Exhibit I

Laura M. Bexfield et al., *Hormones and Pharmaceuticals in Groundwater Used as a Source of Drinking Water Across the United States*, 53 Envtl. Sci. & Tech 2950, (2019)

Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2019, 53, 2950−2960

pubs.acs.org/est

Hormones and Pharmaceuticals in Groundwater Used As a Source of Drinking Water Across the United States

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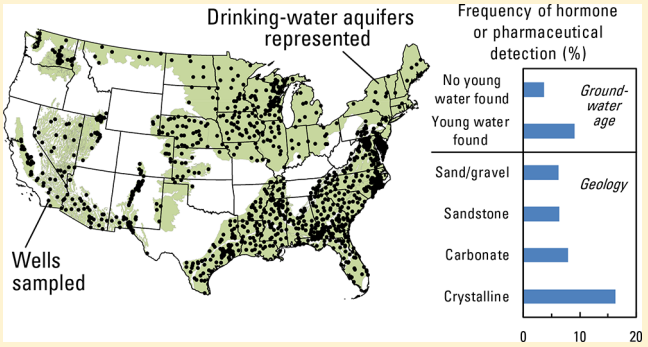
Supporting Information

ABSTRACT: This is the first large-scale, systematic assessment of hormone and pharmaceutical occurrence in groundwater used for drinking across the United States. Samples from 1091 sites in Principal Aquifers representing 60% of the volume pumped for drinking-water supply had final data for 21 hormones and 103 pharmaceuticals. At least one compound was detected at 5.9% of 844 sites representing the resource used for public supply across the entirety of 15 Principal Aquifers, and at 11.3% of 247 sites representing the resource used for domestic supply over subareas of nine Principal Aquifers. Of 34 compounds detected, one plastics component (bisphenol A), three pharmaceuticals (carbamazepine, sulfamethoxazole, and meprobamate), and the caffeine degradate 1,7-dimethylxanthine were detected in more than 0.5% of samples. Hydrocortisone had a concentration greater than a human-health benchmark at 1 site. Compounds with high solubility and low K_{oc} were most likely to be detected. Detections were most common in shallow wells with a component of recent recharge, particularly in crystalline-rock and mixed land-use settings. Results indicate vulnerability of groundwater used for drinking water in the U.S. to contamination by these compounds is generally limited, and exposure to these compounds at detected concentrations is unlikely to have adverse effects on human health.



INTRODUCTION

Hormones and pharmaceuticals are widely used for treatment of humans, domestic animals, and livestock, and they have the potential to enter the environment, including groundwater. Based on 2011−2014 data, about 47% of Americans took at least one prescription drug in the past 30 days, and 22% took three or more.[1] Annually, billions of prescriptions are filled across the U.S.[2] The potential for hormones and pharmaceuticals to be present in drinking water is of concern because unintentional exposure to some of these bioactive compounds could result in adverse effects on human health at low doses, they can exert a wide range of adverse effects including endocrine disruption and antibiotic resistance, and some effects are persistent.[3−8] Hormones and (or) pharmaceuticals have been detected in human, plant, and animal tissues[4,5,9,10] and in surface water,[9−13] including surface water used as a drinking-water source in the U.S.[14−16] Hormone and pharmaceutical compounds currently are not regulated in drinking water in the U.S. (nor typically in other countries), but nine hormones are on the most recent Contaminant Candidate List of the U.S. Environmental Protection Agency (EPA) (CCL4, http://www2.epa.gov/ccl/chemical-contaminants-ccl-4), identifying them as priority contaminants for information collection and potential regulation.

Discharges from wastewater treatment plants and septic systems are potential sources of hormone and pharmaceutical compounds to groundwater because some of these compounds are not substantially removed by typical wastewater treatment processes.[15−21] Several studies have documented the likely roles of these sources in contributing compounds to groundwater.[8,22−26] Other potential sources include leaking sewer lines, landfills, animal feeding operations, and cropland where biosolids have been applied.[6,24,27−29] Where sources are present, factors identified as likely to control the occurrence of hormone and pharmaceutical compounds in groundwater include the mobility and persistence of compounds;[6,19,22,26] redox conditions;[22,25,30] aquifer composition;[8,27,30] unsaturated

Received: October 4, 2018
Revised: February 11, 2019
Accepted: February 16, 2019
Published: March 5, 2019

DOI: 10.1021/acs.est.8b05592
Environ. Sci. Technol. 2019, 53, 2950−2960

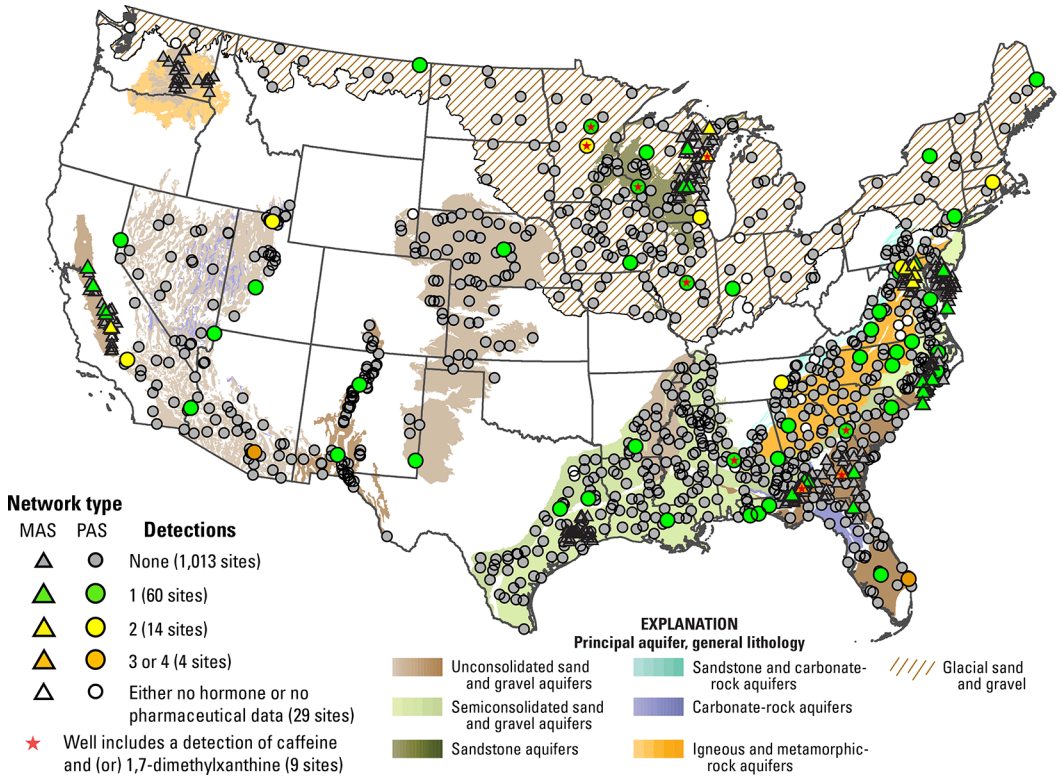


Figure 1. Number of hormone and (or) pharmaceutical compounds detected at each of the 1120 sites sampled in 18 Principal Aquifers, 2013–2015. Sites were part of a Principal Aquifer Survey (PAS) or Major Aquifer Study (MAS). The Floridan aquifer system and Mississippi Embayment aquifer system are each shown with two lithologies.[69]

zone thickness;[25] well depth;[22,31] and density of urban and (or) residential land use.[8,32]

Few studies have examined the occurrence of hormones and pharmaceuticals in groundwater used as a source of drinking water in the U.S. (Supporting Information (SI) Table S1). A reconnaissance of organic wastewater compounds (including hormones, pharmaceuticals, pesticides, solvents, and fire retardants) at 47 groundwater sites of varying use across the U.S. found that detection frequencies for the plasticizer bisphenol A (30%) and the antibiotic sulfamethoxazole (23%) were among the highest for any compound.[31] Two small studies of groundwater resources used for public supply in locations across the country (3 and 25 sites) showed that some individual hormone and (or) pharmaceutical compounds such as bisphenol A and carbamazepine can be present in 20% or more of sources.[14,15] State and local studies of groundwater used for drinking, ranging in size from 20 wells to 1231 wells, also have shown the presence of hormones and (or) pharmaceuticals in water from as few as 2.3% to as many as 60% of domestic or public-supply wells.[8,22,27,32,33] Outside the U.S., a limited number of groundwater surveys have included a substantial number of drinking-water sites on large spatial scales. These surveys across Europe (164 sites),[34] France (494 sites),[35] and England and Wales (2650 sites)[36] found that the most frequently detected hormones and pharmaceuticals were present in up to about 80% of sites that included a combination of well types.

This is the first large-scale (>1000 sites in 46 states), systematic (spatially distributed) study of more than 100 hormone and pharmaceutical compounds in groundwater used for drinking-water supply across the U.S. Samples from 1120 wells or springs in 18 Principal Aquifers providing groundwater supplies used for drinking by an estimated 80 million people were analyzed for as many as 21 compounds using a method targeting primarily hormones and 105 pharmaceutical compounds using a separate method, both with low detection levels generally between 2 and 200 ng/L. Previous studies of hormones and pharmaceuticals in groundwater have included fewer compounds (typically fewer than 10 hormones and 60 pharmaceuticals), covered a substantially smaller geographic area and population served, included groundwater resources not used for drinking, and (or) targeted groundwater in areas with known wastewater sources. The objectives of this study were to systematically determine how often hormones and pharmaceuticals occur in groundwater used as a source of drinking water across the U.S., and to evaluate factors that could contribute to their occurrence. The large number of sampled sites and compounds enabled investigation of the roles of characteristics of the individual compounds and sampling sites, hydrogeologic factors, and land use in compound occurrence. Measured concentrations were compared with human-health benchmarks to assess the potential relevance of detections in a human-health context. Because most relevant human-health benchmarks were not available until 2015, previous investigations generally were unable to provide this context.

MATERIALS AND METHODS

Study Design. The 1114 wells and six springs sampled for this study by the U.S. Geological Survey's (USGS) National Water-Quality Assessment (NAWQA) Project during 2013 through 2015 are in 18 Principal Aquifers (SI Table S2) covering more than 4 million km^2 in 46 states (Figure 1), representing a wide variety of hydrogeologic, climatic, and

DOI: 10.1021/acs.est.8b05592
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land-use settings. Principal Aquifers are regionally extensive aquifers or aquifer systems that have the potential to be used for drinking water.[37] Based on location and depth information, sampling sites were assigned to corresponding Principal Aquifers (SI Table S3), which together supplied about 60% of the groundwater pumped from Principal Aquifers of the U.S. for public supply in 2000.[38] Three to 160 sites (median = 60) were sampled in each Principal Aquifer (SI Table S2). Additional Principal Aquifers have been targeted by NAWQA for subsequent sampling, with the intention to sample aquifers that in all represent more than 75% of the groundwater pumped for public supply.[39] Because the study design targets Principal Aquifers representing the used groundwater resource, which are not evenly distributed across the country, the sampled areas might not be a microcosm of the U.S. with respect to land use and physiography.

Of 1120 sites sampled, 864 sites (77%) in 15 Principal Aquifers were part of a Principal Aquifer Survey (PAS), designed to assess the quality of the groundwater resource used for public supply across an entire Principal Aquifer.[39] PAS sites are almost exclusively public-supply wells; six springs used for public supply also were sampled. The remaining 256 sites (23%) were sampled as part of a Major Aquifer Study (MAS), designed to assess the quality of the groundwater resource used for domestic supply,[40] typically within a targeted subarea of a Principal Aquifer. Most MAS wells are domestic wells, although public-supply, observation, or other wells that represent the resource being used for domestic supply are commonly substituted if a suitable domestic well is not available for sampling. Of all sites sampled, 900 (80%) are public-supply wells (median depth 116 m) or springs used for public supply, 162 (15%) are domestic wells (median depth 46 m), 52 (4.6%) are observation wells (median depth 27 m), and 6 (0.5%) are classified as other wells (median depth 42 m).

PASs and MASs each have a nationally consistent spatially distributed, randomized design for site selection that uses equal-area grids, with one site selected for sampling within each grid cell. Because a PAS includes one well per cell in a grid that typically extends over an entire Principal Aquifer, a given percentage of wells equates to the same percentage of Principal Aquifer area (for example, presence of a compound in 1% of wells equates to its presence in about 1% of aquifer area).[41] Results for an MAS are not spatially representative of, and should not be extrapolated over, an entire Principal Aquifer because the sampling grid extends over only a targeted subarea.

Sample Collection. Untreated (raw) samples were collected at or near the wellhead, prior to any treatment or blending, in accordance with USGS procedures.[42,43] Samples were collected using a Teflon sampling line and filtered through a 0.7 μm baked glass-fiber filter. Samples for hormones were collected in 500 mL clear polyethylene bottles, and samples for pharmaceuticals were collected in 20- or 40 mL amber glass bottles; samples were shipped on ice overnight to the USGS National Water-Quality Laboratory (NWQL) in Denver, CO for analysis. Groundwater samples were analyzed for about 500 additional constituents and isotopes,[44−46] including tritium (^{3}H), which is a tracer of recent (post-1953) recharge investigated as an explanatory variable for this study.

Laboratory Analysis. The NWQL's analytical method for hormones determines 21 compounds in water, including 13 endogenous and three synthetic steroid hormones, two sterols, and three nonsteroidal synthetic chemicals that are known or suspected endocrine disrupting chemicals, including bisphenol A (SI Table S4),[47] all referred to in aggregate as hormones. The analytical method for pharmaceuticals determines 105 human-use pharmaceuticals (prescription and over-the-counter) and pharmaceutical metabolites (SI Table S4); two compounds were omitted in data treatment (see below).[48] SI Section S2.3 provides more detail on the analytical methods and the detection limits (DLs) and reporting limits (RLs) assigned to most compounds.

The DL is defined as the lowest concentration that with 90% confidence will be exceeded no more than 1% of the time when a blank sample is measured (false-positive risk of no more than 1%). To minimize false-negative risk, the RL typically is set at 2 times the DL, or higher if appropriate based on method performance.[47,48] When an analyte is not detected or does not meet qualitative criteria and is below the RL, it is reported as "<" the RL. For analytes assigned DLs and RLs, concentrations are reported for qualitatively identified detections that are less than the DL or the lowest calibration standard. For compounds that were commonly detected in laboratory set blanks (LSBs), a minimum reporting level (MRL) was assigned instead of a DL and RL; no results are reported below the MRL. In the case of sample-specific matrix interferences, results might be reported with a raised reporting limit ("<" a value higher than the RL or MRL) or an estimated ("E") remark code.

For both methods, DLs, RLs, and MRLs were updated in 2016 (SI Table S4). In addition, a 2016 review of quality assurance and quality-control data led the NWQL to censor 2013−2015 hormone concentrations originally reported below the RL as being "<" the RL, and to censor or qualify other results.

Quality Assurance and Quality Control. Details about the evaluation of quality-control samples associated with this study[49−51] are provided in SI section S3; the use of results to characterize potential field and laboratory contamination and measurement bias is briefly summarized here. Field blanks and LSBs were used to examine potential sources of contamination; results prompted some censoring (see Data Preparation Steps section). USGS Quality Systems Branch (https://bqs.usgs.gov/) blind samples composed of reagent water spiked with certain compounds were used to estimate potential false positive and false negative occurrence rates; no censoring was judged to be necessary as a consequence of these results. Examination of laboratory matrix spikes and laboratory reagent-water spikes indicated little bias for hormones (median recovery 80−120%) and a slight low bias for most pharmaceuticals (median recovery typically 80−100%), indicating that reported concentrations for pharmaceuticals could be slightly low.

Data Preparation Steps. Five steps were conducted to prepare the data set for a nationally consistent and rigorous characterization of the occurrence of hormones and pharmaceuticals in drinking-water aquifers of the U.S. These steps maximize confidence that the detections reported in this paper resulted from the occurrence of hormones or pharmaceuticals in groundwater and not from field or laboratory contamination. Details of these steps are provided in SI Section S4.1; the final data set is presented in SI Table S5 and in a USGS data release.[50]

DOI: 10.1021/acs.est.8b05592
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Table 1. For NAWQA Groundwater Samples, Summary of Detections and Detected Concentrations for Hormone and Pharmaceutical Compounds with Detections Meeting Applicable Criteria

Analyte	Concentration used to define detections (ng/L)[a]	Number of detections meeting criteria[a]	Detection frequency (%)	Detection frequency for PAS sites alone (%)	Detection frequency for MAS sites alone (%)	Median of detected concentrations (ng/L)	Maximum of detected concentrations (ng/L)	Human-health benchmark (ng/L)[b]	Human-health benchmark type/source[b]	Lowest therapeutic dose (mg/day)[c]	Maximum concentration as % of HHB	Number of detections > HHB	Number of detections > 10% of HHB	Maximum lifetime cumulative mass as % of LTD[d]
Pharmaceuticals														
1,7-Dimethylxanthine[i]	21	9	0.8	0.7	1.2	160	416	--[e]	--	NA	NA	NA	NA	
Acetaminophen	3.6	4	0.4	0.1	1.2	8.8	17.0	200,000	MDH.HRL		0.009	0	0	
Acyclovir	4.4	1	0.1	0.1	0.0	5.7	5.7	NA	--	600	NA	NA	NA	0.06
Atenolol	4.8	1	0.1	0.1	0.0	8.7	8.7	2,000	MDH.WSV		0.44	0	0	
Bupropion	3.6	3	0.3	0.0	1.2	9.3	22.7	NA	--	300	NA	NA	NA	0.48
Caffeine	65.6	3	0.3	0.0	1.2	212	677	--[e]	--	NA	NA	NA	NA	
Carbamazepine[i]	2.2	18	1.6	1.2	3.2	8.5	162	40,000	MDH.HRL		0.41	0	0	
Carisoprodol	25	1	0.1	0.1	0.0	58.2	58.2	30,000	MDH.WSV		0.19	0	0	
Cimetidine	21	1	0.1	0.1	0.0	23.6	23.6	30,000	MDH.WSV		0.079	0	0	
Citalopram	3.3	2	0.2	0.1	0.4	5.5	7.4	NA	--	20	NA	NA	NA	2.35
Dextromethorphan	1.6	2	0.2	0.2	0.0	3.5	5.2	NA	--	60	NA	NA	NA	0.55
Fenofibrate	7.1	1	0.1	0.0	0.4	32.9	32.9	600	MDH.WSV		5.48	0	0	
Fluconazole	35	1	0.1	0.1	0.0	50.8	50.8	400	MDH.WSV		12.7	0	1	
Fluoxetine	5.4	1	0.1	0.1	0.0	17.1	17.1	200	MDH.WSV		8.54	0	0	
Hydrocortisone	29	1	0.1	0.1	0.0	69.3	69.3	20	MDH.WSV		347	1	1	
Lamivudine	3.2	1	0.1	0.1	0.0	11.4	11.4	NA	--	100	NA	NA	NA	0.73
Lidocaine	19	2	0.2	0.1	0.4	33.6	39.6	NA	--	NA	NA	NA	NA	
Meprobamate[i]	17	8	0.7	0.7	0.8	21.1	164	10,000	MDH.WSV		1.64	0	0	
Metaxalone	7.8	1	0.1	0.1	0.0	22.2	22.2	NA	--	2400	NA	NA	NA	0.06
Metformin	6.6	2	0.2	0.2	0.0	35.6	38.7	4,000	MDH.WSV		0.97	0	0	
Methadone	3.8	1	0.1	0.1	0.0	43.0	43.0	NA	--	5	NA	NA	NA	55.0
Methotrexate	26	3	0.3	0.4	0.0	39.1	86.0	NA	--	0.7[f]	NA	NA	NA	780
Nordiazepam	10	1	0.1	0.1	0.0	17.1	17.1	NA	--	NA	NA	NA	NA	
Pentoxifylline	4.7	1	0.1	0.1	0.0	8.1	8.1	90,000	MDH.WSV		0.009	0	0	
Pseudoephedrine + Ephedrine	5.5	4	0.4	0.0	1.6	8.1	15.2	NA	--	240[g]	NA	NA	NA	0.40
Sulfamethoxazole[i]	13	12	1.1	0.8	2.0	33.8	120	100,000	MDH.RAA		0.12	0	0	
Temazepam	9	1	0.1	0.1	0.0	40.3	40.3	80	MDH.WSV		50.3	0	1	
Theophylline	40	2	0.2	0.2	0.0	70.9	71.3	NA	--	300	NA	NA	NA	1.52
Thiabendazole	5.4	1	0.1	0.1	0.0	6.4	6.4	231,000	HHBP		0.003	0	0	
Trimethoprim	9.5	1	0.1	0.1	0.0	14.9	14.9	4,000	MDH.WSV		0.37	0	0	
Hormones[h]														
4,4'-Bisphenol F	10	1	0.2	0.3	0.0	70.8	70.8	NA	--	NA	NA	NA	NA	
Bisphenol A[i]	160	7	0.6	0.4	1.6	193	430	20,000	MDH.HRL		2.15	0	0	
Cholesterol	400	3	0.3	0.2	0.4	480	570	--[e]	--	NA	NA	NA	NA	
Testosterone	1.6	1	0.1	0.1	0.0	3.0	3.0	7,000	AUS		0.043	0	0	

[a]See Data Preparation Steps section of the text for details of how a detection was defined. [b]Human-health benchmarks (HHBs) in nanograms per liter. Compounds that do not have an HHB are listed with "NA" (not available) for the HHB and "−" for the HHB type/source. HHB types/sources are described in SI Section S5. AUS, Australia; HHBP, Human-Health Benchmark for Pesticides; MDH, Minnesota Department of Health; HRL, Health Risk Limit; HBV, Health-Based Value; RAA, Risk Assessment Advice. [c]Lowest Therapeutic Doses (LTDs), in milligrams per liter per day, are provided for compounds that do not have an HHB. "NA" indicates that no LTD is available. References for individual LTDs are provided in SI Table S4. [d]For compounds without available HHBs, but with LTDs, measured concentrations were converted to the cumulative mass in milligrams that would be consumed by ingesting 2.5 L/day of drinking water containing the maximum detected concentration over a lifetime (70 years). This value was then divided by the daily LTD (mg/day) and multiplied by 100. [e]Guideline values for 1,7-dimethylxanthine, caffeine, and cholesterol are 700, 350, and 7000 ng/L, respectively;[53] these guideline values are not used in this study because they are computed using a different methodology (based on predicted toxicity from structural similarity) than available HHBs for other detected compounds (based on LTDs), except thiabendazole. [f]The draft Lowest Daily Dose of 0.7 mg/day for methotrexate is an average daily dose computed by dividing the LTD of 5 mg/week (taken once weekly) by 7. [g]Dose is for pseudoephedrine. [h]The term "hormone" is used in this study to refer broadly to steroid hormones, sterols, and three nonsteroidal synthetic chemicals that are known or suspected endocrine disrupting chemicals. [i]Compounds highlighted in gray were detected in more than 0.5% of samples.

1. All results for samples that arrived warm at the laboratory and (or) were extracted or analyzed past the holding time (60 days for hormones and 30 days for pharmaceuticals, respectively, when stored at −20 °C) were removed from the data set. After this step, 1095 samples had results for hormones; 1106 samples had results for pharmaceuticals; and 1091 samples had results for both types of compounds.
2. All results for nicotine and cotinine were removed from the data set because of evidence of widespread field contamination. This step resulted in 103 of the 105 compounds on the pharmaceutical schedule being retained.
3. For pharmaceutical compounds, detections were defined as results greater than or equal to the 2016 DL (SI Table S4) to reduce the probability of false positive detections to no more than 1%. Of 339 pharmaceutical laboratory detections remaining after the application of preparation steps 1 and 2, 231 (68%) were below the DL.
4. As needed, more rigorous reporting levels—Study Reporting Levels, or SRLs—were calculated for hormones and pharmaceuticals that were detected in field blank samples. For these compounds, detections were defined as results ≥ SRL to reduce the risk of false positives resulting from field contamination. Application of SRLs resulted in censoring of five caffeine detections and six bisphenol A detections.
5. Detections in groundwater samples were censored during time periods when the running average detection frequencies in LSBs at concentrations greater than or equal to the DL or MRL were >5% in order to reduce the risk of false positives resulting from laboratory contamination.[32] Thirteen pharmaceutical detections (for caffeine, 1,7-dimethylxanthine, thiabendazole, and

DOI: 10.1021/acs.est.8b05592
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benztropine) and no hormone detections were censored for this reason.

Human-Health Benchmarks. To provide a human-health context for study findings, concentrations of detected hormones and pharmaceuticals were compared with human-health benchmarks (HHBs, Table 1, current as of July 2018), where available, obtained primarily from the Minnesota Department of Health[52] or from Australian guidelines[53] (see SI Section S5). The 2016 DLs for nearly all compounds were less than HHBs (SI Table S4), indicating the analytical methods can detect concentrations relevant to human health. For two hormones and seven pharmaceuticals, the DLs were greater than HHBs, meaning that a nondetection for one of these compounds cannot confidently be interpreted to indicate that the compound is not present in the environment at concentrations of potential concern.

For 10 of the 16 detected compounds without available HHBs, measured concentrations were converted to the cumulative mass that would be consumed by ingesting 2.5 L/day of drinking water containing the maximum detected concentration over a lifetime (70 years). Cumulative mass values were compared with the mass in a daily dose based on Lowest Therapeutic Dose (LTD) values (Table 1), where available. LTDs are the amount of an active pharmaceutical ingredient necessary to produce a clinically effective outcome.[52]

Ancillary Data Sets. The rank of each compound included in this study among the top 300 most commonly prescribed human outpatient pharmaceutical compounds in 2014 (by total prescriptions) (SI Table S4) was obtained in February 2018 from http://clincalc.com/DrugStats/, a standardized version of a publicly available database of annual Medical Expenditure Panel Survey results. Water solubility, the log octanol–water partition coefficient (log K_{ow}), and the log organic carbon-normalized sorption coefficient for soil and sediment (log K_{oc}) (SI Table S4) were estimated using EPI Suite version 4.11 (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface),[54] described in SI Section S6.1.

Potential explanatory factors examined for influence on the occurrence of hormones and pharmaceuticals in groundwater included well depth, well type, rock type, groundwater age category, climate (based on aridity), and land use (SI Table S3). Well depth, recorded by USGS field crews, was retrieved from the USGS National Water Information Systems (NWIS) database (https://doi.org/10.5066/F7P55KJN). Well type was identified as public supply, domestic, observation, or other based primarily on information in NWIS. Rock type was assigned based on the primary rock type of the Principal Aquifer to which the sampling site was assigned.[37] A groundwater age category of ^{3}H dead (likely pre-1953 recharge) or ^{3}H live was assigned to all sites, using a threshold of 0.1 tritium units (TU) (see SI Section S6.3). An aridity category of arid, semiarid, dry subhumid, or humid (United Nations Environment Programme; SI Table S18)[55] was assigned to each well based on information from the CGIAR-SCI Global-Aridity Database (http://www.cgiar-csi.org).[56,57] A 60-m land-use data set for 2012[58] was used to assign percentages of major land-use types (agricultural, urban, or natural) within 500 m buffers around each site. A land-use category of agricultural, urban, undeveloped, or mixed was then assigned based on a published classification scheme (SI Table S19).[59]

Statistical Methods. Statistical tests were performed to identify major factors that likely affect the occurrence of hormones and pharmaceuticals in groundwater. Given the large number of compounds, testing generally involved putting compounds or sites into one of two categories: those with one or more detections, and those with no detections. Also, most results for individual hormone and pharmaceutical compounds in this study were nondetections, and the data sets do not conform to any distribution. Therefore, nonparametric statistical methods were used to describe the data and perform hypothesis testing. The rank-sum test[60] was used to test for differences in the distributions of values of ancillary data for compounds or sites separated into two groups based on the presence of a detection. Contingency tables[60] were used to test for differences in detection frequencies among compounds or sites separated into different categories based on ancillary data. The p-value used to indicate statistical significance for all tests was 0.05.

RESULTS AND DISCUSSION

Detections. The total number of detections of hormone and pharmaceutical compounds that passed the data preparation steps was 102, with mixtures of any 2 or more compounds being relatively uncommon. Considering only the 1091 sites that included results for both hormones and pharmaceuticals, a single hormone or pharmaceutical compound was detected at 60 sites (Figure 1), whereas two compounds were detected at 14 sites, and three or four compounds were detected at four sites. At least one compound was detected at 50 (5.9%) of 844 PAS sites, and at 28 (11.3%) of 247 MAS sites, totaling 78 (7.1%) of all sites. For context, publications that provide national estimates of detection frequency at a censoring level of 0.02 μg/L, similar to the typical censoring levels used for this study (defined in steps 3 and 4 of the Data Preparation Steps section), indicate detection rates of 15% for pesticides and 62% for VOCs in public-supply wells,[61] and 12% for pesticides and 46% for VOCs in domestic wells;[62] however, direct comparison is difficult because sites included in those investigations were clustered in targeted study areas. By comparison, the current study indicates that hormones and pharmaceuticals generally occur in U.S. groundwater resources used for drinking less frequently than VOCs do. Whereas VOCs have similar wastewater sources, they also have other important point sources and spatially extensive sources, such as those associated with the distribution and use of chlorinated drinking water. The combined frequency of hormone and pharmaceutical occurrence is roughly comparable to pesticides, despite the generally wider release of pesticides across the landscape, particularly in agricultural areas.

A previous study of pharmaceuticals, hormones, and other organic wastewater contaminants in untreated drinking water sources near known or suspected upgradient wastewater discharges[14,63] found that 9 of 25 groundwater sources (36%) had a detection of a hormone or pharmaceutical that would meet the detection criteria of the current study. The current study differs from previous research by using a spatially distributed, randomized design to obtain samples that are representative of the overall groundwater resource, rather than sites near known wastewater sources. The detection frequency of hormones and pharmaceuticals in the current study is

DOI: 10.1021/acs.est.8b05592
Environ. Sci. Technol. 2019, 53, 2950–2960

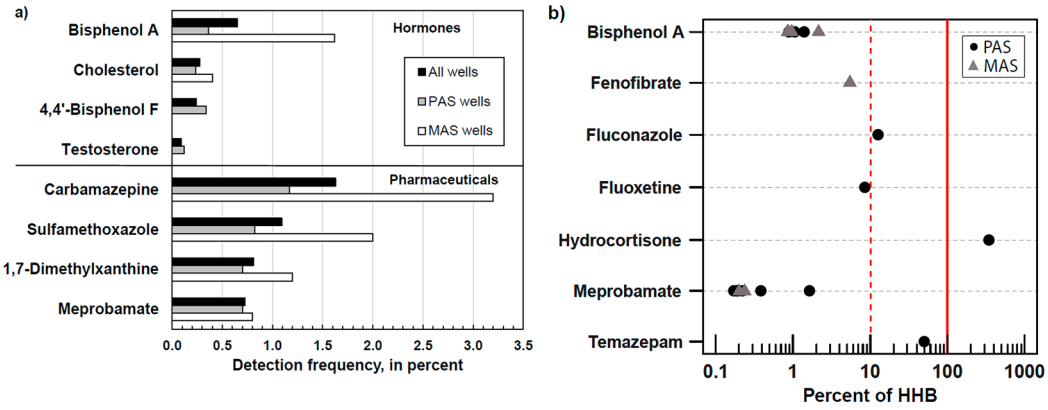

Figure 2. (a) Of 34 detected compounds, detection frequency of the four most commonly detected hormone and pharmaceutical compounds, and (b) concentrations relative to the human-health benchmark (HHB) for hormone and pharmaceutical compounds with a maximum concentration >1% of an HHB. For the additional 11 compounds with HHBs, the maximum concentration ranged from 0.003% to 0.97% of the HHB.

expected to be representative of occurrence of these compounds in groundwater resources used nationally for drinking-water supply.

At least one compound categorized for the purpose of this study as a hormone was detected at 0.8% of PAS sites and 2.0% of MAS sites. The four detected hormone compounds (Table 1; Figure 2a) include two components of plastics that are suspected endocrine disrupting compounds (bisphenol A and 4,4′-bisphenol F), a sterol (cholesterol), and a natural androgen (testosterone), with bisphenol A being most commonly detected (0.6% of sites).

Pharmaceutical compounds were detected more frequently than hormones, with at least one detected at 5.1% of PAS sites and 9.6% of MAS sites. If the RL had been used in place of the DL in Data Preparation Step 3 to define pharmaceutical detections as was done for hormone detections, then these detection rates would be 2.2% and 6.0%, respectively. The higher detection frequency of pharmaceuticals compared with hormones could result at least partly from the inclusion of a greater number of pharmaceuticals in sample analysis. The 30 detected pharmaceutical compounds (Table 1) have a variety of uses (SI Table S4). The four most frequently detected pharmaceutical compounds (Figure 2a) were an anticonvulsant/mood stabilizer (carbamazepine), an antibiotic (sulfamethoxazole), a caffeine degradate (1,7-dimethylxanthine), and an antianxiety medication (meprobamate), each detected at between 0.7 and 1.6% of all sites. Compounds most often detected together were carbamazepine with sulfamethoxazole (four sites), carbamazepine with meprobamate (three sites), and caffeine with its degradate, 1,7-dimethylxanthine (all three sites with caffeine).

The most frequently detected hormone and pharmaceutical compounds in this study also were among the most frequently detected in previous groundwater studies;[14,32,34−36] meprobamate was not included as an analyte in these prior large-scale studies, but has been detected in ≥15% of wells in local groundwater studies.[8,22] The detection rate of 5.1% for pharmaceutical compounds at PAS sites in the current study is larger than the rate of 2.3% for pharmaceutical compounds in a similarly designed study of aquifers used for public supply across the large and geographically diverse state of California;[32] however, that study analyzed for only 17 pharmaceutical compounds, which could be a contributing factor to the difference in detection rates. Metformin, which was the most frequently detected pharmaceutical in a study of 59 streams in the southeastern U.S.[64] and was among the five most frequently detected pharmaceutical compounds in the study of groundwater across France,[35] was tied for 10th in occurrence in the current study.

Concentrations. Hormone concentrations ranged from 3.0 ng/L to 570 ng/L, with the highest being for cholesterol (SI Figure S4a). Pharmaceutical concentrations ranged from 1.7 ng/L to 677 ng/L, with the highest being for caffeine (SI Figure S4b). Maximum concentrations for the five hormone and pharmaceutical compounds that were detected at more than 0.5% of sites ranged from 120 ng/L for sulfamethoxazole to 430 ng/L for bisphenol A (Table 1). Maximum concentrations for the most frequently detected compounds in the current study generally were within an order of magnitude of the maximum concentrations for the same compounds in previous groundwater studies,[14,32,34−36] except two studies observed higher bisphenol A concentrations.[35,36]

HHBs are available for two of the four detected hormones, and for 16 of the 30 detected pharmaceuticals (Table 1). LTDs are available for 10 of the 14 detected pharmaceutical compounds that do not have HHBs. The concentration of a hormone or pharmaceutical exceeded the HHB for one PAS site (0.1%) and no MAS sites, indicating only rare vulnerability of drinking-water sources to concentrations of potential concern. For comparison, a summary of USGS studies of water quality in targeted subareas of aquifers across the U.S. used for domestic supply indicated that VOC concentrations were greater than an HHB for 0.6% of wells and pesticide concentrations were greater than an HHB for 0.9% of wells;[40] as with hormones and pharmaceuticals, some VOCs and pesticides do not have an HHB, meaning that their potential implications for human health could not be evaluated. The one HHB exceedance was for hydrocortisone (Figure 2b) at a PAS well located in the Mississippi Embayment-Texas Coastal Uplands aquifer systems (SI Figure S1). The well is deep and ^{3}H dead, but located in an area of mixed land use, where wastewater sources could be present. Concentrations >10% of the HHB were observed for fluconazole and temazepam at one PAS site each, located in the Valley and Ridge and Piedmont and Blue Ridge carbonate-rock aquifers and the Mississippi Embayment-Texas Coastal Uplands aquifer systems, respectively.

For 9 of the 10 detected pharmaceuticals with an LTD but no HHB (Table 1), the estimated maximum cumulative masses that would be ingested in drinking water over 70 years

DOI: 10.1021/acs.est.8b05592
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ranged from 0.06% to about 55% of the mass that would be ingested in one daily LTD. In other words, the maximum estimated exposure to these compounds from well water alone over a lifetime generally would be less than a single daily dose. For methotrexate, the cumulative mass was about 780% of the mass in a daily LTD (nearly eight daily doses). Because concentrations of detected compounds generally were less than the maximum concentrations used in the mass calculations, these may be maximum estimates of potential exposure to these compounds. However, this analysis does not take into account potential harmful effects that may occur below therapeutic doses, nor the potential synergistic effects of compounds occurring in mixtures.

Relations of Occurrence with Compound Characteristics, Site Characteristics, Hydrogeologic Factors, and Land Use. *Compound Characteristics.* Common use and mobility are factors that could contribute to detection of the 34 compounds listed in Table 1. Although magnitude of use is expected to be a factor in determining the presence of compounds in groundwater, even a highly used compound that is largely absorbed or metabolized in the body, or is immobile in the environment, is relatively unlikely to be transported to groundwater. The resistance of a compound to degradation and differences in detection levels among compounds are other potential factors contributing to detection in groundwater and are discussed in SI Sections S7.3–S7.4.

Sixty-nine hormones or pharmaceuticals that appeared on the 2014 list of the 300 most prescribed compounds, and 13 of their degradates, were included in this study; only 19 of these 82 compounds were detected, confirming that use is only one factor in occurrence. The other 16 detected compounds either are not prescribed medications or were presumably ranked lower than 300. About 200 compounds on the 2014 list were not included in this study (some compounds are present in more than one medication), which could result in an underrepresentation of the occurrence of hormones and pharmaceuticals in groundwater sampled for this study. Of the five most frequently detected compounds in this study, four have relatively high use or a parent compound with high use. Bisphenol A is a high production volume chemical (1.1 billion kg produced in the U.S. in 2007) used in manufacturing polycarbonate plastics, epoxy resins, and certain other products.[65] Carbamazepine and sulfamethoxazole ranked 233 and 112, respectively, on the list of most prescribed compounds; meprobamate was not listed. Caffeine, a stimulant and the parent of the frequently detected 1,7-dimethylxanthine, is widely used, with the mean daily caffeine intake of the adult population estimated to be 300 mg per person in 2008.[66]

All hormone and pharmaceutical compounds included in the analysis were divided into categories of high versus low solubility (threshold 100 mg/L), log Koc (threshold 2.4 L/kg), and log Kow (threshold 2.7), where estimated values were available (SI Table S4) (see SI Section S6.1). Compounds were significantly more likely to be detected if they had high solubility (Figure 3a), low log K_{oc}, and (or) low log K_{ow} (contingency table p-values 0.014 to 0.022). Similarly, detected compounds were found to have significantly higher solubility, lower log K_{oc}, and lower log K_{ow} than compounds that were not detected (SI Figure S7; rank-sum p-values of 0.011 or less). These results are consistent with previous findings that compounds with a greater tendency to be present in water and a lower tendency to sorb to soils, sediment, or rock are more likely to occur in groundwater.[67] The 5 most frequently detected compounds all have high solubility, low log K_{oc}, and (or) low log K_{ow}.

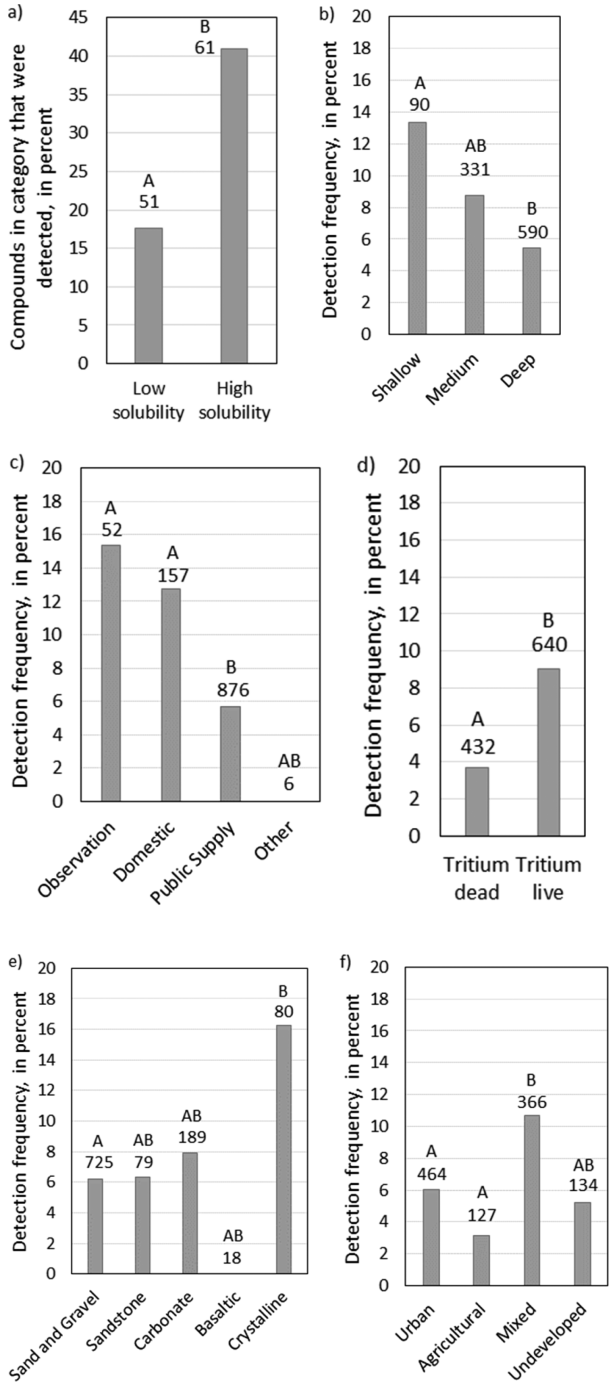

Figure 3. Percent of hormone and pharmaceutical compounds in each solubility category that were detected at one or more sites (a), and detection frequency of one or more hormone or pharmaceutical compounds for sites categorized by (b) well depth, (c) well type, (d) groundwater age category, (e) generalized rock type, and (f) land use. Numbers shown at the top of bars indicate the number of sites in each category. Letters at the top of bars indicate which categories have statistically significant differences in detection frequency (different letters) and which do not (same letter).

Well Characteristics. The 1,011 wells with depth information were divided into categories of shallow (<23 m), medium (23 to 76 m), and deep (≥76 m) to compare detection frequency across categories (Figure 3b). These

DOI: 10.1021/acs.est.8b05592
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divisions were selected with the intent to separate depths most likely to be affected by human activities from those less likely to be affected. Occurrence of hormone and pharmaceutical compounds was significantly different among well-depth categories (contingency table p-value of 0.011), with detection frequency in shallow wells (13%) greater than in medium-depth wells (8.8%) and deep wells (5.4%). Wells with a detection were significantly shallower than wells without a detection (SI Figure S8a; rank-sum p-value 0.003). A previous study of 47 groundwater sites across the U.S. also found a significant correlation with well depth,[31] but that study targeted groundwater near known wastewater sources and included shallower groundwater not used for drinking. The current study indicates that the relation of hormone and pharmaceutical occurrence with well depth, which likely reflects the higher likelihood of shallower groundwater having been influenced by human activities at the land surface, is apparent even when only the generally deeper groundwater resource used for drinking is examined, and without the targeting of areas with known wastewater sources.

Occurrence of hormone and pharmaceutical compounds also was significantly different among the four well-type categories (observation, domestic, public supply, and other) (contingency table p-value 0.001). The detection frequencies for observation wells (15%) and domestic wells (13%) were higher than for public-supply wells (5.7%) and other wells (0%; with only six wells a detection is not expected given the overall detection frequencies) (Figure 3c). These differences could be driven largely by the substantial differences in the typical depth of wells in each category of well type; this conclusion is supported by the observation that shallow wells in each well-type category (except "other," which includes no shallow wells) have a relatively high detection frequency of ≥12%.

Hydrogeologic Factors. The presence of measurable ^{3}H in a water sample indicates that at least some water from a well was recharged since 1953 (see SI Section S6.3), corresponding with a period when most anthropogenic chemicals were released to the environment; thus, ^{3}H live groundwater is expected to be more likely to contain hormones and pharmaceuticals than ^{3}H dead groundwater. Wells producing ^{3}H live groundwater had a significantly higher detection frequency of hormones and pharmaceuticals (9.1%) than wells producing ^{3}H dead groundwater (3.7%) (Figure 3d; contingency table p-value 0.001), confirming more common occurrence of these compounds for wells with a greater likelihood of influence by human activities at the land surface. The observation that some ^{3}H dead wells (presumably unlikely to be affected by landscape activities) had detections of hormone or pharmaceutical compounds could reflect the fact that many wells produce a mixture of groundwater recharged before and since 1953, which can result in very low ^{3}H values; the sensitivity of the hormone and pharmaceutical methods might still identify the presence of at least one compound introduced by the component of young groundwater. All but 1 of the 16 wells producing ^{3}H dead water with a hormone or pharmaceutical detection are in areas of urban or mixed land use, meaning that potential sources of these compounds to groundwater are likely to be present. However, it is possible that some reported hormone or pharmaceutical detections for wells producing ^{3}H dead groundwater reflect the occasional occurrence of a false positive result that was not excluded by the multiple quality-control criteria applied to the data set.

Wells with a hormone or pharmaceutical detection also had significantly higher ^{3}H concentrations (SI Figure S8b; rank-sum p-value <0.001) than wells without a detection. These relations were evident even though atmospheric ^{3}H concentrations are known to vary across the U.S.[68] Well depth is likely a substantial contributor to the observed relations of hormone and pharmaceutical occurrence with groundwater age, given that shallower wells generally are more likely to produce groundwater with a young component than are deeper wells (SI Figure S5).

Based on the assigned Principal Aquifer, each sampling site was placed into a generalized rock type category of sand and gravel (including unconsolidated and glacial), sandstone, carbonate rock, basaltic rock, or crystalline rock. Most wells (65%) were in sand and gravel aquifers. Occurrence of hormone and pharmaceutical compounds was found to be significantly different among rock types (contingency table p-value of 0.013), with detection frequency for crystalline rocks (16%) higher than for other rock types (0 to 7.9%) (Figure 3e). This result could reflect relatively rapid migration of groundwater through fractures in crystalline rock, compared with much slower migration through sand and gravel.

Hormone and pharmaceutical occurrence was examined for relations with aridity as an indicator of climate, with the expectation that more arid areas having lower recharge rates might have less young groundwater containing hormones and pharmaceuticals. No differences were indicated for aridity as either a categorical variable (using contingency tables) or a continuous variable (using the rank-sum test to compare distributions of the aridity index for wells with and without a detection).

Land Use. The occurrence of hormone and pharmaceutical compounds differs significantly across land-use categories (agricultural, urban, undeveloped, or mixed) (contingency table p-value 0.009), with the detection frequency being highest for sites with mixed land use (11%) (Figure 3f). The next highest detection frequency was for sites with urban land use (6.0%), followed by undeveloped (5.2%), and then agricultural (3.1%). Sampled wells are deepest in urban areas, which could partially contribute to a lower detection frequency in these areas relative to mixed land-use areas. Determining the driving factor in this significant difference in compound occurrence between urban and mixed land uses is beyond the scope of this paper, but future studies could consider the density of septic systems, which might act as sources of hormone and pharmaceutical compounds. Also, an increasing amount of sewering with increasing urbanization could reduce infiltration of wastewater in areas of urban relative to mixed land use.

No differences were indicated in percent urban land use in 500 m well buffers when testing across two groups based on whether any hormone or pharmaceutical compounds were detected or not; this was true when testing for differences across all wells, across wells of a single type, or across just shallow wells. This result implies that other factors, such as well depth, are more important to compound occurrence than the dominance of urban land near the site.

Implications. This first large-scale, systematic assessment of a substantial portion of the groundwater resource used for drinking water across the U.S. indicates vulnerability to contamination by hormones and pharmaceuticals is not widespread, and where these compounds are detected, they generally are at concentrations that are not expected to have

DOI: 10.1021/acs.est.8b05592
Environ. Sci. Technol. 2019, 53, 2950−2960

adverse human-health effects. However, based on the available data, which are more limited in number and spatial scale for the resource used for domestic compared with public supply, compound occurrence is higher in the groundwater resource used for domestic supply, indicating that the population on domestic supply is more likely to be exposed to these compounds in drinking water. Compounds most likely to be detected have relatively high solubility and low tendency to sorb onto soil, sediment, or rock, but are not necessarily among the most used. They are most common in shallower wells with a component of young groundwater, particularly in crystalline-rock settings (where the detection frequency is 16%), likely reflecting the presence of recent recharge that has been affected by human activities. Detection frequency is highest in areas of mixed land use, where further investigation would be needed to identify major sources and controlling factors. The observed detection frequencies and concentrations indicate similar or substantially lower occurrence compared with other classes of organic compounds (pesticides, VOCs) in groundwater used for drinking, with similarly rare HHB exceedances. However, some high-use pharmaceutical compounds were not included in this study, and some detected compounds do not have HHBs, which could result in underrepresentation of groundwater vulnerability and human-health implications. Nevertheless, information from this study can be used to prioritize hormone and pharmaceutical compounds and environmental settings for future monitoring and research into environmental fate and potential human-health risks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b05592.

Additional information on particular topics as noted in the text, with figures (PDF)

Data tables as noted in the text (XLSX)

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The manuscript was written through contributions of all authors. All authors have given approval to the current version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the USGS NAWQA project. The study would not have been possible without the hard work of numerous USGS field crews, and the assistance of the participating well owners and operators. We also greatly appreciate the contributions of Tyler Johnson in processing ancillary data; Julia Norman in compiling human-health benchmark information and physical/chemical properties; Suranne Stineman and Delicia Beaty in compiling and examining external Quality Systems Branch performance data; NWQL personnel who analyzed samples and assisted in quality-control evaluations; and reviewers of this article. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

■ ABBREVIATIONS

DL	detection limit
HHB	human-health benchmark
LSB	laboratory set blank
LTD	lowest therapeutic dose
MAS	Major Aquifer Study
MRL	minimum reporting level
NAWQA	National Water-Quality Assessment
ng/L	nanograms per liter
NWQL	National Water-Quality Laboratory
PAS	Principal Aquifer Survey
RL	reporting limit
SRL	study reporting level
U.S. EPA	U.S. Environmental Protection Agency
USGS	U.S. Geological Survey.

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