed a small fraction of 1 μg/L, may pose concerns with regard to microbial community structures in native environments (122), no evidence has emerged regarding the potential for any type of effect from the ng/L concentrations that occasionally occur in FDW. Perhaps of more interest might be the possible role of biofilms in distribution pipes as a source of resistant bacteria and antibiotic resistance genes (ARGs) (123); ARGs as pollutants in their own right have received growing attention (124-126). Also of interest is that low-levels of antibiotics might affect the functioning of biofilms in drinking water distribution systems or in release of cells from biofilms; while still too high for FDW, concentrations of 500 ng/L of phenazone, amoxicillin, or erythromycin in FDW affected the initial surface-adhesion of bacteria (sometimes enhancing it and other times inhibiting it) (127).

Reverse Osmosis:

Little data has been published on the removal of APIs by full-scale reverse osmosis. Radjenovic et al. (35) published one of the only examinations of APIs handled by DWTPs using reverse osmosis (RO) and nanofiltration (NF). Of 31 APIs targeted in the source ground water, 12 (acetaminophen, carbamazepine, diclofenac, gemfibrozil, glibenclamide, hydrochlorothiazide, ketoprofen, mefenamic acid, metoprolol, propyphenazone, sotalol, sulfamethoxazole) were frequently detected at average concentrations ranging from 4.3 ng/L (sotalol) to 137 ng/L

(ketoprofen), with excursions up to the hundreds of ng/L (carbamazepine, diclofenac, gemfibrozil, ketoprofen, propyphenazone) or thousands of ng/L (hydrochlorothiazide). Full-scale NF and RO DWTPs consistently eliminated all but four APIs to average concentrations below the detection limit. Average concentrations remaining in the finished drinking water (permeate) for hydrochlorothiazide, metoprolol, carbamazepine, and mefenamic acid were all less than 8 ng/L, with excursions of hydrochlorothiazide up to 117-330 ng/L. Of significance, however, were the residues of all 12 APIs that remained in the concentrate (brine stream). These ranged from averages of 0.8 ng/L (mefenamic acid) to 429 ng/L (ketoprofen), with excursions up to 520 (diclofenac), 692 (carbamazepine), 695 (ketoprofen), and 6,336 (hydrochlorothiazide). This points to the problem associated with physical removal processes (e.g., activated carbon, membrane filtration), which generate a waste stream with APIs at concentrations 3- to 5-fold higher than in the raw source waters; these brine streams are often then discharged.

Illicit Drugs:

Finally, given that illicit drugs experience broad use throughout society and given their marked biological effects and potencies, surprisingly little data is available on their occurrence in FDW (or the presence of their metabolites or synthesis products). Historically, interest in the occurrence of pharmaceutical ingredients in the environment (including FDW) has focused almost exclusively on the APIs contained in medications and diagnostics dispensed legally by pharmacies and consumed for their accepted medical purposes. In parallel, however, a huge market exists for a variety of drugs that are sold illegally. Some of these drugs also have legitimate medical uses, but the remainder have no known medical uses; many of the latter are included on (or are covered by) the DEA's list of Schedule I controlled substances - those substances that have "no currently accepted medical use in treatment in the United States." This group is informally termed "illicit drugs" and includes the substances obtained illegally belonging to the general groups: anabolic steroids, narcotics (opiates), stimulants, depressants (sedatives), hallucinogens, and cannabis. More accurately, illicit drugs are those drugs that are trafficked or consumed illegally – including those that are manufactured legally.

The striking aspect of illicit drugs is that their active ingredients clearly have marked potential for biological effects - some being quite potent - but comparatively little attention has been devoted to whether the ingredients from those drugs having major illicit markets occur in the environment. Almost no attention has focused on whether the active ingredients in illicit drugs occur in FDW. The two groups of ingredients - legal and illicit - should be considered seamlessly in characterizing and assessing risk incurred from environmental exposures.

The two major studies to date that examine illicit drugs in drinking water are Huerta-Fontela et al. (83) and Boleda et al. (79). Boleda targeted five opiates in raw drinking water in Spain: morphine, codeine, norcodeine, methadone, and EDDP (primary methadone metabolite) and found concentrations ranging from near zero (norcodeine) to 75 ng/L (codeine). Residues of four (not morphine) survived ozonation, and portions of EDDP (0.2-2.9 ng/L) and methadone (0.1-1.7 ng/L) survived carbon filtration and chlorination.

Huerta-Fontela et al. (83) presented perhaps the first data on the stepwise removal of Schedule 1 or 2 controlled substances throughout a treatment train used to generate FDW at a municipal DWTP (in Spain). A 300 MGD DWTP used water from a river and a treatment train of

prechlorination, physical coagulation/filtration, ozonation, carbon sorption, and post-chlorination. Among the targeted analytes were cocaine, benzoylecgonine (BE: a primary cocaine metabolite), amphetamine, methamphetamine, MDMA (ecstasy: 3,4-methylene-dioxymethamphetamine, the methylenedioxy derivative of methamphetamine), and its N-demethylated metabolite (MDA: 3,4-methylenedioxyamphetamine).

Removals after prechlorination and filtration to below detection limits occurred for the amphetamines except for MDMA; the intake concentrations for amphetamine, methamphetamine, and MDA had ranges of 5-90, 0.2-2, and 2-50 ng/L, respectively. MDMA, however, was reduced at this step by only 23% (unless its intake concentration was below 10 ng/L), and cocaine and BE were removed by only 13% and 9%, respectively (with intake concentration ranges of 3-120 and 20-1,350 ng/L, respectively). After ozonation, cocaine, BE, and MDMA had been removed by 24, 43, and 28%, respectively. After carbon sorption, more than 99% of cocaine was removed (yielding concentrations below 80 pg/L), while MDMA and benzoylecgonine were removed by 88% and 72%, respectively. After the final post-chlorination, no MDMA was detected (less than 170 pg/L), but more than 10% of the BE persisted. In 22 of 24 FDW samples, the mean concentration of BE was 45 ng/L and its maximum was 130 ng/L. Ketamine, PCP, LSD, and fentanyl were never found in the raw waters.

Clearly, some of these substances (e.g., BE) have the same potential to persist at very low levels in FDW as do many of the APIs from legal drugs.

Unapproved Drugs:

A parallel issue regards unapproved drugs and "designer" drugs undeclared as active ingredients (new pharmacologic molecules) and whose existence may or may not be known to the FDA (128). These include not just new analogs of anabolic steroids, but also new (and untested) analogs of registered drugs. The latter, for example, are used not infrequently in OTC supplements (129). Whether they occur in the environment (or in FDW) is completely unknown. Adulterants in herbal supplements or OTC/Rx drugs often occur at high levels. An example is the analogs of the approved phosphodiesterase type 5 (PDE-5) inhibitors (used primarily in treating erectile dysfunction), such as sildenafil, vardenafil, and tadalafil (e.g., see: 130,131). Further, the emerging possibility of new APIs using isotopic substitution (deuterated analogs) could pose yet further analytical challenges for water surveys (1); olanzapine-Cd3 (an atypical antipsychotic) is but one example.

Major Unanswered Questions

A major unanswered question is the extent to which APIs have been targeted in FDW monitoring studies but have not occurred above the limits of detection (or quantitation). Such data of absence are of particular interest if they occur in the complete absence of any positive data of occurrence, as this would contribute to a preponderance of evidence for the probability of an API's occurrence in FDW as being diminishingly low. This type of valuable information would require a separate intensive examination of the literature. Comprehensive data of absence would provide justification for targeting alternative APIs for FDW monitoring and greatly reducing or eliminating any future efforts targeted at the lower-probability APIs. For example, in the literature examined here, those APIs with data of absence and lacking any data of

presence (reported by more than one study) include: atorvastatin, *p*-hydroxy atorvastatin, triclocarban, testosterone, cyclophosphamide, and albuterol.

A parallel question of equal or greater importance is which APIs have never been targeted for FDW monitoring - that is, those for which neither occurrence data nor data of absence exist (namely, those with absence of data). Data of complete absence (supported by a critical number of studies) coupled with complete absence of data, would be indispensable in guiding future investigations to focus monitoring on other APIs not yet examined. Given the sheer number of APIs in use today, the scope of APIs never before examined but deserving of attention could be greatly reduced by use of published data on environmental occurrence, modeling, and potential for adverse health effects. An alternative approach is non-targeted characterization of unknowns, such as by accurate mass screening (92).

The question can now be posed as to what more can be gained by continued monitoring of FDW for the same limited set of APIs. One possible advantage, which the CCL3 (19) might have the opportunity to evaluate, is whether significant excursions in concentrations occur for the set of APIs targeted by the CCL3.

Is the body of data on APIs in FDW sufficiently comprehensive that we can be assured that ephemeral, transient, or seasonal excursions do not frequently occur significantly beyond the currently known maximum concentrations? For example, excursion could occur from seasonal fluctuations in waste dilution (e.g., effluent dominance during dry weather) or in drug use (types and quantities), sporadic disposal practices (resulting in brief transient excursions), or other special circumstances. Studies of seasonal fluctuations of APIs in FDW are rare. As one example, Kormos (51) monitored FDW from two DWTPs in Ontario for bezafibrate, carbamazepine, gemfibrozil, and ibuprofen. Reliance on grab sampling instead of time-integrative sampling increases the likelihood that spikes in concentrations will be missed. Carbamazepine concentrations varied by over two orders of magnitude over the course of 12 months (from 2.9-721 ng/L), showing the possible difficulties with obtaining grab samples that are representative over time. Buschini et al. (132) have shown the possible importance of establishing the potential for sustained exposure over longer periods of time rather than via intermittent grab samples.

While most APIs experience relatively constant usage throughout the seasons (especially maintenance medications), others undergo seasonal cycles. One example is medications associated with the flu. An extreme example would be antivirals such as oseltamivir, which could experience usage rates orders of magnitude higher than usual during epidemics. Time-averaged usage rates are not necessarily a good predictor of which APIs (or respective metabolites) have the potential to enter waterways and source waters. Also, specific or unique characteristics of individual locales can result in usage patterns completely different than indicated by overall sales data (e.g., emissions from hospitals). Worst-case modeling has predicted oseltamivir (and its carboxylate active metabolite) each in drinking water at over 100 µg/L (133); other antivirals (such as acyclovir, nevirapine, penciclovir, stavudine, and zidovudine) are now known to persist in treated wastewater (134).

Risk and APIs in Drinking Water

Discussions regarding the presence of APIs in FDW inevitably devolve into concerns surrounding the ramifications for human health. Given the extremely low individual and combined concentrations of the very limited subset of APIs currently known to sometimes be present in FDW (sixty-some APIs among more than 1,500 in common use), the focus gravitates toward two major aspects of toxicology: (1) the unknowns surrounding the potential for biological effects at the extreme low end of dose-response curves and (2) the complexities associated with mixture effects (both additive and interactive). These unknowns are greatly exacerbated by the fact that a large array of other microconstituents unrelated to APIs - both anthropogenic and naturally occurring - also contaminate even the purest of waters. Intertwined are arguments regarding toxicity thresholds and chronic, vulnerability exposure windows, and transgenerational exposure. Teasing apart the toxicological significance of APIs from that of all the other ultra-trace contaminants is currently not possible.

Two stances bookend the extremes of the overall toxicological concern. On the one extreme, no empirical evidence has emerged indicating a known hazard of APIs in FDW - pointing to no reason for concern. On the other, an inevitable question is whether it should be acceptable at the outset to allow any detectable amounts of APIs in FDW if multiple-log removals could be achieved with best available technologies or if they can be prevented from entering the water cycle to begin with (by implementing any number of a large spectrum of pollution prevention measures). This latter extreme stance is motivated largely by the fact that APIs derive from sewage, and, as such, serve as direct measures of the length of wastewater-drinking water hydrologic connection and therefore as markers for the possible presence of other, still unidentified contaminants conveyed by sewage.

One extreme scenario posing a possible health hazard comprises the special situations where APIs are released to source waters in unusually large quantities - reflecting idiosyncrasies of particular geographic locales. Examples include historic waste spills or landfills with hydrologic connectivity to groundwater, or exceptionally high levels discharged in waste streams from manufacturing or hospitals (or sewage overflow events) to surface waters that serve as immediate source waters for DWTPs using only nominal treatment technologies.

Risk Overview:

Quite a number of studies of varying rigor have presented assessments of risk from trace levels of APIs in FDW. Almost without exception, these all share a similar approach. The therapeutic dose (TD), coupled with a series of safety or uncertainty factors (which are used to infer limits such as the ADI - acceptable daily intake), is almost always used as the benchmark with which to compare known or worst-case modeled API-FDW concentrations and assumptions regarding water consumption (perhaps most accurately assumed to be 20 mL/kg/day on a body-weight basis). The TD, however, may not be a relevant benchmark against which to judge risk.

Assessing the potential for risk from APIs in FDW is a topic deserving a comprehensive examination and far exceeds the scope of this review. A truly comprehensive, holistic assessment has never really been published but a recent examination by Bull et al. (135) is one of the most

comprehensive. Some general points can be made, however, regarding what has been published to date.

First, for further reading, assessment of risk from general chemical exposure in drinking water (especially recycled water) has been covered in a number of publications, several of which are: Asano and Cotruvo (136), Chapman et al. (137), Falconer (138), Howd and Fan (139), and Rodriguez et al. (140).

Examinations of risk targeted specifically at APIs in drinking water began only 10 years ago and include: Bercu et al. (141), Blanset et al. (142), Bull et al. (135), Christensen (28), Collier (143), Cunningham et al. (144), Daughton (3), Dorne et al. (145), Global Water Research Coalition (146), Illinois EPA (54), Johnson et al. (147), Jones et al. (6), Kümmerer and Al-Ahmad (148), Mons et al. (149), National Water Quality Management Strategy (150), Rahman et al. (151), Randon (152), Reddersen et al. (73), Rowney et al. (153), Schulman et al. (154), Schwab et al. (155), Snyder et al. (9), Watts et al. (133), and Webb et al. (156); note, however, that some of these assessments were based on predicted rather than measured concentrations. Human exposure to APIs in drinking water was the focus of a 2008 National Academy of Sciences workshop (157).

Low-Dose Exposure:

Even fewer studies have presented empirical data, especially data pointing to the potential for human effects at low API concentrations; examples include Pomati et al. (158,159) and Vosges et al. (160). Perhaps the data of most direct relevance for human health impacts has come from epidemiological studies of worst-case human exposures. These have focused on communities using drinking water that comprised significant portions of recycled water; examples include Cook et al. (161) and Rodriguez et al. (162), and others cited in Daughton (163). The assumption is made that the concentrations of APIs in recycled water would be higher than in FDW from most municipal DWTPs using "natural" source waters. While any effects specific to APIs cannot be isolated from the effects of all other contaminants, the uniform absence of adverse health impacts from these epidemiological studies makes this concern moot. But even if adverse outcomes were to be documented, distinguishing correlation from causation would be extremely difficult.

Predicting human response to ultra-low dose (ULD) exposures currently relies on linear extrapolation from higher-dose exposures in animal test systems. Higher doses are required to have sufficient statistical power to detect responses (primarily cancers) above background. Sufficient power at ultra-low doses can only be obtained by using very large test populations. Such an approach has been used with trout as the test species. Over 40,000 trout have been used to test ultra-low doses of several known carcinogens (164,165). Of most significance is that linear extrapolations were shown to be both overly and under conservative depending on the carcinogen, pointing to the unknowns associated with predicting responses from ULD exposures.

Therapeutic Dose as a Point of Departure:

In general, assessment of risk from API exposure has been predicated on using the therapeutic dose (TD) as a point of departure (POD) (e.g., see: 135); margins of exposure between FDW concentrations and minimum therapeutic doses can then be calculated and ranked (135). Use of

the TD as the POD has been justified on the basis that (by definition) the therapeutic effect is positive (desired), rather than adverse, and therefore that doses below the TD would be without consequence. From the published data on APIs in FDW (Table I), it is hard to dispute that APIs in FDW occur at concentrations so low that daily water consumption would have to be sustained for a lifetime before a dose approaching even a small fraction of a single recommended daily dose might be reached. Many studies have emphasized this point. This appears to be true for the vast majority of all APIs (those that are not direct-acting genotoxicants) but perhaps not for a few very potent APIs such as EE2 (e.g., see: 143). Even for APIs such as EE2, however, usage rates are so small that their routine occurrence in drinking water is doubtful - a fact supported by the published literature's data of absence (Table I).

The TD has been used as the POD for assessing risk presumably because it is readily available and is a central aspect of all medication. Its use in assessing risk from ULD exposures, however, has never been justified or cogently rationalized. Few evaluations, however, have deviated from this general approach. Collier (143) is one example. Use of the TD as the POD probably introduces the most uncertainty in assessing the risk from APIs in FDW. Many issues point to the TD as being far too high for the POD. Therapeutic doses (and endpoints) may not be the appropriate benchmark against which to assess risk (3). Attention to doses that are known to elicit any type of effect, regardless of how subtle, may be more relevant.

Much discussion centers on the relevance to environmental exposures of high-dose testing. At ever-lower exposure levels, there is perhaps always some type of effect. These effects just may not be measurable (perhaps obscured by natural variation in homeostasis), or we may not yet know to look for them. Exposures to ever-lower levels may lead to effects from a changing variety of mechanisms or pathways. That effects can vary with dose is known as “mixed-mode dose-response” or "dose-dependent transitions in mechanisms of toxicity." This is partly a result of multiple effector sites, all having different ligand affinities and resulting in crosstalk among different signaling pathways.

The possible significance of low-dose exposures and the many issues surrounding low-dose extrapolations, dose-response thresholds, and transitions in mechanisms of action are discussed by Gore et al. (166), Holsapple and Wallace (167), Kortenkamp et al. (168), Myers et al. (169), Welshons et al. (170), and White et al. (171), among others.

Some of the questions regarding the relevance of the TD as a POD for assessing risk include:

- TD might be unrelated to other subtle endpoints or adverse effects. Is it valid to assume that the potential for adverse effects is a function of the therapeutic dose (potency)?
- Side effects that are not considered “adverse” may well still be considered unacceptable to the public if the exposure is not known, unexpected, or unwelcome. When an exposure is not expected, any type of effect that perturbs homeostasis may be deemed by the public as unacceptable. Whether the effect is normally deemed even beneficial can be irrelevant. Perceived risks need not be associated with adverse outcomes (12,18), and adverse outcomes can result solely from negative expectations in the absence of any hazard. This is known as the nocebo response (3).

- For many APIs, the approved route of administration for therapy is not oral. Does exposure to an API by ingesting drinking water emulate the route(s) used in therapy? For example, might there be any unforeseen consequences of ingesting drugs intended solely for external administration (86), or of pulmonary exposure to APIs entrained in aerosols (such as during showering) but never intended for inhalation?
- ADIs (acceptable daily intakes) refer to exposure levels likely to not result in adverse effects. They do not, however, necessarily translate to an absence of effects. Determining ADIs assumes that effects diminish with dose until a threshold is reached. They are derived from the "no observable adverse effect level" (NOAEL). The key aspect of the NOAEL is whether an effect has been observed. Subtle effects and latent or delayed-onset effects can be difficult to spot. A NOAEL is not a threshold. Rather, a NOAEL simply means that a particular, anticipated adverse effect has not been observed - not that one which escapes current detection or which has a delayed-onset will not occur. Are techniques available for detecting and measuring effects sufficiently sensitive for low-level exposures, or are there no effects to detect? Are the types of possible subtle effects even sufficiently understood? Thresholds also may not apply to APIs having the same mechanism of action as endogenous chemicals - sex steroids are one example - since the thresholds may often already be exceeded since they are in addition to the endogenous production (166).
- TDs are determined on comparatively extremely small, specifically targeted sub-populations before marketing an API. Often excluded from these trials are the chemically sensitive such as children, pregnant women, immune-compromised individuals, and others. Perhaps the majority of adverse effects are really only revealed post-market because longer-term exposure for a much larger test population is required to detect less frequent (and perhaps subtle) effects; the expanded population includes those receiving the API for off-label purposes. Adverse events often surface post-market partly because they can go unreported during trials as a result of the use of "human guinea pigs" in clinical trials - "professional volunteers" who are motivated to transition quickly between trials (172). Also, large segments of the population are excluded by the use of usually narrowly targeted populations that are the focus of the intended therapeutic treatments.
- Data obtained from clinical trials rarely simulate the higher frequency and duration (even transgenerational) of possible exposure via FDW.
- An argument used against the potential for low-dose effects is that the need to invoke previously unknown mechanisms of action is not plausible. This argument is not supported by the history of pharmacology, however, where new mechanisms of action are commonly revealed as new drug targets are discovered.

When evaluating the literature on ULD effects, the question needs to be "what is the evidence pointing to the potential for <u>any</u> type of biological response from exposure to concentrations of APIs found in FDW"? Deeming whether these responses could be “adverse” is a subjective judgment. Treatments can have biological activity but not be clinically effective. The published literature could potentially be biased by the relative under-representation of published studies finding seemingly inconsequential effects that were deemed of no clinical significance. Therefore, the concern is whether *any* type of response is possible - not just whether the targeted response is obtained.

Studies Using Ultra-Low Doses and Micro-Dosing:

Instead of a focus on therapeutic doses, the issue of APIs in FDW could be more informed by the current research on sub-therapeutic doses. In the last decade, one aspect of pharmacology that continues to develop - yielding new insights into the properties of dose-response - is the study of so-called "ultra-low" doses (ULD) and the practice of "micro-dosing." The literature surrounding these two could be mined and synthesized for its possible utility in assessing the risk of APIs in FDW. The literature in both of these areas, however, has been largely ignored in the environmental exposure arena.

While models based on minimal therapeutic doses have served to advance the assessment of risk for APIs in FDW, more relevant PODs will need to be vetted before more realistic assessments can be performed. This was alluded to in 2003 by Daughton (93) in highlighting the pioneering work of Crain and Shen with ultra-low dosing of naltrexone and its potentiation of various aspects of nociception in rats by morphine. Having shown dramatic nociceptive effects in rats from combining opiate agonist and antagonist (e.g., naltrexone) at doses approaching 6 orders of magnitude below 1 μg/kg (e.g., minimum doses of 1 pg/kg), APIs occurring in FDW at the ng/L level clearly hold a theoretical potential for yielding effects even after consumption of a single liter of FDW; note, however, that while naltrexone serves as an example of an API with the potential for effects at ultra-low doses, it has never been reported in drinking water (although it has also perhaps never been targeted).

Increasing numbers of studies are pushing the documented range for API effects ever lower. Superficial examination of the literature quickly shows that a range of biological effects have already been demonstrated (but for a limited number of APIs) at doses much lower than the TD established during clinical trials. These lower doses can range from a couple to more than 6 orders of magnitude below TDs. Unfortunately, study of ultra-low doses is probably somewhat slowed by its mistakenly perceived entanglement with homeopathy and its Law of Infinitesimals (see debate at: 173). Clinical studies have ignored ultra-low doses because the potential effects have traditionally been viewed as not being relevant to achieving therapeutic goals.

Microdose (MD) studies (also known as human Phase-0 studies) are performed at the early stage of drug development. MD studies can quickly and safely obtain human pharmacokinetic (PK) data on drug candidates before committing to more expensive Phase-I clinical trials. A microdose can be as low as 1% of the predicted TD. PK data from MS studies is more relevant to the exposure levels of APIs in FDW than are TDs; but even these levels far exceed those experienced with the ambient environment or FDW. Significantly, PK data from MD experiments is sometimes found to differ from the PK data obtained from TDs; PK data from even lower doses could deviate yet further.

The potential for biological responses at ultra-low doses of APIs had been little explored up until the 1990s. Numerous examples have emerged, some showing complex alternating W-shaped or multimodal dose-response curves as doses are varied over many orders of magnitude. Three examples are: (i) a single μg/kg dose of tetrahydrocannabinol can adversely affect the cognitive ability of mice (174); (ii) different combined doses of naltrexone and a cyclic AMP-phosphodiesterase inhibitor such as rolipram (down into the pg/kg range) induce varying analgesia or hyperalgesia (175); (iii) femtomolar concentrations of dextromethorphan afford

neuroprotection from inflammatory damage, reported by the authors as demonstrating for the first time that a small molecule (dextromethorphan) can exert neuroprotection at such low concentrations (176).

Threshold of Toxicological Concern:

In the absence of empirical dose-response data at extremely low concentrations, an alternative to using the TD as a POD is the threshold of toxicological concern (TTC). Rodriguez et al. (140) proposed the TTC for assessing the risk of individual microconstituents in recycled water used for drinking. Daughton (3) suggested the TTC be used for assessing the potential toxicological significance of exposure to multiple APIs. With a worst-case assumption that all APIs were genotoxicants (and therefore requiring a TTC of 1 μg/L), upwards of 50 APIs could be perpetually present in drinking water at individual levels of 10 ng/L while maintaining a lifetime excess cancer risk of less than 10^{-6} (3). If the simultaneous exposures were only intermittent, then the total number of APIs that could be present would be upwards of 6,000 - clearly far exceeding any possible exposure scenario.

With the studies on APIs in FDW surveyed here (Table I), of those identified as co-occurring in individual studies of FDW, no individual study has identified more than a dozen APIs in any given sample. These include the studies of: Benotti et al. (39), Snyder et al. (36), Snyder (40), Stackelberg et al. (42), Ternes (46), and Vanderford and Snyder (41). The reported individual concentrations for all of these APIs were well below 1 μg/L.

Sensitive Subpopulations:

A major concern regarding exposure to APIs via FDW is not just exposure via routes never intended for the API but also for populations inappropriate for the API. Unique and vulnerable subpopulations are perhaps the major focus of concern regarding inappropriate API exposure via FDW. Among these, children and the fetus possess many unique and complex aspects of physiology and API pharmacokinetics that make low-dose exposure a particular concern; this is especially true given that few relevant empirical data exist for many API classes (particularly for in utero exposure and for antineoplastics). These complexities are covered by: Aksglaede et al. (177), Genuis (178,179), Houlihan et al. (180), and the WHO (181), among many others.

A particularly important variable in the vulnerability of a subpopulation is critical windows of vulnerability, which involve the timing of exposure relative to key events in biological development or intercellular communication. Dose timing is already established as a key determinant in certain drug therapies - where knowledge of chronobiology can reveal how the actual time of dose administration can alter therapeutic outcomes (182). Perhaps more significantly, with respect to low-dose exposure, are windows of vulnerability for fetal development. Better established in animal models, studies are just emerging regarding the timing of fetal exposure to ambient levels of xenobiotics. The first study investigating prenatal exposure to bisphenol A and childhood behavior found correlations between certain behaviors in 2-year old girls and maternal exposure (as measured by urine concentration), especially as measured at 16 weeks of gestation (183).

Epigenetics:

A weakness cited regarding hypotheses involving low-dose effects is that even if effects were to occur, they would be transient. Absent direct-acting genotoxicants, no other mechanism has been advanced for the possibility of lasting effects from brief low-dose exposures. Other than for direct-acting carcinogens (for which a single mutation might theoretically be sufficient), the assumption has been that certain minimum thresholds exist for indirect-acting carcinogens and non-carcinogens simply because no mechanism has seemed possible whereby a single molecular event could persist.

Not mentioned in these discussions, however, is a possible role of epigenetic alterations - a non-genetic pathway that began attracting attention in the early 2000's as an explanation for low-level effects from endocrine disruptors (e.g., 170).

Epigenetics involves heritable change in gene expression in the absence of alteration to the underlying DNA sequence itself. The most common mechanism for epigenetic alteration is via DNA methylation - specifically, cytosine methylation in CpG dinucleotides within promoter regions known as CpG islands. Methylation by methyltransferases at the cytosine C-5 position forms 5-methylcytosine - sometimes termed the "5th base," in recognition of its profound importance; more recently discovered variants such as 5-(hydroxymethyl)cytosine also might play roles. Other types of epigenetic change include modification of histones, such as by acetylation, phosphorylation, and ubiquitination/SUMOylation.

Unlike the genome, the epigenome is plastic, dynamic, extraordinarily complex, and varies across tissues and individuals; it is also sensitive to a wide array of non-chemical environmental influences. Of most significance, epigenetic alterations can accumulate, resulting in delayed-onset outcomes that can persist long after exposure has ceased - even across several generations.

Given the thousands of publications devoted to APIs as environmental pollutants, few address the possible role of epigenetics in human (or even aquatic) health. Epigenetics has been mentioned only in passing in perhaps a dozen or so of the thousands of published works; most of these have been published since 2006. In a forward-looking examination by the National Research Council (184) of the future of the life sciences and areas of focus and collaboration ("A New Biology for the 21st Century") and in the US EPA's "Strategic Plan for Evaluating the Toxicity of Chemicals" (185), epigenetics is mentioned only briefly.

Epigenetics provides a route by which very small numbers of discrete, isolated events (e.g., post-replication cytosine methylation) could persist. They could then accumulate from chronic low-level exposure, eventually reaching levels sufficient for measurable change (via alteration in gene expression). The concept of “thresholds of minimum exposure” would no longer need to be based on discrete exposure events, but rather on cumulative exposure - that point in the trajectory of accumulated epigenetic alterations at which phenotypic change emerges. Needed instead would be a way to evaluate the threshold of cumulative epigenetic alterations (each alteration perhaps being inconsequential by itself) leading to dysfunction or disruption of homeostasis. **Exposure would then not be considered in terms of discrete molecular events (each required to meet a threshold), but rather could be viewed as a continuum of accumulated events, whose combined, sustained accretion could eventually reach a threshold.**

Indeed, the accumulation of seemingly innocuous, individual methylation events ("stochastic methylation events" leading to "methylation spreading") has been hypothesized as a major determinant of aging (186). Surprisingly little is known, however, regarding epigenetics and pharmaceuticals. Epigenetics research with regard to environmental contaminants has been limited to a select few chemicals, such as bisphenol A, vinclozolin, and estrogenic hormones.

Epigenetics is a mechanism being explored, however, as a source of side effects (and possible explanation of mechanisms of action) for many medications. A comprehensive overview of the possible direct and indirect epigenetic actions of APIs is provided by Csoka and Szyf (187). The major unknown is whether there are thresholds for discrete epigenetic alterations to occur. Epigenetic pathways are also being used as targets for new drugs (e.g., histone deacetylase inhibitors – valproic acid being one existing example). Csoka and Szyf (187) provide a list of drugs/classes known or postulated to effect epigenetic alterations; they maintain that any API-induced side effect caused by epigenetic alterations might persist after cessation of drug treatment. Many of these same APIs have been identified in FDW. General epigenetic effects such as hyper- or hypo-methylation of DNA shared by many different drugs would be a mechanism for additive effects across disparate drug classes.

But while mechanisms of epigenetic modification by APIs are becoming clear, low-dose epigenetic alterations are another question. It is still unknown whether the required minimum levels of epigenetic modifiers can be as low as those in the environment. The fundamental questions persists - is there a threshold level below which an epigenetic modifier cannot result in a discrete alteration? In the final analysis, the debate regarding effects at vanishingly low levels is tethered to the fundamental question of toxicological thresholds. What level of receptor interaction is required for an effect - regardless of how subtle it might be? A mechanism around this requirement would be one where infinitesimally small numbers of receptor interactions can accumulate over time, eventually reaching the threshold. Epigenetics may provide a means for this to occur.

CONCLUSIONS

Quantitative data exists for over 60 active pharmaceutical ingredients (APIs) and metabolites in finished drinking water (FDW). These derive from roughly 50 publications. An unknown but possibly large number of publications report negative data for a wide spectrum of additional APIs. For roughly half of the APIs having positive occurrence data, corroborating occurrence data from more than a single isolated study do not exist. No more than a dozen APIs have been reported in any single FDW sample. Only one API has been reported in any FDW sample at a concentration exceeding 1 μg/L (1 ppb) – and it was for a single sample. The vast majority of APIs when present in FDW are probably at concentrations below 50 ng/L. Many have maximum reported concentrations of only several ng/L. Those APIs most frequently reported and in the highest concentrations are carbamazepine, ibuprofen, and clofibric acid. For six Anatomical Therapeutic Chemical (ATC) classification system main groups (A, B, H, L, R, and S), no API has been reported. No antineoplastic or immunomodulating agent has been reported in FDW, nor have any radiologicals. The relative lack of data for commercial bottled water is notable. Only two APIs used primarily in veterinary medicine have been reported in FDW: monesin and

tylosin. Surveys of FDW for illicit and unapproved drugs seem comparatively under-represented, even though some are known to have the potential to persist.

That APIs can occur in drinking water certainly poses complex questions regarding the significance of long-term human exposure. Although the minute concentrations when compared with therapeutic doses appear to be far below those that might pose any health concerns, the possibility of delayed-onset health effects cannot yet be ruled out. The possibility of cumulative epigenetic alterations as a possible mechanism of ultra-low-dose effects deserves attention. Even if sufficient knowledge eventually exists for setting scientifically defensible FDW standards for APIs, APIs will perhaps always exist in water - albeit at ever-lower levels, given anticipated advancements in treatment technology and as detection limits in analytical chemistry improve.

API occurrence in drinking water also poses challenges in communicating the risk regarding the inevitable implementation of widespread water recycling. Is it acceptable to have active pharmaceuticals in drinking water even at subtherapeutic levels regardless of the absence of predicted risks? Perhaps the issue is really the knowledge that the minute levels of APIs one might drink originated from others (unplanned potable reuse) or from oneself (planned potable reuse). Drugs in drinking water essentially serve as road signs for the water cycle - as billboards that say "this water used to be sewage." They serve as the chemical equivalent of garden weeds - not necessarily harmful but certainly unwelcome or undesired. APIs in FDW can serve as a major barrier to public acceptance of reused water, especially for drinking. Summaries of risk perception and risk communication regarding APIs in FDW can be found in Daughton (3,18), Ragain (188), and Randon (152).

With these concerns aside, however, perhaps the most important aspect of APIs in drinking water is that it serves to highlight for the public the intimate, direct, and complex interconnections between human activities, the environment, and human health. While state-of-the-art engineering end-of-pipe controls can reduce APIs and other water micropollutants to ever-diminishing concentrations, a sustainable approach will need to be holistic - with a focus on reducing the numerous routes and mechanisms by which APIs gain entry to the environment to begin with. A bewildering array of modifications and reengineering of consumer behavior, medical practices, and healthcare administration holds the potential to greatly reduce the entry of APIs to the environment. Progress in this direction is already underway; see: Bengtsson et al. (189), Daughton and Ruhoy (190), Hempel and Kümmerer (191), Keil et al. (192), and Kümmerer (193). Perhaps most significantly is the possibility that pollution prevention efforts targeted at API release also holds the collateral potential for reducing healthcare cost and improving healthcare outcomes (190), making such an approach not just sustainable - but, more importantly, the optimal solution.

Postscript

After completion of this review, a new DWTP monitoring study was released by the Ontario Ministry of the Environment's Drinking Water Surveillance Program: Ontario MOE. "Survey of the Occurrence of Pharmaceuticals and Other Emerging Contaminants in Untreated Source and Finished Drinking Water in Ontario." Ontario Ministry of the Environment (MOE), Canada, 2010 (January), 31 pp; http://www.ene.gov.on.ca/publications/7269e.pdf.

The Ontario MOE study represents one of the largest yet completed. It targeted 47 APIs (more than half being antibiotics) in 123 samples from 17 DWTPs in Ontario, Canada. Among all 123 samples, 22 APIs were detected. Of these APIs, 16 had been previously reported (according to Table I). The three most frequently detected were **carbamazepine** (25% of samples from 8 of 17 sites; median 0.21 ng/L, max 601), **gemfibrozil** (15% of samples from 6 of 17 sites; median 0.5 ng/L, max 4), and **ibuprofen** (15% of samples from 9 of 17 sites; median 0.33 ng/L, max 25). These data comport with the data compiled in Table I. The frequency of occurrence for only two APIs seemed to be higher than indicated by previous work: **monensin** (7% of samples from 4 of 17 sites) and **tylosin** (6% of samples from 4 of 17 sites). The frequency of detection for the remaining APIs was less than 4%. Of note were six APIs that were reported in FDW for the first time (all but one being an antibiotic), but all occurring infrequently: **enrofloxacin** (3% of samples from 4 of 17 sites), **norfloxacin** (1% of samples from 1 of 17 sites), **meclocycline** (1% of samples from 1 of 17 sites), **tetracycline** (4% of samples from 5 of 17 sites), **sulfachloropyridazine** (2% of samples from 2 of 17 sites), and **equilin** (1% of samples from 2 of 17 sites). Four APIs were detected in FDW samples but not in any untreated source water (clofibric acid, diclofenac, equilin, and sulfachloropyridazine).

The findings from the Ontario MOE study do not alter any of the conclusions or trends developed in the review compiled here. The data from the study largely comport with what is currently known.

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