EPA Public Access

Author manuscript

Sci Total Environ. Author manuscript; available in PMC 2020 February 13.

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Published in final edited form as:

Sci Total Environ. 2017 February 01; 579: 1629–1642. doi:10.1016/j.scitotenv.2016.03.128.

Nationwide Reconnaissance of Contaminants of Emerging Concern in Source and Treated Drinking Waters of the United States: pharmaceuticals

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Abstract

Mobile and persistent chemicals that are present in urban wastewater, such as pharmaceuticals, may survive on-site or municipal wastewater treatment and post-discharge environmental processes. These pharmaceuticals have the potential to reach surface and groundwaters, essential drinking-water sources. A joint, two-phase U.S. Geological Survey-U.S. Environmental Protection Agency study examined source and treated waters from 25 drinking-water treatment plants from across the United States. Treatment plants that had probable wastewater inputs to their source waters were selected to assess the prevalence of pharmaceuticals in such source waters, and to identify which pharmaceuticals persist through drinking-water treatment. All samples were analyzed for 24 pharmaceuticals in Phase I and for 118 in Phase II.

In Phase I, 11 pharmaceuticals were detected in all source-water samples, with a maximum of nine pharmaceuticals detected in any one sample. The median number of pharmaceuticals for all 25 samples was five. Quantifiable pharmaceutical detections were fewer, with a maximum of five pharmaceuticals in any one sample and a median for all samples of two. In Phase II, 47 different pharmaceuticals were detected in all source-water samples, with a maximum of 41 pharmaceuticals detected in any one sample. The median number of pharmaceuticals for all 25 samples was eight. For 37 quantifiable pharmaceuticals in Phase II, median concentrations in source water were below 113 ng/L.

Substantially fewer pharmaceuticals were detected in treated water samples than in source-water samples. Seven different pharmaceuticals were detected in all Phase I treated water samples, with a maximum of four detections in any one sample and a median of two pharmaceuticals for all samples. In Phase II a total of 26 different pharmaceuticals were detected in all treated water samples, with a maximum of 20 pharmaceuticals detected in any one sample and a median of 2 pharmaceuticals detected for all 25 samples. Source-water type influences the presence of pharmaceuticals in source and treated water. Treatment processes appear effective in reducing concentrations of most pharmaceuticals. Pharmaceuticals more consistently persisting through

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treatment include carbamazepine, bupropion, cotinine, metoprolol, and lithium. Pharmaceutical concentrations and compositions from this study provide an important base data set for further sublethal, long-term exposure assessments, and for understanding potential effects of these and other contaminants of emerging concern upon human and ecosystem health.

Graphical Abstract

Keywords

pharmaceuticals; contaminants of emerging concern; drinking water; source water; treated water

Introduction

Since the earliest reports of the widespread presence and distribution of pharmaceuticals and other contaminants of emerging concern (CECs) in surface water, groundwater, wastewater effluent, and other water resources (Kolpin et al., (2002); Stackelberg et al., 2004; 2007; Benotti et al., 2009a; Boleda et al., 2011; Focazio et al., 2008; Gibbs et al., 2007; Glassmeyer and Shoemaker, 2005; Glassmeyer et al., 2005; Kostich et al., 2014; Richardson and Ternes, 2011), the presence and distribution of CECs in water supplies, and potential consumer exposure to these CECs in drinking water, has been of substantial scientific and public interest. Bruce et al. (2010) concluded that exposure through drinking water is likely to be a common route of exposure for many human populations even though it is likely a less important route of exposure when compared to direct exposure through normal or routine use of prescription and over-the-counter drugs, which provide substantially larger doses of the active pharmaceutical ingredient than consumption of drinking water. A comprehensive assessment of the widest range of CEC classes and types, including but not limited to pharmaceuticals, is necessary to more fully document and clarify the potential for exposure

to mixtures of pharmaceuticals and other contaminants of emerging concern in drinking water.

Between October 2007 and March 2012, the U.S. Environmental Protection Agency (USEPA) and the U.S. Geological Survey (USGS) conducted a joint, two-phase sampling study of CECs in source and treated drinking waters in the United States. In Phase I, source and treated water samples from nine drinking water treatment plants (DWTPs) were analyzed for 24 pharmaceuticals, reflecting a wide range of therapeutic uses (Table 1). The Phase I study allowed assessment of the potential compositions and the range of expected concentrations of CECs present in these water types, tested a centrally administered sampling design and quality assurance/quality control (QA/QC) protocol, and allowed evaluation of how well the complex sample collection protocol could be carried out by DWTP plant personnel without prior experience in collecting samples for CEC analysis.

The success of Phase I resulted in an expanded Phase II, wherein 25 DWTPs from throughout the United States (including five of the nine plants [DWTPs 1–5] from Phase I) were sampled to more comprehensively assess the possible presence and distribution of a substantially wider range of CECs in water supplies used for human consumption. About three years passed between Phase I (2007) and Phase II (2010) sampling campaigns. In Phase II, the QC protocol was refined and expanded, and the categories of analytes determined also were substantially expanded to include a wider array of pharmaceuticals, perfluorinated chemicals, estrogenic hormones, inorganic elements, bacteria, viruses, and estrogenicity (as determined by bioassay), as well as all CECs measured in Phase I (Table 2).

The DWTPs sampled in both phases of this study included surface- and groundwater sources, represented a range of geographic locations within the United States, included most common treatment practices, and spanned a range of sizes. Each plant was sampled prior to and after treatment, and sample collection was timed to the hydraulic residence time of the DWTP to determine the relative reduction of CECs during treatment. Comprehensive quality assurance/quality control (QA/QC) designs were used to assess bias and variability of CEC determinations at environmental concentrations.

This paper is one in a series describing the presence, persistence, and concentrations of CECs and microorganisms in source and treated drinking waters of the United States. This project, a joint effort of the USEPA and the USGS, is part of a long-term interagency agreement. A primary goal of this study is to provide accurate, objective data to assess the potential for human exposure to these CECs by consuming drinking water. A secondary goal is to estimate reduction, if any, of CECs from source waters by currently used drinking water treatment processes under conventional plant operating conditions, and thus identify possible candidate compounds or microorganisms that may be amenable to enhanced reduction or removal. An overview of this comprehensive national study is provided in (Glassmeyer et al., 2016); the reader is encouraged to read this paper to understand the overall project design, population and treatment characteristics of the DWTPs studied, QA/QC and sample collection design applied to all samples, and how the results described in this paper fit into the overall objectives of this larger study. This paper describes the presence and ambient

concentrations of pharmaceuticals in source and treated waters in the two phases of the study (Phase I, 24 pharmaceuticals; Phase II 118 pharmaceuticals). We also assess concentration reduction between source water intake and treated water production by comparing concentrations from samples for which DWTP residence time had been accounted for in the timing of sample collection.

Analytical Methods

The specific pharmaceuticals determined in each Phase were based on methods available at the time each Phase began. The criteria used to select pharmaceuticals in each method were similar: pharmaceutical production volumes and usage data, previous detection in environmental water samples, and amenability to the extraction, isolation, and analysis approaches used in each method. Specific details are provided in each method report, and the specific methods used for each Phase are described briefly below and described in Table S1.

Phase I

Two analytical methods were used in the first phase of this study to determine pharmaceuticals (Table 1). For each method used, ambient pharmaceutical concentrations were determined in each of two discrete replicate samples collected concurrently at each sampling point. A detailed description of the sampling protocol for these and other samples collected in this phase is provided elsewhere (Glassmeyer et al., 2016). Briefly, grab samples were first collected at the source-water intake, typically after screening to remove debris. At a later time, consistent with the hydraulic residence time of a water parcel through the plant, finished-water grab samples were collected after final disinfection but prior to the clear well.

After collection at either sampling point, one sample was designated and analyzed as the environmental sample. Based on sequence in which DWTPs were sampled, the second sample was alternately designated, then analyzed, as either an environmental duplicate sample or a laboratory-fortified matrix spike sample (amended in the laboratory prior to analysis). In Phase I all pharmaceutical samplers were determined from laboratory filtered 1-L water samples (0.7 micron glass-fiber filter). In the method for human-use pharmaceuticals (Cahill et al., 2004; Furlong et al., 2008) analytes were isolated by solid-phase extraction (SPE) and analyzed by high-performance liquid chromatography/mass spectrometry (HPLC/MS). A suite of antidepressants and antidepressant degradates also were determined using the method of Schultz and Furlong 2008. In this method, the pharmaceuticals were isolated from filtered 1-L water samples by SPE and analyzed by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS). Both pharmaceutical analyses were performed at the USGS National Water Quality Laboratory (NWQL)

Phase II

In Phase II the QA/QC sample design was adjusted to collect a duplicate and matrix spike sample at each source- and treated-water sampling point. For each method used, ambient pharmaceutical concentrations were determined in two discrete, duplicate samples collected

concurrently at each sampling point and analyzed separately. The first sample collected was designated the primary environmental sample and the second was the environmental duplicate. A third discrete replicate from each sampling point was amended with method pharmaceuticals and analyzed as a laboratory-fortified matrix spike. A field blank also was processed through all sample collection steps at each sampling site and analyzed by all methods. Details on the overall sampling and QC designs of this phase are in (Glassmeyer et al., 2016).

Six different analytical methods were used to determine 118 pharmaceuticals (Tables 2, S1). Samples were filtered after collection and shipment to the laboratory by the procedures documented in each method report. Three of the methods (Batt et al., 2008; Furlong et al., 2008; Schultz and Furlong, 2008) used SPE to concentrate pharmaceuticals prior to analysis. One method (Batt et al., 2008) uses SPE to pre-concentrate and selectively isolate 43 pharmaceuticals and six pharmaceutical metabolites from a 500-mL water sample. An aliquot of the concentrated extract was analyzed by HPLC/MS/MS to identify pharmaceuticals, using isotopically labeled internal standards to quantify pharmaceuticals at low ng/L concentrations. An analogous HPLC/MS/MS method (Schultz and Furlong, 2008) was also used to determine bupropion isolated from a liter of filtered water by SPE; this method also was used in Phase I. The method of Furlong et al. (2008), also used in Phase I to determine codeine, uses SPE isolation from 1 L of water followed by HPLC with quadrupole MS (HPLC/MS). One compound, clofibric acid, was determined using an adaptation of a previously published method that used SPE extraction followed by HPLC/MS/MS analysis (Ternes et al., 2005).

Seven steroidal estrogens, including several prescribed pharmaceutically, were determined using SPE of filtered water samples, followed by accurate mass analysis using a Orbitrap mass spectrometer (Conley et al., 2016). Spectral matching and accurate mass confirmation of fragment ions was used for qualitative identification. Quantitation was based upon the internal standard method using stably labeled analogues of each hormone.

Direct HPLC/MS/MS analysis of a filtered aliquot of water (Furlong et al., 2014) was used to determine 64 pharmaceuticals and pharmaceutical degradates in source and treated water samples. The filtered sample was amended with an aliquot of an isotope-dilution standard mixture of 19 stable isotope-labeled pharmaceutical analogues for purposes of quantitation. Pharmaceuticals in a 100- μ L injection of the filtered, amended sample were separated by reversed-phase HPLC using an aqueous ammonium formate/methanol gradient. The pharmaceuticals were ionized by electrospray ionization operated in the positive mode, and protonated molecular ions of the pharmaceuticals were fragmented and analyzed using multiple reaction monitoring (MRM) of two unique product ions for each compound.

Lithium was determined in filtered water samples as part of a suite of trace elements using inductively-coupled plasma emission spectroscopy, according to EPA Method 200.7 (Martin et al., 1994).

The six methods in Phase II were used to determine a total of 220 pharmaceuticals and trace elements. Within this set of 220 unique pharmaceutical-method pairs, 43 pharmaceuticals

were common to two or more methods. Method performance for each pharmaceutical and method pair, a total of 47, was then assessed using laboratory reagent spike and matrix spike sample recoveries and frequency of pharmaceutical detection in field and laboratory blank samples. Where one pharmaceutical was determined by more than one method, the method with the lower Lowest Concentration Minimum Reporting Limit (LCMRL; [J. J. Martin et al., 2007]) was preferentially used. From this assessment 118 individual pharmaceutical and method pairs were identified as preferred results and are listed in Table 2. The 48 pharmaceutical-method pairs common to two or more methods that were not used are listed in Table S2 with the specific pharmaceuticals, alternative methods, and their relevant LCMRLs. Detailed descriptions of the methods and their intramethod and intermethod performance in this study is assessed in a separate, related paper (Batt et al., 2016).

Pharmaceutical detections were divided in two categories, qualitative and quantitative detections. Qualitative detections meet identification criteria for each method, but some calculated concentrations were not considered quantitative. Thus qualitative detections were assessed only for frequency of occurrence. Quantitative detections were a subset of qualitative detections where the calculated concentration also met the following QA/QC criteria:

1. the concentration was greater than the compound LCMRL (Martin et al., 2007),
2. recovery of the associated matrix spike was between 50 and 150%,
3. within-sample surrogate recoveries were within method-specific acceptance levels, and:
4. field or laboratory reagent blank contributions were present at less than three times the environmental concentration.

Quantitative detections met all identification criteria and the above quantitation criteria and were used for frequency of occurrence and statistical analysis of concentrations. Laboratory- or field-matrix spike (LMS or FMS) recoveries were not used to adjust ambient environmental concentrations because of concerns that such adjustments may incorrectly revise results, particularly for low ambient concentrations resulting from matrix effects, and because several different methods, with potentially different adjustment factors, were used to produce a single data set (Thompson et al., 1999).

Results were censored and not used as either qualitative or quantitative detections if any of the following criteria were found true:

1. the ambient environmental sample concentration does not exceed 3 times the concentration in either a field or laboratory blank sample concentration;
2. the median recovery was less than 50% for either the LMS, or, as appropriate the source water FMS or treated water FMS; or;
3. the failure frequency of a class of spike samples greater than 40%, that is, no detectable recovery of a pharmaceutical in either more than 40% of either the aggregated laboratory blank water samples, the aggregated source matrix water samples, or the aggregated finished water matrix samples.

Bias and variability of the quantitative detections were assessed from LMS matrix spike and duplicate samples, respectively, collected as part of the larger project QA/QC design (Glassmeyer et al., 2016). Matrix spike results are summarized in Table S3. The grand median of median recoveries for all pharmaceuticals was 97%, with an interquartile range (the range between the 25th and 75th percentile) of 90–101%. The grand median of relative standard deviation of recovery was 16%, with an interquartile range of 13–24%. Together, these data suggest that overall bias was minimal for the methods used for each pharmaceutical in this study and that concentrations reported are acceptably accurate.

Duplicate samples were collected to assess variability at nanogram-per-liter ambient environmental concentrations. Regardless of whether source or treated samples are considered, ambient concentration variability was acceptable, as reflected by determination of relative percent differences (RPD; the absolute value of the difference between the primary and duplicate result divided by the mean of the two results, in percent) of individual pharmaceuticals detected in both primary and duplicate sample pairs. Typical relative percent differences for the 12 pharmaceuticals detected in both primary and duplicate source samples range between five and 25% RPD. Some compounds, such as bupropion, had substantially wider distributions of RPDs. This wider range of RPDs likely results from the low ambient concentrations observed for these pharmaceuticals, and illustrates ambient variability near the method reporting level that is typical for these and similar pharmaceuticals. These data suggest that variability in observed concentrations of individual pharmaceuticals at ambient concentrations is acceptable.

Field blank samples were not collected for pharmaceuticals in Phase I because each DWTP provided a limited volume of in-house blank water, and other methods were considered to be more likely to have field contamination requiring assessment through field blank samples. Caffeine, carbamazepine, and cotinine also were determined in Phase I field blank samples analyzed for wastewater indicator compounds, which used a full-scan electron impact GC/MS method (Zaugg et al., 2006); these three pharmaceuticals were not detected in any Phase I field blank samples.

In Phase II, a common source of field blank water was distributed to all DWTPs to process and submit to all laboratories for analysis by all methods to assess potential for contamination from sample handling processes occurring during sample collection at each DWTP. In Phase II, 43 pharmaceuticals were detected in at least one of the 25 field blank samples; 10 compounds were detected in three or more field blank samples (Table S4; desmethyl diltiazem, verapamil, metoprolol, norverapamil, propranolol, fluticasone, diltiazem, caffeine, valsartan, and cotinine). Median concentrations for pharmaceuticals detected three or more times in the field blanks were low, typically 0.55–4.85 ng/L, with the exception of caffeine, detected four times with a median concentration of 21.3 ng/L. All reported environmental sample detections were qualified by comparison to field blanks. Overall, field contamination as reflected by field blanks samples had a minor effect on the data set.

Results and Discussion

Occurrence of pharmaceuticals in source-water samples

Phase I—Summary statistics for the 24 pharmaceuticals determined in Phase I are shown in Table 1. Thirteen of the 24 pharmaceuticals investigated in Phase I were detected (defined as sum of qualitative and quantitative detections for a compound) at least once in either source or treated water samples. Among detected pharmaceuticals, 46% were in source-water samples and 29% were in treated-water samples. Nine pharmaceuticals were never detected in either source or treated water samples (Table 1). The most commonly detected chemicals in the source water were bupropion (89%), carbamazepine (78%), venlafaxine (78%), caffeine (67%), and sulfamethoxazole (56%). The reporting levels (RLs) for these frequently detected pharmaceuticals range between 0.58 and 100 ng/L (Table 1), which encompasses the range of RLs for all Phase I pharmaceuticals. Previous research by others has shown an inverse relation between frequency of detection and RLs (Kolpin et al., 1995). Excepting carbamazepine with a reporting level (RL) of 40 ng/L, a similar pattern appears for Phase I pharmaceuticals, with venlafaxine (RL=0.58 ng/L) and bupropion (RL=0.66 ng/L) having higher frequencies of detection than caffeine (RL=60 ng/L) and sulfamethoxazole (RL=100 ng/L).

All but one DWTP (#7) had 3 or more detectable pharmaceuticals in Phase I source waters. Between three (DWTP 1) and nine (DWTP 4) of 24 different pharmaceuticals determined were detected at least once. Five or more pharmaceuticals were detected in six source-water samples (Table S5; DWTPs 4, 2, 5, 6, and 3, with 9, 6, 6, 6, and 5 detections, respectively), while four or fewer pharmaceuticals were present in four source-water samples (DWTPs, 8, 9, 1, and 7, with 4, 4, 3, and 0 detections, respectively). The median number of pharmaceuticals detected in the source waters of the nine DWTPs of Phase I was five, showing that pharmaceuticals and other CECs typically occur as mixtures in source water. Source-water detections and concentrations of pharmaceuticals in for Phase I for each DWTP are detailed in Table S5.

Concentrations overall were relatively low in all Phase I source water samples. The summed concentrations of all quantified pharmaceuticals varied between 0 and 270 ng/L, with a median concentration of 11.8 ng/L. The source water samples with highest total pharmaceutical concentrations were DWTPs 4 and 5, at 171 and 272 ng/L, respectively. The high concentrations in DWTP 5 resulted from a single detection of carbamazepine at 269 ng/L, and low and sub-ng/L concentrations of bupropion, fluoxetine, and venlafaxine. Distributions of concentrations in DWTP 4 were more widespread (Table S5), with caffeine (124 ng/L), venlafaxine (41.9 ng/L) and low and sub-ng/L concentrations of bupropion, fluoxetine, and venlafaxine, likely reflecting the sensitivity and selectivity of the method used (Schultz and Furlong, 2008).

Phase II—Table 2 provides a summary of qualitative and quantitative detection frequencies, and median and maximum concentrations of the 118 pharmaceuticals in Phase II source- and treated-water samples. Figures 1 and 2 show the distribution of quantified pharmaceuticals, ordered by frequency of detection, in source- and treated-water samples.

Tables S6 and S7 provide qualitative detections and quantitative concentrations observed in each DWTP source- and treated-water sample.

In source-water samples, 58 different pharmaceuticals were identified at least once in the 25 Phase II DWTPs (Tables 2, S6). Lithium was the only pharmaceutical detected in the source-water of DWTP 24, at a concentration of 36.3 ug/L whereas 41 pharmaceuticals were detected in the source water of DWTP 4. Between 13 and 41 pharmaceuticals were detected in eight source-water samples (Table S7); Between 6 and 10 pharmaceuticals were present in seven samples, and from one to five pharmaceuticals were detected in 10 samples. The median number of total pharmaceutical detections in all Phase II source-water samples was eight, reflecting that pharmaceuticals and other CECs typically occur as mixtures.

The numbers of different quantifiable pharmaceuticals in Phase II source-water samples were substantially lower than total pharmaceutical detections, ranging from none (DWTPs 11, 12, 14, and 23) to 20 (DWTP 4), with a median of two detections, reflecting overall low quantifiable concentrations of pharmaceuticals (excepting lithium) in the DWTPs (Table S7). Thirty-seven different pharmaceuticals were present in quantifiable concentrations. Thirteen pharmaceuticals were quantified 3 or more times in different DWTPs; 24 pharmaceuticals were quantified in one or two source–water samples. The lower number of quantifiable pharmaceutical detections relative to the total number of pharmaceutical detections reflects the low ambient concentrations of most pharmaceuticals in source waters, with a large fraction of the pharmaceutical mixture in any source water being qualitatively identifiable, but below reporting levels.

Ten or more quantifiable detections were measured for four DWTPs (4, 3, 27, and 22 with 20, 18, 12, and 11 detections, respectively). These plants had high numbers of total detections as well (41, 32, 21, and 14 respectively); DWTPs 4 and 3 also were sampled in Phase I and contained higher numbers of detections in that phase of the study. All other DWTP source-water samples contained nine or fewer quantifiable pharmaceuticals, with no quantifiable pharmaceutical detections occurring in DWTPs 11, 12, 14, and 23. Total detection frequencies, that is, the sum of quantitative and qualitative detections, were similar, with DWTPs 4, 3, 27, and 22 having total detections of 41, 32, 21, and 14 detections in source-water samples, respectively. However, when qualitative detections are considered, all Phase II source-water samples contain detectable pharmaceuticals with source-water samples from DWTPs 11, 12, 14, and 23 having 5, 3, 3, and 2 qualitative detections, respectively. The larger numbers of detections in Phase II over Phase I source-water samples reflects the expanded range of pharmaceuticals determined (118 in Phase II versus 24 in Phase I) as well as the improvements in sensitivity in the methods deployed in Phase II.

Lithium, the most frequently quantified pharmaceutical, had a maximum concentration of 46 µg/L. Lithium, measured as part of the suite of trace elements, was considered a pharmaceutical for the purpose of this study because it continues to be used as a first-line treatment for bipolar disorder (Dinan, 2002; Jefferson, 2002), is present in U.S. Water supplies (Kszos and Stewart, 2003) and evidence that lithium from pharmaceutical use may be discharged in wastewater (Barber et al., 2006a), contributing to stream lithium concentrations. However, the percentage of lithium attributable to pharmaceutical-derived

wastewater or petrogenic contributions to source-water samples in this study could not be determined with information available.

Excluding lithium, individual pharmaceutical concentrations ranged between 0.02 to 163 µg/L, (Figure 1); sulfamethoxazole, metoprolol, carbamazepine, estrone, and hydrochlorthiazide were the most frequently detected pharmaceuticals in source water samples at maximum concentrations of 160, 38, 36, 0.29, and 67 ng/L, respectively. Pharmaceuticals detected in Phase II source-water samples typically fall below 36 ng/L, as reflected by the 75th percentile of concentrations (Figure 1; with the exception of lithium with a 75th percentile of concentration of 33 µg/L).

Occurrence of pharmaceuticals in treated-water samples

Phase I—In treated-water samples, qualitative and quantitative detection frequencies decreased substantially from those observed in source-water samples (Table 1). No detectable pharmaceuticals were present in DWTPs 1 and 7. The number of detections ranged between one (DWTPs 2 and 3) and four (DWTPs 4 and 9), and the median number of detections for all DWTPs was two, indicating the substantial reduction of concentrations of parent pharmaceuticals during treatment. Location-specific detections of pharmaceuticals in treated-water samples are detailed in Table S6.

Six pharmaceuticals were detected in one or more treated-water samples. Caffeine and carbamazepine, the only compounds detected in more than 50% of the samples, were qualitatively present at 66% and 55%, respectively, in all DWTPs with the highest quantifiable concentrations of 88 ng/L (DWTP 4) and 586 ng/L (DWTP 5), respectively. The single carbamazepine concentration detected in the treated-water sample in DWTP 5, 586 ng/L, was more than double the maximum detected in wastewater effluents from a previous study (Glassmeyer et al., 2005). The location with the highest reported concentration, DWTP 5, uses groundwater as its only source of water, and discussion with the operator suggested possible contamination from septage sources in the shallow subsurface. The majority of pharmaceuticals detected in treated-water samples were below reporting levels. Bupropion (3.3 ng/L) and caffeine (88 ng/L) were quantified in the sample from DWTP 4; carbamazepine was quantified at 586 ng/L in the sample from DWTP 5; and bupropion concentrations of 0.97 and 2.0 ng/L were quantified in samples from DWTPs 8 and 9, respectively.

Phase II—Thirty-five different pharmaceuticals were qualitatively or quantitatively detected at least once in the 25 DWTPs sampled in Phase II. Compared to source-water samples, fewer pharmaceuticals were detected in Phase II treated-water samples (Figure 2; Table 2, Table S8). Five Phase II treated-water samples contained six or more qualitative pharmaceutical detections. DWTPs 4, 26, 27, 3, and 20, had the highest numbers of total detections, 20, 9, 7, 6, and 6, respectively. Twenty DWTPs had three or fewer detectable pharmaceuticals of the 118 determined in Phase II. Treated-water samples from DWTPs 11, 13, 14, 24, 25, and 29 contained one detectable pharmaceutical and DWTP 12 contained none.

Quantifiable pharmaceutical detections were substantially lower in Phase II source-water samples, however, than in treated-water samples. Seven different pharmaceuticals were quantified in two or more samples, and seven pharmaceuticals were quantified once. DWTPs 4, 27, 5, and 26 contained 5, 4, 3, and 3 pharmaceuticals, respectively. Sixteen DWTPs contained 1 or two detectable pharmaceuticals, while DWTPs 16, 12, 18, 29, and 11 contained no detectable pharmaceuticals.

Lithium was the most frequently detected pharmaceutical, with a maximum concentration of 43 µg/L (DWTP 20). Excepting lithium, the most frequently detected pharmaceuticals in treated-water samples were bupropion, metoprolol, carbamazepine, and cotinine at maximum concentrations of 11, 18, 11, 26 and 16 ng/L, respectively. The maximum concentration of any non-lithium pharmaceutical detected in treated-water samples was 92 ng/L for clofibric acid, measured in one DWTP (DWTP 14).

The differences in numbers and distributions of quantified pharmaceuticals between source and treated water are apparent when Figures 1 and 2 are compared. As can be seen by the number of detections per analyte in each figure, more pharmaceuticals are detected in source than treated water and, at higher frequencies and somewhat higher concentrations overall. The overall decrease in concentrations from source to treated samples also is reflected in the median concentrations of source- and treated-water samples (Table 2). Excluding lithium, the grand median (median of all median concentrations) for source- and treated water samples, are 14.2 and 10.6 ng/L, respectively. If the grand medians for both source- and treated-water samples are limited to the 14 pharmaceuticals quantified in treated water, the grand medians for source- and treated-water samples are 13.4 and 10.6 ng/L respectively.

There were 24 pharmaceuticals that were measured in both Phase I and Phase II samples from DWTPs 1–5 (Table S9), albeit by different methods. In eight cases, both detections were quantifiable, 13 cases where detection was qualitative and the other quantitative, and four cases where both detections were qualitative. There were 16 cases of a single detection in the pair that was detectable qualitatively and 14 cases of a single unmatched quantitative detection in the pair. Of the eight common quantifiable detections, six occurred in source water and two occurred in treated water. All common quantifiable detections were in samples from DWTPs 3, 4, and 5, with one detection each occurring in the treated samples from DWTPs 4 and 5. The average relative percent difference of the eight pairs was 114 %. The relatively low numbers of pharmaceuticals detected in common between Phase I and Phase II is not surprising given the three year difference between sampling campaigns and changes in the analytical methodologies and reporting levels, and is overall reflective of source and treated waters with relatively low pharmaceutical concentrations.

Factors affecting the presence of pharmaceuticals in source and treated water

Glassmeyer et al (2016) provides an overview of the operational and water-source characteristics of the DWTPs studied in Phase II, and these characteristics may have some influence on the presence of pharmaceuticals in source waters. The numbers of pharmaceuticals detected in a source-water sample may be reflected in the type of water source. The source-water types for all 25 DWTPs in Phase II are listed in Table S10. Source water for three of the DWTPs (#s 5, 12, and 24) was totally, or in part, from groundwater,

and the source-water samples from these sites contained 7, 3, and 1 qualitative pharmaceutical detections respectively, and 4, 0, and 1 quantifiable pharmaceutical detections respectively (Table S10). Similarly, source waters for six DWTPs (#s 28, 13, 14, 25, 29, and 23) are from lakes or reservoirs. For these source waters, two or three qualitative pharmaceutical detections and one to two quantifiable detections were typical, with the exception of DWTP 28, where 10 total and five quantifiable pharmaceutical detections were observed. In contrast, the highest numbers of qualitative and quantifiable detections are associated with surface-water sources (Table S10). The 10 DWTP source-water samples with the highest numbers of detections all obtain their source water from a river or stream.

Reduction of pharmaceuticals in treated water may reflect the effect of treatment type, particularly when source-water type was considered. Table S10 lists the primary disinfectant and a simplified treatment train used at each DWTP, as well as the percentage and fractional reduction in numbers of pharmaceuticals detected for each DWTP. The DWTPs with the greatest percentage reduction, particularly those with surface-water sources and substantial numbers of detectable pharmaceuticals, for example, DWTPs 21, 3, 1, and 2, used more advanced treatments: ozone, ultraviolet irradiation, and in particular, granular or powdered active carbon filtration. Disinfecting oxidant types, such as chlorine, chloramine, ozone, and ultraviolet radiation, were all used in DWTPs with effective reduction of pharmaceuticals, suggesting that the type of disinfecting oxidant may be less important in reducing pharmaceutical concentration in treated water than other components of the treatment process.

Although the numbers of individual pharmaceuticals detected and quantified in each DWTP's source- and treated-water samples varied substantially (Tables S6 and S7, respectively), a few plants contain substantially higher numbers and concentrations of pharmaceuticals and are illustrative of DWTPs where source water may be affected by upstream or up-gradient discharges of treated wastewater. Source-water samples from DWTPs 3, 4, 22, and 27 each contained 18, 20, 11, and 12 quantified detections, respectively, while the number of quantitative detections were 32, 41, 14, and 21, respectively. The source-water concentrations of quantifiable pharmaceuticals from all four DWTPs are shown in Figure 3. The pharmaceuticals along the X-axis of the figure are ordered from left to right in decreasing frequency of occurrence; carbamazepine, desvenlafaxine, and lithium (units of $\mu\text{g/L}$) were quantifiable in all four DWTP source-water samples. The concentrations of estrone in DWTPs 3 and 4, and progesterone in DWTP 4, just discernible in the figure, are 0.18 and 0.29 ng/L , and 0.15 ng/L , respectively. Eight of the 34 pharmaceuticals quantified in these four DWTPs (desvenlafaxine, carbamazepine, lithium, sulfamethoxazole, caffeine, hydrochlorthiazide, metoprolol, and bupropion) were present in source-water samples from at least three of these DWTPs. The variation in detected pharmaceuticals and their concentrations among these plants suggests that while there are still considerable differences in the compositions of detected pharmaceuticals among plants, there are a core set of frequently detected pharmaceuticals, common to many source waters.

The persistence of some of these frequently detected compounds is illustrated by frequency of detection and concentrations in both study phases. In Phase I source water samples, 11

different pharmaceuticals were detected, seven of which were quantifiable (Table 1). In comparison, six different pharmaceuticals were detected, three of which were quantifiable in treated-water samples, suggesting substantial reduction in the numbers of pharmaceuticals present after treatment. However, bupropion and carbamazepine, two of the three quantifiable pharmaceuticals present in nine plants sampled in Phase I, persist through treatment without substantial reduction, as reflected by maximum and individual DWTP concentrations (Tables 1, S6). In Phase II, 32 of 37 pharmaceuticals present in treated-water samples also were present in source water samples (Table 2). Similarly 13 of the 17 quantifiable pharmaceuticals present in treated-water samples also were present in source water samples. Median and maximum concentrations in Table 2 also suggest that a subset of pharmaceuticals generally persist through treatment.

Comparing matched Phase II source- and treated-water samples pairs (Figure 4) also suggests the behavior of these variably persistent pharmaceuticals. Assuming minimal within-plant volumetric water losses during sampling, decreases in concentration between source- and treated-water samples reflect overall concentration decreases resulting from treatment. In Figure 4, twenty-seven pairs of quantified pharmaceutical concentrations from matched source and treated drinking-water samples from all Phase II DWTPs are plotted. The most matched pairs were for lithium (13 pairs); followed by bupropion and metoprolol (3 pairs each); cotinine; pseudoephedrine (2 pairs each); and carbamazepine, norverapamil, sulfamethoxazole, and verapamil (1 pair each). Pharmaceuticals that fall below the line of 1:1 correspondence in the figure reflect compounds whose concentrations decreased during the treatment process.

Verapamil, norverapamil, and the one detection of metoprolol fall farthest below the line of one-to-one correspondence (Figure 4), reflecting the largest apparent concentration decreases from source to treated water. Other than for lithium in Figure 4, most pharmaceuticals present in treated water are at lower, but detectable, concentrations than in source water. This difference indicates partial but incomplete reduction of several pharmaceuticals during treatment, presuming source and treated samples were collected to reflect the mean DWTP treatment residence time (provided/determined by each plant), and thus were reflective of the same water parcel. The minority of pharmaceuticals above the line of one-to-one correspondence likely reflects measurement error or mismatch in the timing of source- and treated-water sample collection.

Note also that as calculated this reduction reflects the removal of parent pharmaceutical only. A range of transformation products, which have been shown by others to occur as a result of drinking water treatment (Canonica et al., 2008; de Jongh et al., 2012; S. Glassmeyer and Shoemaker, 2005), are likely present but not accounted for by the methods used in this study; true removal, that is, remineralization of the pharmaceutical to elemental constituents, would need to account for these abiotic or biotic transformation products. Future assessments of pharmaceutical presence and concentrations in drinking water will likely detect more pharmaceuticals and their transformation products in source and treated water as the reporting limits of analytical methods for pharmaceuticals improve and more transformation products are identified and incorporated into analytical methods.

Lithium displayed the most consistently conservative behavior of all pharmaceuticals detected in this study. Lithium concentrations ranged between 5.1 and 46 µg/L. The correlation coefficient between lithium concentrations in paired source and treated lithium samples was 0.980 for 13 matched pairs. A linear regression of the lithium results with source results as the X variable and treated result as the Y variable produces a curve fit with the formula: $f(x) = 0.9254262x + 0.1213057$, and an $R^2 = 0.960$ (Figure 4). No other pharmaceuticals were detected in more than three matched pairs; thus additional correlations or linear regressions were not determined. This near one-to-one correspondence suggests minimal or no removal of lithium during treatment, consistent with lithium's being characterized as a conservative inorganic tracer (Barber et al., 2006b; Dierberg and DeBusk, 2005; Kim et al., 2002).

The preceding discussion notes that some pharmaceuticals are resistant to reduction through treatment; however, the reduction of detectable pharmaceuticals in individual DWTPs is substantial, with mean and median reductions from detection to non-detection of 59 and 67 % respectively. The reduction to undetectable concentrations between source and treated water samples for many pharmaceuticals in both phases of this study are comparable to other studies of source and treated water (Benotti et al., 2009b; Loos et al., 2010; Snyder et al., 2007; Stackelberg et al., 2007). For example, in their study of source and treated drinking waters, Benotti et al. (2009a) also observed a pattern of reduction in concentrations of pharmaceuticals after treatment. Interestingly carbamazepine was reduced in their studies, as were other pharmaceuticals, such as atenolol, meprobamate or gemfibrozil, and naproxen, that were not measured in Phase I samples or included in earlier USGS studies (Stackelberg et al., 2007; Focazio et al., 2008; Stackelberg et al., 2007)

In summary, the results from this study show that multiple pharmaceuticals are present at concentrations typically below 1,000 ng/L in both source and treated drinking waters. Following the application of the treatment processes evaluated in this study, detection frequencies typically decreased, and concentrations of pharmaceuticals were generally, but not always, lower. The types of pharmaceuticals observed in this study reflect the diverse array of anthropogenic practices and water uses that affect the watersheds that provide source water to these DWTPs, and the observed results are likely reflective of the pharmaceutical compositions present in many commonly used drinking-water sources of the United States. Inclusion of more advanced treatment processes, such as activated carbon treatment, have been demonstrated to be highly effective in removing pharmaceuticals (Huerta-Fontela et al., 2011), and DWTPs in this study that used frequently renewed, deep bed depth, activated carbon treatment (for example, DWTP 2), showed similar effective removals.

There are fewer detections of any one compound in treated water when compared to source water, reflective of the overall effectiveness of removal by the treatment processes used in the DWTPs studied. Several pharmaceuticals persisted through treatment, or were minimally reduced. Future research should emphasize the formation of degradates and pharmaceutical-derived disinfection byproducts, in light of the fact that many of the compounds detected in source water in this study were not detected in treated waters and the potential for formation of transformation products resulting from drinking water disinfection processes. As a whole,

the source and treated waters evaluated in this study contain relatively few of the pharmaceuticals determined above the reporting levels of the methods. Exposure assessment should emphasize the subset of pharmaceuticals and CECs that were detected in both source and treated water samples and that likely persisted through treatment.

Understanding the potential for human-health and ecosystem effects from the presence and distribution of pharmaceuticals in source and treated waters continues to be an area of active research and assessment. In particular, the potential risks associated with long-term exposure to pharmaceuticals and other CECs, singly or in combinations, remains a knowledge gap of global interest (World Health Organization, 2012). The pharmaceutical and other CEC results from this two-phase study provide a baseline for comprehensive, multiple contaminant assessment of sublethal toxicological effects. As methodologies and approaches are developed that quantify more nuanced effects, such as changes in gene expression or organism behavioral changes, the results from this study will provide essential data linking observed environmental and drinking-water concentrations to these subtle indicators of effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclaimers and Acknowledgements

The authors declare no competing financial interest. The information in this document has been funded partially or wholly by the U.S. Environmental Protection Agency. The research described in this article has been funded in part by the U.S. Environmental Protection Agency through Interagency Agreement DW14922330 to the U.S. Geological Survey, and through programmatic support of the USGS' Toxic Substances Hydrology Program and the USEPA's Office of Research and Development, Office of Water, Office of Chemical Safety and Pollution Prevention, and Region 8. Information Collection Rule approval for the Phase II Questionnaire was granted under USEPA ICR No. 2346.01, OMB Control No. 2080-0078. This manuscript has been subjected to review by the National Exposure Research Laboratory and approved for publication. Approval does not signify that the contents reflect the views of the USEPA and mention of trade names or commercial products does not constitute endorsement or recommendation for use by USEPA. This document has been reviewed in accordance with USGS policy and approved for publication. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government. The authors would like to thank all participating DWTPs for their involvement in the project and for their assistance in collecting the samples. The authors would also like to thank the following personnel for sample and data analysis assistance: Steve Werner, Laura Coffey, and Laura Rosenblum.

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Figure 1.

Frequency of occurrence and range of concentrations of the most frequently detected pharmaceuticals in source water samples from 25 drinking water treatment plants sampled in Phase II of this study. Results plotted on a logarithmic scale.

Figure 2.

Frequency of occurrence and range of concentrations of the most frequently detected pharmaceuticals in treated water samples from 25 drinking water treatment plants sampled in Phase II of this study. Results plotted on a logarithmic scale.

Figure 3.

Concentrations of the most frequently detected pharmaceuticals in the four drinking water treatment plants (DWTPs) with the highest frequencies of pharmaceutical detection sampled in Phase II of this study.

Figure 4. Comparison of paired source-finished drinking water sample pairs from 25 drinking water treatment plants, plotted on a linear scale.

Table 1. Median and maximum concentrations and frequencies of detection of the 24 pharmaceuticals determined in Phase I source- and treated-water samples.

Compound	CASRN ^a	Method	Estimated log K _{ow}	Molecular weight	Therapeutic use	Reporting level, in ng/L ^b	Source-water samples			Treated-water samples		
							Qualitative frequency, in percent	Quantitative frequency, in percent	Median concentration, in ng/L	Maximum concentration, in ng/L	Qualitative frequency, in percent	Quantitative frequency, in percent
1,7-dimethylxanthine	611-59-6	Cahill et al. (2004)	-0.39	180.164	Adenosine receptor agonist	100	0	0	NA ^c	NA	0	0
Acetaminophen	103-90-2	Cahill et al. (2004)	0.27	151.163	Analgesic, antipyretic	80	0	0	NA	NA	0	0
Albuterol	18559-94-9	Cahill et al. (2004)	0.64	239.311	Beta-adrenergic agonist	40	0	0	NA	NA	0	0
Bupropion	34911-55-2	Schultz and Furlong (2008)	3.85	239.741	Antidepressant	0.66	89	67	1.23	3.19	44	33
Caffeine	58-08-2	Cahill et al. (2004)	0.16	194.191	Central nervous system stimulant	60	67	11	124	124	66	11
Carbamazepine	298-46-4	Cahill et al. (2004)	2.25	236.269	Analgesic, anticonvulsant	40	78	11	269	269	55	11
Citalopram	59729-33-8	Schultz and Furlong (2008)	3.74	324.392	Antidepressant	0.9	33	11	0.90	0.90	0	0
Codine	76-57-3	Cahill et al. (2004)	1.28	299.364	Opioid analgesic	40	0	0	NA	NA	0	0
Cotinine	486-56-6	Cahill et al. (2004)	0.34	176.215	Nicotine metabolite	28	11	0	NA	NA	11	0
Dehydronifedipine	67035-22-7	Cahill et al. (2004)	3.15	344.319	Nifedipine metabolite	60	0	0	NA	NA	11	0
Diltiazem	42399-41-7	Cahill et al. (2004)	2.79	414.518	Antihypertensive, vasodilator	40	11	0	NA	NA	0	0
Diphenhydramine	58-73-1	Cahill et al. (2004)	3.11	255.355	Histamine antagonist	23	11	0	NA	NA	0	0
Duloxetine	116539-59-4	Schultz and Furlong (2008)	4.68	297.415	Antidepressant	0.48	0	0	NA	NA	0	0
Fluoxetine	54910-89-3	Schultz and Furlong (2008)	4.65	309.326	Antidepressant	0.5	11	11	0.53	0.53	0	0
Fluvoxamine	54739-18-3	Schultz and Furlong (2008)	3.09	318.335	Antidepressant	0.48	0	0	NA	NA	0	0
Norfluoxetine	83891-03-6	Schultz and Furlong (2008)	4.18	295.299	Antidepressant degradate	0.56	0	0	NA	NA	0	0
Paroxetine	61869-08-7	Schultz and Furlong (2008)	2.57	329.365	Antidepressant	0.64	0	0	NA	NA	0	0
Ranitidine	66357-35-5	Cahill et al. (2004)	0.29	314.404	Stomach acid reducer	25	0	0	NA	NA	0	0

Compound	CASRN ^a	Method	Estimated log K _{ow}	Molecular weight	Therapeutic use	Reporting level, in ng/L ^b	Source-water samples				Treated-water samples			
							Qualitative frequency, in percent	Quantitative frequency, in percent	Median concentration, in ng/L	Maximum concentration, in ng/L	Qualitative frequency, in percent	Quantitative frequency, in percent	Median concentration, in ng/L	Maximum concentration, in ng/L
Sertraline	79617-96-2	Schultz and Furlong (2008)	5.29	306.23	Antidepressant	0.42	22	22	0.54	0.66	0	0	NA	NA
Sulfamethoxazole	723-46-6	Cahill et al. (2004)	0.48	253.278	Antibiotic	100	56	0	NA	NA	11	0	NA	NA
Thiabendazole	148-79-8	Cahill et al. (2004)	2.00	201.248	Fungicide, nematocide	40	0	0	NA	NA	0	0	NA	NA
Trimethoprim	738-70-5	Cahill et al. (2004)	0.73	290.318	Antibiotic	20	0	0	NA	NA	0	0	NA	NA
Venlafaxine	93413-69-5	Schultz and Furlong (2008)	3.28	277.402	Antidepressant	0.58	78	78	10.84	41.90	0	0	NA	NA
Warfarin	81-81-2	Cahill et al. (2004)	2.23	308.328	Anticoagulant	60	0	0	NA	NA	0	0	NA	NA

^aChemical Abstracts Service Registry Numbers (CASRN)@.

^bReporting levels are from the appropriate citation and are in nanograms per liter.

^cNot applicable.

Table 2. Median and maximum concentrations and frequencies of detection of the 118 pharmaceuticals in Phase II source-treated-water samples.

Pharmaceutical	Method	CASRN ^d	Estimated log K _{ow} or log P ^e	Molecular weight	Therapeutic use	LCMR _L ^b , in ng/L	Source-water Samples				Treated-water Samples			
							Qualitative frequency, in percent	Quantitative frequency, in percent	Median concentration, in ng/L ^c	Maximum quantified concentration, in ng/L	Qualitative frequency, in percent	Quantitative frequency, in percent	Median concentration, in ng/L	Maximum concentration, in ng/L
1,7-Dimethylxanthine	Furlong et al. (2014)	611-59-6	-0.39	180.164	Adenosine receptor agonist	17.5 ^e	4	4	29.18	29.18	0	0	NA	NA
10-Hydroxyamitriptyline	Batt et al. (2008)	64520-05-4	3.41	293.403	Amitriptyline degradate	5.0	4	0	NA ^d	NA	0	0	NA	NA
Abacavir	Furlong et al. (2014)	136470-78-5	1.62	286.332	Antiviral	4	0	0	NA	NA	0	0	NA	NA
Acetaminophen	Batt et al. (2008)	103-90-2	0.27	151.163	Analgesic, antipyretic	11.0	0	0	NA	NA	0	0	NA	NA
Aciclovir	Furlong et al. (2014)	59277-89-3	-4.27	225.205	Antiviral	82	44	0	NA	NA	12	0	NA	NA
Albuterol	Furlong et al. (2014)	18559-94-9	0.64	239.311	Beta-adrenergic agonist	5.3	0	0	NA	NA	0	0	NA	NA
Alprazolam	Batt et al. (2008)	28981-97-7	3.87	308.765	Anxiolytic	7.6	0	0	NA	NA	0	0	NA	NA
Amitriptyline	Batt et al. (2008)	549-18-8	4.95	277.403	Antidepressant	4.0	4	4	12.10	12.10	0	0	NA	NA
Amlodipine	Batt et al. (2008)	111470-99-6	2.07	408.876	Antihypertensive	15.0	0	0	NA	NA	0	0	NA	NA
Amphetamine	Batt et al. (2008)	51-63-8	1.76	135.206	Central nervous system stimulant	4.0	0	0	NA	NA	0	0	NA	NA
Antipyrine	Furlong et al. (2014)	60-80-0	0.59	188.226	Analgesic	28	0	0	NA	NA	0	0	NA	NA
Atenolol	Batt et al. (2008)	29122-68-7	-0.03	266.336	Antihypertensive, antiarrhythmic	23.0	28	4	29.80	29.80	12	0	NA	NA
Atorvastatin	Batt et al. (2008)	298-46-4	6.11*	558.640	Statin	16.0	0	0	NA	NA	0	0	NA	NA
Benzatropine	Batt et al. (2008)	86-13-5	4.28	307.429	Anticholinergic	9.0	0	0	NA	NA	0	0	NA	NA
Betamethasone	Furlong et al. (2014)	378-44-9	1.72	392.461	Glucocorticoid	150	0	0	NA	NA	0	0	NA	NA
Bupropion	Schultz and Furlong (2008)	34911-55-2	3.85	239.741	Antidepressant	0.66	20	20	6.36	9.41	12	12	10.33	10.91
Caffeine	Furlong et al. (2014)	58-08-2	0.16	194.191	Central nervous system stimulant	42	32	12	70.29	90.89	8	0	NA	NA
Carbamazepine	Batt et al. (2008)	298-46-4	2.25	236.269	Analgesic, anticonvulsant	7.1	56	28	15.90	35.70	8	8	17.75	26.50
Carisoprodol	Furlong et al. (2014)	78-44-4	2.36	260.330	Muscle relaxants	81	16	4	5.01	5.01	4	0	NA	NA
Citalopram	Furlong et al. (2014)	59729-33-8	3.74	324.392	Antidepressant	24	8	0	NA	NA	0	0	NA	NA

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Clofibrate	USGS adaptation of Ternes et al. (2005)	637–07–0	3.62	242.699	Antilipidemic	25 ^f	0	0	NA	NA	4	4	91.72	91.72
Clonidine	Batt et al. (2008)	4205–91–8	1.85	230.094	Antihypertensive	27.0	0	0	NA	NA	0	0	NA	NA
Codaine	Furlong et al. (2008)	76–57–3	1.28	299.364	Opioid analgesic	46	0	0	NA	NA	0	0	NA	NA
Cotinine	Furlong et al. (2014)	486–56–6	0.34	176.215	Nicotine degrades	4.4	20	8	15.30	18.86	16	8	10.98	15.81
Dehydronifedipine	Furlong et al. (2014)	67035–22–7	3.15	344.319	Nifedipine degrades	12	4	0	NA	NA	4	0	NA	NA
Desmethyl diltiazem	Batt et al. (2008)	130606–60–9	2.34*	436.952	Diltiazem degrades	4.4	8	8	5.40	6.00	4	0	NA	NA
Desmethyl sertraline	Batt et al. (2008)	87857–41–8	4.82	292.203	Sertraline degrades	6.0	0	0	NA	NA	0	0	NA	NA
Desvenlafaxine	Furlong et al. (2014)	93413–62–8	2.72	263.375	Venlafaxine degrades, antidepressant	15	28	16	28.34	60.43	4	0	NA	NA
Dextromethorphan	Furlong et al. (2014)	125–71–3	3.60	271.397	Antitussive	48	4	0	NA	NA	0	0	NA	NA
Diazepam	Furlong et al. (2014)	439–14–5	2.70	284.740	Anxiolytic, muscle relaxant, sedative	2.5	0	0	NA	NA	4	4	0.85	0.85
Diltiazem	Batt et al. (2008)	33286–22–5	2.79	414.518	Antihypertensive, vasodilator	6.8	20	8	11.65	15.50	8	0	NA	NA
Diphenhydramine	Furlong et al. (2014)	58–73–1	3.11	255.355	Histamine antagonist	6.9	16	4	10.28	10.28	0	0	NA	NA
Duloxetine	Furlong et al. (2014)	116539–59–4	4.68	297.415	Antidepressant	1100	0	0	NA	NA	0	0	NA	NA
Enalapril	Batt et al. (2008)	76095–16–4	2.45	376.447	Antihypertensive	4.4	0	0	NA	NA	0	0	NA	NA
Erythromycin	Furlong et al. (2014)	114–07–8	2.60*	733.927	Antibiotic	55	0	0	NA	NA	0	0	NA	NA
Estradiol	Conley et al. (2016)	50–28–2	3.94	272.382	Estrogen	<0.1	4	0	NA	NA	8	0	NA	NA
Estriol	Conley et al. (2016)	50–27–1	2.81	288.381	Estrogen	0.092	8	0	NA	NA	4	0	NA	NA
Estrone	Conley et al. (2016)	53–16–7	3.43	270.366	Estrogen	0.092	52	24	0.16	0.29	4	0	NA	NA
Ethinylestradiol	Conley et al. (2016)	57–63–6	4.12	296.403	Estrogen, contraceptive	0.43	0	0	NA	NA	4	0	NA	NA
Ezetimibe	Furlong et al. (2014)	163222–33–1	3.94	409.425	Cholesterol reducer	280	0	0	NA	NA	0	0	NA	NA
Fadrozole	Furlong et al. (2014)	102676–47–1	3.20	223.273	Antineoplastic	17	0	0	NA	NA	0	0	NA	NA
Famotidine	Furlong et al. (2014)	76824–35–6	–0.65	337.445	Stomach acid reducer	68	0	0	NA	NA	0	0	NA	NA

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Fenofibrate	Furlong et al. (2014)	49562–28–9	5.19	360.831	Cholesterol reducer	19	0	0	NA	NA	0	0	NA	NA
Fexofenadine	Furlong et al. (2014)	83799–24–0	2.94*	501.656	Histamine antagonist	25	12	8	112.17	163.09	8	0	NA	NA
Fluconazole	Furlong et al. (2014)	86386–73–4	0.25	306.271	Antifungal	40	8	4	33.67	33.67	8	0	NA	NA
Fluoxetine	Batt et al. (2008)	59333–67–4	4.65	309.326	Antidepressant	2.7	0	0	NA	NA	0	0	NA	NA
Fluticasone propionate	Batt et al. (2008)	80474–14–2	3.72*	500.571	Glucocorticoid, antiallergenic	15.0	0	0	NA	NA	0	0	NA	NA
Fluvoxamine	Furlong et al. (2014)	54739–18–3	3.09	318.335	Antidepressant	270	4	0	NA	NA	4	0	NA	NA
Furosemide	Batt et al. (2008)	54–31–9	2.32	330.744	Antihypertensive, diuretic	14.0	4	4	17.50	17.50	0	0	NA	NA
Genfibrozil	Batt et al. (2008)	25812–30–0	4.77	250.333	Antilipidemic	20.0	8	0	NA	NA	0	0	NA	NA
Glipizide	Batt et al. (2008)	29094–61–9	3.35	445.535	Hypoglycemic agent	22.0	0	0	NA	NA	0	0	NA	NA
Glyburide	Furlong et al. (2014)	10238–21–8	4.79	494.004	Hypoglycemic agent	48	0	0	NA	NA	0	0	NA	NA
Hydrochlorothiazide	Batt et al. (2008)	58–93–5	–0.10	297.739	Antihypertensive, diuretic	10.0	24	20	47.40	67.30	0	0	NA	NA
Hydrocodone	Batt et al. (2008)	125–29–1	2.16	299.364	Antitussive, opioid analgesic	4.1	4	4	8.10	8.10	0	0	NA	NA
Hydrocortisone	Batt et al. (2008)	50–23–7	1.62	362.460	Glucocorticoid, anti-inflammatory	17.0	0	0	NA	NA	0	0	NA	NA
Hydroxyzine	Furlong et al. (2014)	68–88–2	2.36	374.904	Anxiolytic, sedative	7.1	0	0	NA	NA	0	0	NA	NA
Ibuprofen	Batt et al. (2008)	15687–27–1	3.79	206.281	Anti-inflammatory	6.9	8	8	15.85	17.70	0	0	NA	NA
Iminostilbene	Furlong et al. (2014)	256–96–2	4.06	193.244	Benzodiazepine	75	0	0	NA	NA	0	0	NA	NA
Lamivudine	Furlong et al. (2014)	134678–17–4	–2.62	229.256	Antiretroviral	25	0	0	NA	NA	4	4	27.73	27.73
Lidocaine	Furlong et al. (2014)	137–58–6	1.66	234.337	Local anaesthetic	28	20	8	29.65	29.70	0	0	NA	NA
Lithium	EPA 200.7	7439–93–2	–0.770	6.941	Bipolar disorder treatment	3.7 ^g	56	56	10.70	46.00	56	56	10.80	42.70
Loperamide	Furlong et al. (2014)	53179–11–6	5.15	477.038	Antidiarrhoeal	46	0	0	NA	NA	0	0	NA	NA
Loratadine	Furlong et al. (2014)	79794–75–5	5.66	382.883	Histamine antagonist, antipruritic	14	4	0	NA	NA	4	0	NA	NA

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Lorazepam	Furlong et al. (2014)	846-49-1	3.98	321.158	Anxiolytic, sedative	200	0	0	NA	NA	0	0	NA	NA
Meprobamate	Furlong et al. (2014)	57-53-4	0.98	218.250	Anxiolytic, sedative	69	32	4	14.18	14.18	16	0	NA	NA
Metaxalone	Furlong et al. (2014)	1665-48-1	2.60	221.252	Muscle relaxant	16	4	0	NA	NA	0	0	NA	NA
Metformin	Furlong et al. (2014)	657-24-9	-1.40	129.164	Hypoglycemic agent	23	40	0	NA	NA	16	0	NA	NA
Methadone	Furlong et al. (2014)	76-99-3	4.17	309.445	Opioid analgesic, antitussive	43	8	0	NA	NA	0	0	NA	NA
Methocarbamol	Furlong et al. (2014)	532-03-6	-0.26	241.240	Muscle relaxant	27	36	8	29.11	32.30	16	0	NA	NA
Methotrexate	Furlong et al. (2014)	59-05-2	-1.28	454.439	Antineoplastic; antirheumatic	81	0	0	NA	NA	0	0	NA	NA
Methylprednisolone	Batt et al. (2008)	83-43-2	1.82	374.471	Glucocorticoid, anti-inflammatory	7.7	0	0	NA	NA	0	0	NA	NA
Metoprolol	Batt et al. (2008)	56392-17-7	1.69	267.364	Antihypertensive	4.7	52	32	11.40	37.80	28	12	8.50	18.40
Morphine	Furlong et al. (2014)	57-27-2	0.72	285.338	Opioid analgesic	57	0	0	NA	NA	0	0	NA	NA
Nadolol	Furlong et al. (2014)	42200-33-9	1.17	309.401	Antihypertensive	28	0	0	NA	NA	0	0	NA	NA
Nevirapine	Furlong et al. (2014)	129618-40-2	3.89	266.298	Antiviral	3.02 ^e	0	0	NA	NA	0	0	NA	NA
Nicotine	Furlong et al. (2014)	54-11-5	1.00	162.232	Stimulant	85	12	0	NA	NA	0	0	NA	NA
Nordiazepam	Furlong et al. (2014)	1088-11-5	3.89	270.714	Anxiolytic, diazepam degradate	67	0	0	NA	NA	0	0	NA	NA
Norethindrone	Batt et al. (2008)	68-22-4	2.99	298.419	Contraceptive, progestogen	10.0	0	0	NA	NA	0	0	NA	NA
Norfluoxetine	Batt et al. (2008)	83891-03-6	4.18	295.299	Antidepressant degradate	8.7	0	0	NA	NA	0	0	NA	NA
Norverapamil	Batt et al. (2008)	67018-85-3	4.59	440.575	Verapamil degradate	8.5	20	8	28.75	47.20	16	4	22.20	22.20
Oseltamivir	Furlong et al. (2014)	196618-13-0	0.95	312.405	Antiviral	32	0	0	NA	NA	0	0	NA	NA
Oxazepam	Furlong et al. (2014)	604-75-1	3.34	286.713	Anxiolytic, sedative	160	0	0	NA	NA	0	0	NA	NA
Oximated dihydrotestosterone	Conley et al. (2016)				Testosterone degradate	UND ^h	4	4	0.32	0.32	0	0	NA	NA

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Oxycodone	Batt et al. (2008)	76-42-6	0.66	315.364	Opioid analgesic, antitussive	11.0	0	0	NA	NA	0	0	NA	NA
Paroxetine	Batt et al. (2008)	110429-35-1	2.57	329.365	Antidepressant	4.7	0	0	NA	NA	0	0	NA	NA
Penciclovir	Furlong et al. (2014)	39809-25-1	-3.71	253.258	Antiviral	120	4	0	NA	NA	0	0	NA	NA
Pentoxyfylline	Furlong et al. (2014)	6493-05-6	0.56	278.307	Vasodilator	16	0	0	NA	NA	0	0	NA	NA
Phenazopyridine	Furlong et al. (2014)	94-78-0	2.77	213.238	Local anaesthetic	17	0	0	NA	NA	0	0	NA	NA
Phendimetrazine	Furlong et al. (2014)	634-03-7	1.70	191.270	Stimulant	83	0	0	NA	NA	0	0	NA	NA
Phenytoin	Furlong et al. (2014)	57-41-0	2.16	252.268	Anticonvulsant	320	0	0	NA	NA	0	0	NA	NA
Piperonylbutoxide	Furlong et al. (2014)	51-03-6	4.29	338.439	Insecticidal synergist	3.2	8	0	NA	NA	0	0	NA	NA
Prednisolone	Batt et al. (2008)	50-24-8	1.40	360.444	Glucocorticoid, antineoplastic	12.0	0	0	NA	NA	0	0	NA	NA
Prednisone	Batt et al. (2008)	53-03-2	1.59	358.428	Glucocorticoid, antineoplastic	9.6	0	0	NA	NA	0	0	NA	NA
Progesterone	Conley et al. (2016)	57-83-0	3.67	314.462	Progestogen	0.13	12	4	0.15	0.15	4	4	0.20	0.20
Promethazine	Batt et al. (2008)	58-33-3	4.49	284.419	Antiemetic	8.6	0	0	NA	NA	0	0	NA	NA
Propranolol	Batt et al. (2008)	525-66-6	2.60	259.343	Antihypertensive, antiarrhythmic, anxiolytic	1.5	4	0	NA	NA	12	8	2.35	2.50
Propoxyphene	Batt et al. (2008)	469-62-5	5.27	339.471	Opioid analgesic, antitussive	233.0	0	0	NA	NA	0	0	NA	NA
Pseudoephedrine	Furlong et al. (2014)	90-82-4	0.68	165.232	Decongestant	5.5 ^e	24	20	2.77	4.45	12	8	2.16	3.75
Raloxifene	Furlong et al. (2014)	84449-90-1	6.09	473.583	Anti-estrogen	600	0	0	NA	NA	4	0	NA	NA
Ranitidine	Batt et al. (2008)	66357-59-3	0.29	314.404	Stomach acid reducer	5.3	4	4	13.10	13.10	0	0	NA	NA
Sertraline	Batt et al. (2008)	79559-97-0	5.29	306.230	Antidepressant	5.9	0	0	NA	NA	0	0	NA	NA
Simvastatin	Batt et al. (2008)	79902-63-9	5.19	418.566	Antilipidemic	36.0	0	0	NA	NA	0	0	NA	NA
Sitagliptin	Furlong et al. (2014)	486460-32-6	1.39	407.314	Antihyperglycemic	96	12	0	NA	NA	4	0	NA	NA
Sulfadimethoxine	Furlong et al. (2014)	122-11-2	1.17	310.329	Antibiotic	31	8	4	6.99	6.99	0	0	NA	NA

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Sulfamethizole	Furlong et al. (2014)	144–82–1	0.41	270.331	Antibiotic	86	0	0	NA	NA	0	0	NA	NA
Sulfamethoxazole	Batt et al. (2008)	723–46–6	0.48	253.278	Antibiotic	6.5	60	40	50.10	161.10	4	4	8.20	8.20
Testosterone	Conley et al. (2016)	58–22–0	3.27	288.424	Androgen	0.1	4	4	0.15	0.15	0	0	NA	NA
Theophylline	Furlong et al. (2014)	58–55–9	−0.39	180.164	Vasodilator	120	0	0	NA	NA	0	0	NA	NA
Thiabendazole	Furlong et al. (2014)	148–79–8	2.00	201.248	Fungicide, nematicide	39	8	0	NA	NA	0	0	NA	NA
Tramadol	Furlong et al. (2014)	27203–92–5	3.01	263.375	Analgesic	8.7	32	16	107.4	23.04	0	0	NA	NA
Trenbolone	Conley et al. (2016)	10161–33–8	2.65	270.366	Anabolic agent	UND ^h	16	0	NA	NA	24	0	NA	NA
Triamterene	Furlong et al. (2014)	396–01–0	0.80	253.263	Diuretic	28	8	0	NA	NA	0	0	NA	NA
Trimethoprim	Batt et al. (2008)	738–70–5	0.73	290.318	Antibiotic	3.5	28	16	6.40	9.90	8	0	NA	NA
Valacyclovir	Furlong et al. (2014)	124832–26–4	−3.41	324.336	Antiviral	170	0	0	NA	NA	0	0	NA	NA
Valsartan	Batt et al. (2008)	396–01–0	3.65	435.519	Antihypertensive	7.2	20	12	35.70	79.20	0	0	NA	NA
Venlafaxine	Furlong et al. (2014)	93413–69–5	3.28	277.402	Antidepressant	6.2	12	8	21.47	26.30	0	0	NA	NA
Verapamil	Batt et al. (2008)	137862–53–4	4.80	454.602	Vasodilator	7.8	20	4	45.90	45.90	8	4	26.70	26.70
Warfarin	Furlong et al. (2014)	81–81–2	2.23	308.328	Anticoagulant	8.5	0	0	NA	NA	0	0	NA	NA

^aChemical Abstracts Service Registry Numbers (CASRN)@.

^bLowest-concentration minimum reporting level (Martin et al. 2007), in nanograms per liter.

^cUnits for all pharmaceuticals are in nanograms per liter, except lithium, which are in micrograms per liter.

^dNot applicable.

^eLCMRL not calculable using LCMRL procedure; EPA method detection limit (MDL) from Furlong et al. (2014) used instead.

^fEstimated reporting limit.

^gEstimated reporting limit, in micrograms per liter (µg/L) from EPA method 200.7.

^hUndetermined.