



Juxtaposition of intensive agriculture, vulnerable aquifers, and mixed chemical/microbial exposures in private-well tapwater in northeast Iowa

Paul M. Bradley^{a,*}, Dana W. Kolpin^b, Darrin A. Thompson^c, Kristin M. Romanok^d, Kelly L. Smalling^d, Sara E. Breitmeyer^d, Mary C. Cardon^{e,1}, David M. Cwertyny^c, Nicola Evans^e, R. William Field^c, Michael J. Focazio^{f,1}, Laura E. Beane Freeman^g, Carrie E. Givens^h, James L. Grayⁱ, Gordon L. Hager^g, Michelle L. Hladik^j, Jonathan N. Hofmann^g, Rena R. Jones^g, Leslie K. Kanagyⁱ, Rachael F. Lane^k, R. Blaine McCleskey^l, Danielle Medgyesi^g, Elizabeth K. Medlock-Kakaley^e, Shannon M. Meppelink^b, Michael T. Meyer^{k,1}, Diana A. Stavreva^g, Mary H. Ward^g

^a U.S. Geological Survey, Columbia, SC, USA

^b U.S. Geological Survey, Iowa City, IA, USA

^c University of Iowa, Iowa City, IA, USA

^d U.S. Geological Survey, Lawrenceville, NJ, USA

^e U.S. Environmental Protection Agency, Durham, NC, USA

^f U.S. Geological Survey, Reston, VA, USA

^g National Cancer Institute/NIH, Rockville, MD, USA

^h U.S. Geological Survey, Lansing, MI, USA

ⁱ U.S. Geological Survey, Lakewood, CO, USA

^j U.S. Geological Survey, Sacramento, CA, USA

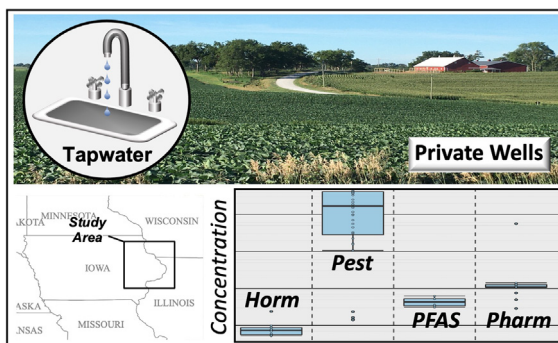
^k U.S. Geological Survey, Lawrence, KS, USA

^l U.S. Geological Survey, Boulder, CO, USA

HIGHLIGHTS

- Private-well tapwater contaminant exposures are a global public-health data gap.
- 47 home tapwaters assessed in hydrologically-vulnerable ag-intensive northeast Iowa.
- 437 organics/35 inorganics/11 microbial indicators/5 bioactivities analyzed.
- 51 organics (primarily pesticides)/26 inorganics/microbial indicators detected.
- Common exceedances of human risk screening level indicate increased monitoring need.

GRAPHICAL ABSTRACT



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* Corresponding author.

E-mail address: pbradley@usgs.gov (P.M. Bradley).

¹ Retired.

ABSTRACT

In the United States and globally, contaminant exposure in unregulated private-well point-of-use tapwater (TW) is a recognized public-health data gap and an obstacle to both risk-management and homeowner decision making. To help address the lack of data on broad contaminant exposures in private-well TW from hydrologically-vulnerable (alluvial, karst) aquifers in agriculturally-intensive landscapes, samples were collected in 2018–2019 from 47 northeast Iowa farms and analyzed for 35 inorganics, 437 unique organics, 5 in vitro bioassays, and 11 microbial assays. Twenty-

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Human health
Organics
Inorganics
Microbial

six inorganics and 51 organics, dominated by pesticides and related transformation products (35 herbicide-, 5 insecticide-, and 2 fungicide-related), were observed in TW. Heterotrophic bacteria detections were near ubiquitous (94 % of the samples), with detection of total coliform bacteria in 28 % of the samples and growth on at least one putative-pathogen selective media across all TW samples. Health-based hazard index screening levels were exceeded frequently in private-well TW and attributed primarily to inorganics (nitrate, uranium). Results support incorporation of residential treatment systems to protect against contaminant exposure and the need for increased monitoring of rural private-well homes. Continued assessment of unmonitored and unregulated private-supply TW is needed to model contaminant exposures and human-health risks.

1. Introduction

Given the magnitude of anthropogenic (human-driven/-synthesized) chemicals in commerce and by extension in the environment (Wang et al., 2020) and the persistent challenges of geogenic contaminants (Lombard et al., 2021) and water-borne disease outbreaks (Collier et al., 2021; Craun et al., 2010), the paucity of realistically broad assessments of potentially co-occurring organic, inorganic, and microbial contaminants in point-of-use (POU) drinking water (tapwater, TW) is a growing concern in the United States (US) and globally (Bondy and Campbell, 2018; Bradley et al., 2018; Bradley et al., 2021a). In the US, many anthropogenic and naturally-occurring drinking-water contaminants and water-borne pathogens are regulated in public supplies (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023) but not in private supplies (U.S. Environmental Protection Agency, 2021c), even though 40 million people in the US rely on private wells for drinking water (Dieter et al., 2018). The responsibility for protection, monitoring, and treatment of these private wells falls on property owners, who frequently lack the requisite knowledge and financial resources for effective risk management (Nigra, 2020; Rogan and Brady, 2009; Zheng and Flanagan, 2017).

Previous research has documented a range of contaminant concerns in unregulated private-well drinking water (Charrois, 2010; Focazio et al., 2006; Rogan and Brady, 2009). Due to high analytical costs, commonplace confusion of organoleptic quality with safety, and a range of other socioeconomic factors, private-well water-quality data remain scarce and, where available, are typically limited to a few targeted (e.g., coliform bacteria) contaminants (Focazio et al., 2006; Seltenrich, 2017; Zheng and Flanagan, 2017). Consequently, the potential for unrecognized contaminant exposures and adverse health effects is notably elevated for private wells (American Academy of Pediatrics, 2009; Charrois, 2010; Rogan and Brady, 2009), as illustrated by a recent comparison of private- and public-supply TW exposures from a sole-source aquifer in a suburban/urban landscape (Bradley et al., 2021a). Comparable characterization of contaminant exposures in private wells in rural, agricultural landscapes is currently lacking.

The U.S. Geological Survey (USGS) collaborates with the U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Cancer Institute (NCI), National Institute of Environmental Health Science (NIEHS), tribal nations, universities, utilities, and communities to inform drinking-water exposure and water-supply data gaps by assessing TW inorganic/organic/microbial contaminant mixtures and associated drivers in a range of socioeconomic and source-water vulnerability settings across the US (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b; Bradley et al., 2022). Herein, simultaneous exposures to an extensive suite of potential inorganic, organic, and microbial contaminants were assessed in TW from 47 rural farm homes in northeastern Iowa in 2018–19 to 1) provide initial insight into cumulative contaminant risk (Moretto et al., 2017; National Research Council, 1983) to human health of private-well TW in an agriculturally-intensive landscape overlying hydrologically-vulnerable aquifer sources and 2) further expand the national perspective on inorganic/organic/microbial contaminant exposures in POU TW by maintaining the same sampling protocol and an analytical toolbox similar to that employed in previous studies by this group across the US (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b; Bradley et al., 2022; Bradley et al., 2023).

For this study, exposure was operationally represented as detections (and concentrations) of 35 inorganic and 448 organic (437 unique) analytes, 11 microbial groups, and 5 in vitro bioactivities in residential TW samples. Potential human-health risks of individual and aggregate TW exposures were explored based on 1) cumulative detections and concentrations of designed-bioactive (e.g., pesticides, pharmaceuticals) chemicals (Bradley et al., 2020; Bradley et al., 2018) and 2) cumulative Exposure-Activity Ratio(s) (Σ_{EAR}) (Blackwell et al., 2017) and hazard indices (HI) (Goumenou and Tsatsakis, 2019; U.S. Environmental Protection Agency, 2011) of cumulative benchmark-based Toxicity Quotients (Σ_{TQ}) (Corsi et al., 2019). In line with previous POU drinking-water studies by this research group (Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b; Bradley et al., 2022) and others (Focazio et al., 2006; Rogan and Brady, 2009), simultaneous exposures to multiple inorganic, organic, and microbial constituents of potential human-health concern were expected to occur in these private-well TW samples (Hypothesis I). Consistent with hydrologically-vulnerable (alluvial, karst) aquifer sources in an agriculturally-intensive setting, agricultural pesticides and nutrients were expected to dominate TW exposures, with cumulative detections and concentrations generally higher than those observed in previous TW studies by this group in non-agricultural settings (Hypothesis II).

2. Materials and methods

2.1. Site selection and sample collection

A subset of 47 rural farm, private-well dependent, residences within an area of intensive crop (primarily corn, soybean) and animal (poultry, swine, cattle) agriculture in northeast Iowa (Table S1; Fig. 1) were selected from enrollees in the Agricultural Health Study (AHS) (Alavanja et al., 1996) Biomarkers of Exposure and Effects in Agriculture (BEEA) subcohort (Hofmann et al., 2015). Additional participant eligibility criteria included active farming at the time of sample collection, permanent residence since 1995 (AHS inception), a private well screened (depth range: 8.5–88 m) in a hydrologically-vulnerable (karst or alluvial) aquifer setting, and proximity to an overnight shipping center. Untreated kitchen cold-water taps were sampled once between December 2018 and February 2019. Samples were collected at the residents' convenience throughout the day without pre-cleaning, screen removal, or Lead and Copper Rule (U.S. Environmental Protection Agency, 2008; U.S. Environmental Protection Agency, 2020b) stagnant-sample protocols, as described (Romanok et al., 2018).

2.2. Methods

Briefly, TW samples were analyzed by the 1) USGS using 7 target-organic (437 unique analytes), 3 inorganic (35 analytes), 3 field parameter, and 11 microbial methods (Table S2), as described (Bradley et al., 2021a; Romanok et al., 2018), 2) Center for Health Effects of Environmental Contamination and Iowa State Hygienic Laboratory at the University of Iowa for 6 neonicotinoid insecticides (acetamiprid, clothianidin, dinotefuran, imidacloprid, thiacloprid, thiamethoxam), as described (Evelsizer and Skopec, 2018; Thompson et al., 2021), 3) EPA using 3 in vitro bioassays targeting 3 (androgen [AR], estrogen [ER], and glucocorticoid [GR]) receptor classes (Medlock Kakaley et al., 2020; Medlock Kakaley et al., 2021), and 4) NCI using in vitro bioassays targeting 5 (AR, ER, GR, aryl

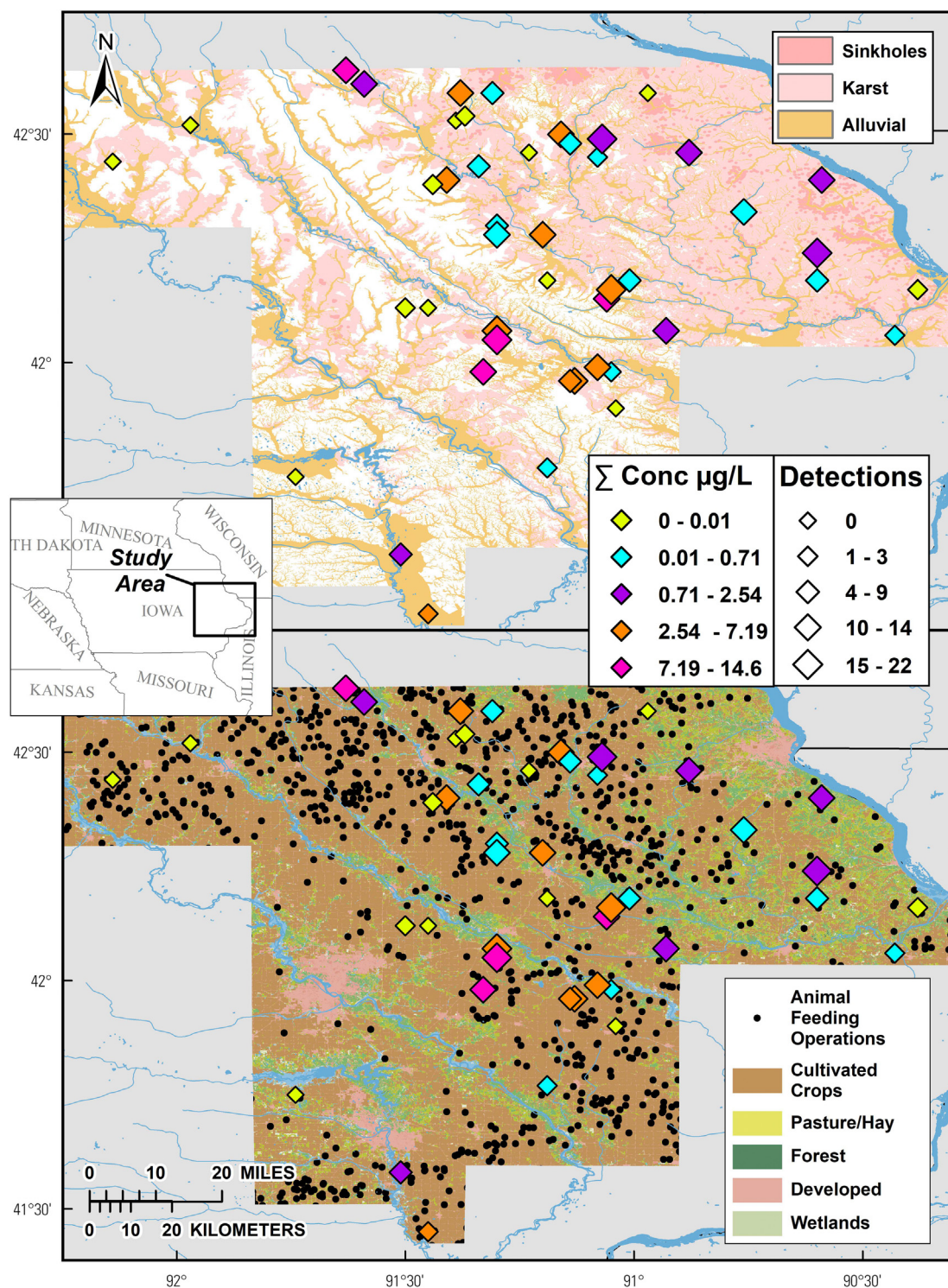


Fig. 1. Cumulative (sum of all detected) concentrations ($\mu\text{g L}^{-1}$) and numbers of organic compounds (diamonds) in samples of private-well tapwater collected during 2018–19 in northeast Iowa. **Top:** Color shadings indicate karst (Iowa Department of Natural Resources, 2021a) and alluvial (U.S. Geological Survey, 2002) aquifer areas. **Bottom:** Color shadings and black circles indicate land cover (U.S. Geological Survey, 2021) and animal feeding operations (Iowa Department of Natural Resources, 2021b), respectively. Sample locations are anonymized.

hydrocarbon [AhR], thyroid hormone [TR]) receptor classes (Jones et al., 2020; Stavreva et al., 2012; Stavreva et al., 2016) (see SI for details/citations). A subset of 10 replicate TW samples was sent to the USGS Organic Chemical Research Laboratory for comparative analysis of the 6 neonicotinoid analytes, as described (Hladik and Calhoun, 2012). All results are in Tables S3–S6 and in Meppelink et al. (2023).

2.3. Quality assurance

Quantitative (\geq limit of quantitation, \geq LOQ) and semi-quantitative (between LOQ and long-term method detection limit, MDL (Childress et al., 1999; U.S. Environmental Protection Agency, 2020a)) results were treated as detections (Childress et al., 1999; Foreman et al., 2021; Mueller

et al., 2015). Chemical quality-assurance/quality-control included 5 field blanks (inorganics, organics) as well as laboratory blanks (inorganics, organics), spikes (organics), and stable-isotope surrogates (organics). The median organic surrogate recovery (Table S4c) was 99.8 % (interquartile range: 84–106 %). Only sulfate (0.5 mg L^{-1}), calcium (0.01 mg L^{-1}), and hexamethylenetetramine ($0.14 \text{ } \mu\text{g L}^{-1}$) were detected in blanks at concentrations in the range observed in TW samples; corresponding results were censored at twice the maximum blank concentrations, as footnoted (Tables S3 and S4a). Microbial quality-assurance/quality-control included 4 field blanks as well as 8 laboratory blanks; microbial results were censored based on blanks, as footnoted (Tables S5a-b).

2.4. Statistics

Differences (centroids and dispersions) between TW-sample groups were assessed by nonparametric one-way PERMANOVA ($n = 9999$ permutations) on Euclidean distance (Paleontological Statistics, PAST, v. 4.03) (Hammer et al., 2001). Relations between detections/concentrations of selected TW contaminants were assessed by Spearman rho (ρ) correlation (SigmaPlot, v. 13, Systat Inc., Palo Alto, California). Organic-contaminant concentration patterns and potential contributing factors were assessed across all sites using principal component analysis (PCA) to reduce multivariate dimensionality (SigmaPlot, v. 13).

2.5. Risk assessments

Screening-level assessments (Goumenou and Tsatsakis, 2019; U.S. Environmental Protection Agency, 2011) of cumulative effects potentials were based on cumulative Exposure-Activity Ratio(s) (Σ_{EAR}) (Blackwell et al., 2017) and HI (Goumenou and Tsatsakis, 2019; U.S. Environmental Protection Agency, 2011; U.S. Environmental Protection Agency, 2012) of cumulative benchmark-based Toxicity Quotients (Σ_{TQ}) (Corsi et al., 2019), as described (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b). ToxEval v. 1.2.0 (De Cicco et al., 2018) of the open source statistical software R (R Development Core Team, 2019) was used to sum (non-interactive concentration addition model (Altenburger et al., 2018; Cedergreen et al., 2008; Stalter et al., 2020)) individual ToxCast™ based (U.S. Environmental Protection Agency National Center for Computational Toxicology, 2019; U.S. Environmental Protection Agency National Center for Computational Toxicology, 2020) exposure-activity ratio(s) (EAR) or benchmark-based toxicity quotient(s) (TQ), respectively. For the latter, the most protective human-health benchmark (i.e., lowest benchmark concentration) among maximum contaminant level (s) (MCL) goal(s) (MCLG) (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023), World Health Organization (WHO) Guideline Value(s) (GV) and provisional GV (pGV) (World Health Organization (WHO), 2011), EPA Human Health Benchmark(s) for Pesticides (HHBP) (U.S. Environmental Protection Agency, 2021b), USGS Health-Based Screening Level(s) (HBSL) (Norman et al., 2018), and state drinking-water MCL or health advisory(ies) (DWHA) was used, with MCLG of zero (no safe-exposure level for sensitive sub-populations, including infants, children, elderly, and immunocompromised) (U.S. Environmental Protection Agency, 2021a; U.S. Environmental Protection Agency, 2023) set to the method reporting limit or $1 \text{ } \mu\text{g L}^{-1}$ for Pb (Lanphear et al., 2016). Cumulative EAR (Σ_{EAR}) and TQ (Σ_{TQ}) results, ToxCast exclusions, and benchmarks are summarized in Tables S7-S8 (additional details in SI).

3. Results and discussion

Regulated and unregulated chemical (inorganic, organic) and microbial contaminants were frequently detected in TW samples in this agriculturally-intensive, hydrologically-vulnerable northeast Iowa study area (Tables S3-S5; Figs. 1-4), with two or more detections commonly observed per sample (Hypothesis I). Fifty-one (12 %) of the 437 unique organic-indicator analytes assessed in this study were detected at least once, with detections per sample ranging 0–22 (median: 8). Pesticide-

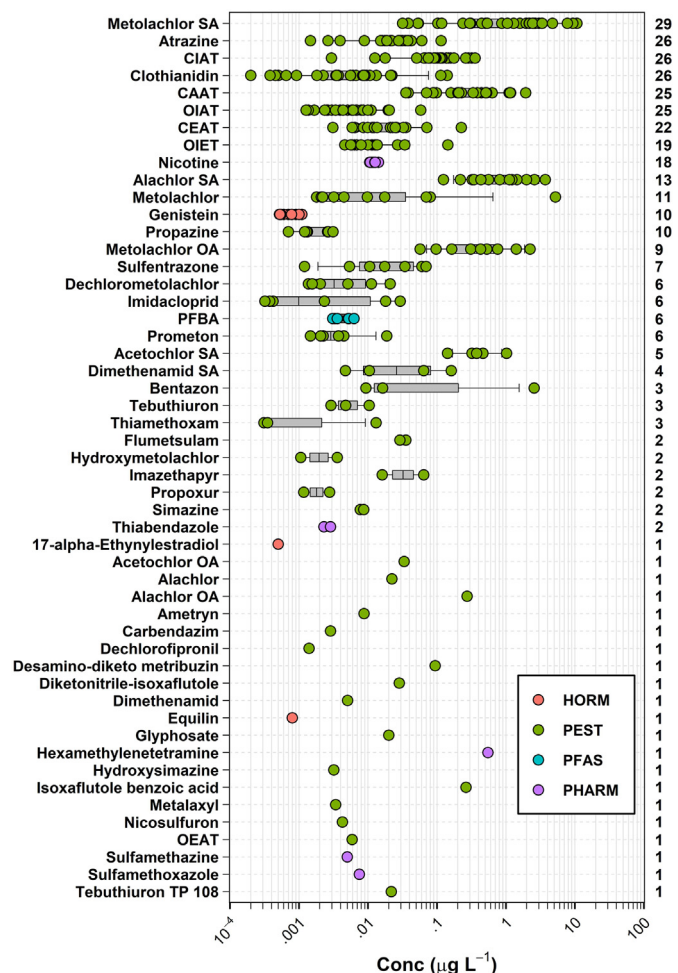


Fig. 2. Detected concentrations (circles, $\mu\text{g L}^{-1}$) and number of sites (right axis) for 52 organic analytes (left axis, in order of decreasing total detections) detected in samples of private-supply tapwater collected during 2018–19 in northeast Iowa. Circles (●) are data for individual samples. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. Symbol colors identify hormone (HORM), pesticide (PEST), per/polyfluoroalkyl substances (PFAS), and pharmaceutical (PHARM) classes.

related compounds comprised 82 % (42/51) of TW contaminant detections. Twenty-seven (77 %) of the 35 inorganic analytes were detected. Heterotrophic bacteria detections were near ubiquitous (94 % of the samples), with detection of total coliform bacteria in 28 % of the samples and frequent detection of growth on at least one putative-pathogen selective media across all TW samples.

Herein we provide Safe Drinking Water Act (SDWA) MCL for regulatory context, but the organ/organism-level human-health effects of individual contaminant exposures are screened based on MCLG and other human-health advisories, which generally provide a margin-of-exposure concentration below which there is no known risk to the health of presumptive “most vulnerable” (e.g., infants, children, pregnant women, elderly, immunocompromised) sub-populations (U.S. Environmental Protection Agency, 2021a). MCL are set as close to the MCLG as feasible, considering technical and financial drinking-water treatment limitations (U.S. Environmental Protection Agency, 2021a), and are enforceable only in public supplies (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023).

3.1. TW exposure-benchmark comparisons – inorganics

Few exceedances of human-health advisories for inorganics were observed in TW samples in this study, with the notable exception of

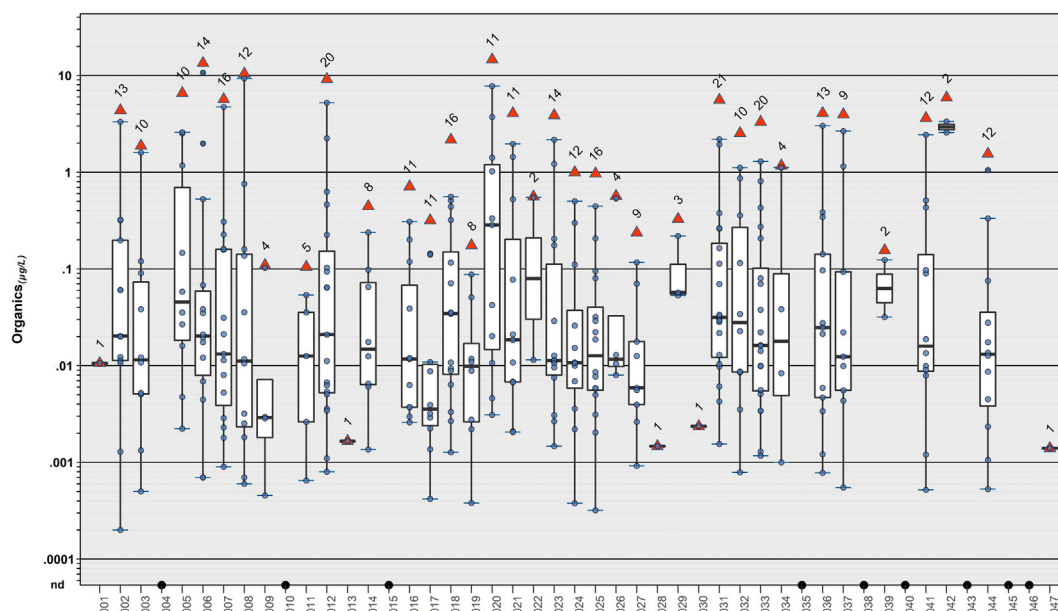


Fig. 3. Individual (circles, ●) and cumulative (sum of all detected; red triangles, ▲) concentrations ($\mu\text{g L}^{-1}$) of 51 organic analytes detected in samples of private-supply tapwater collected during 2018–19 in northeast Iowa. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. Numbers above each boxplot indicate total detected organic analytes. “nd” indicates not detected.

nitrate-nitrogen ($\text{NO}_3\text{-N}$) concentrations (Table S3a, Fig. S1). $\text{NO}_3\text{-N}$ was near ($>9.5 \text{ mg L}^{-1}$) or above (15 samples) the MCLG (10 mg L^{-1}) established to protect against bottle-fed infant (<6 months) methemoglobinemia (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023), in 36 % (17/47) of collected TW samples. Elevated groundwater $\text{NO}_3\text{-N}$ concentrations are well-documented in the US Midwest, including Iowa (Kolpin et al., 1994). Importantly, TW exposures to $<\text{MCLG}$ $\text{NO}_3\text{-N}$ concentrations recently have

been associated with several adverse outcomes (Ward et al., 2005; Ward et al., 2018) including specific cancers (Jones et al., 2016; Jones et al., 2017; Quist et al., 2018), thyroid disease (Aschebrook-Kilfoy et al., 2012), and neural tube defects (Brender et al., 2013). $\text{NO}_3\text{-N}$ concentrations $>2 \text{ mg L}^{-1}$ were observed in 49 % (23/47) of TW samples. While microorganisms, including fecal indicator bacteria and potential human bacterial pathogens, were detected in this study, the general lack of human-use pharmaceutical co-contaminants other than nicotine (Table S4a) and

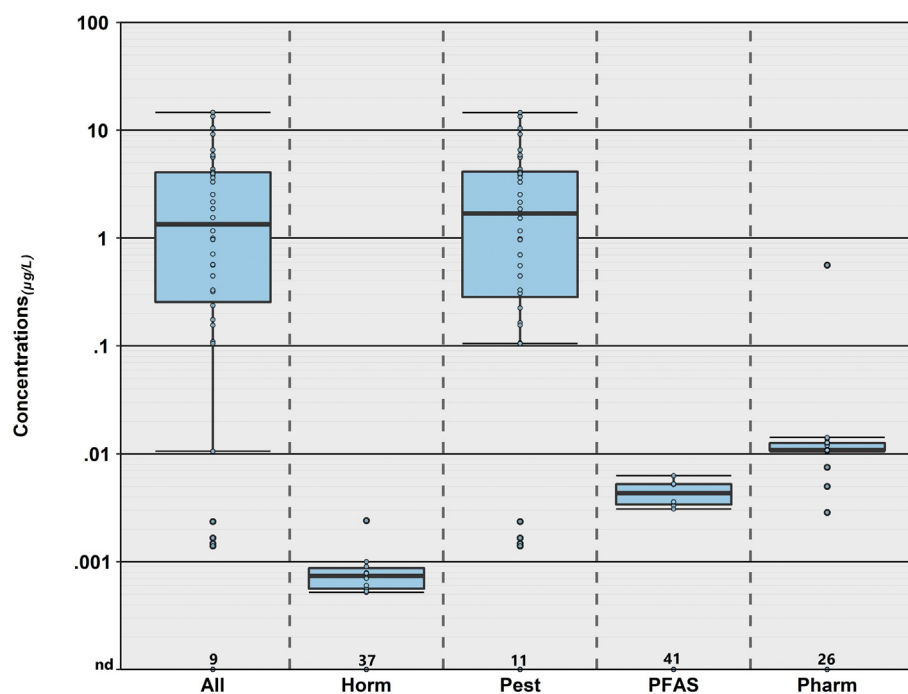


Fig. 4. Cumulative concentration ($\mu\text{g L}^{-1}$) of all organic analytes and classes of organic analytes detected in samples of private-supply tapwater collected during 2018–19 in northeast Iowa. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. “nd” indicates not detected. HORM, PEST, PFAS, and PHARM indicate hormone, pesticide, per/polyfluoroalkyl substances, and pharmaceutical classes, respectively.

corresponding lack of relation between $\text{NO}_3\text{-N}$ concentrations and pharmaceutical detections/concentrations (Fig. S2) indicate that human-waste infrastructures (septic systems) were not primary drivers of elevated TW $\text{NO}_3\text{-N}$ concentrations. Strong correlations between $\text{NO}_3\text{-N}$ concentrations and pesticide-related contaminant detections (Spearman rho: $\rho \geq 0.823$; p-value < 0.0001) or concentrations (Spearman rho: $\rho \geq 0.744$; p-value < 0.0001) indicate that agricultural treatments (e.g., inorganic/organic fertilizers or animal waste) were probable sources of elevated TW $\text{NO}_3\text{-N}$ concentrations.

Other TW inorganic results of note included infrequent detections of uranium (U) and generally low fluoride (F) concentrations. The redox-reactive geogenic radionuclide U was detected in four TW samples in this study. No level of exposure is considered safe to vulnerable subpopulations (i.e., MCLG zero) (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023). Drinking-water U is associated with nephrotoxicity (Magdo et al., 2007; Seldén et al., 2009) and osteotoxicity (Kurtio et al., 2005) in humans, inhibition of DNA-repair mechanisms in human embryonic kidney 293 (HEK293) cells (Cooper et al., 2016), and estrogen-receptor effects in mice (Raymond-Whish et al., 2007). Consistent with national surveys (DeSimone et al., 2015; McMahon et al., 2020), F concentrations observed in these TW samples were well below the EPA MCL (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023) for toxic effects. However, almost all samples also were below the U.S. Public Health Service (2015) optimum of 0.7 mg L^{-1} to prevent dental caries in children, consistent with previous concerns for the dental health of children on private wells in the US (American Academy of Pediatrics, 2009). Concentrations of F were $< 0.6 \text{ mg L}^{-1}$ in all but two TW samples and $< 0.3 \text{ mg L}^{-1}$ in 85 % (40/47) of TW samples; supplementation is recommended from 3 to 16 years of age for children with TW F $< 0.6 \text{ mg L}^{-1}$, beginning at 6 months if TW F is $< 0.3 \text{ mg L}^{-1}$ (American Academy of Pediatrics: Committee on Nutrition, 1995; Kohn et al., 2001).

3.2. TW exposure-benchmark comparisons - organics

Among the 51 organic analytes detected in this study (Fig. 3), 27 (53 %) were detected in ≤ 2 samples, with 21 (41 %) detected only once. At least one organic analyte was detected in 81 % (38/47) of the TW samples, with more than one detected in 70 % (33/47) of samples (Fig. 4, Table S4a). Consistent with the hydrologically-vulnerable (alluvial, karst) aquifer sources in an agriculturally-intensive setting and with Hypothesis II, on average (median) 91 % of cumulative detections (IQR: 83–100 %) and 100 % of concentrations (IQR: 100–100 %) in TW samples with detectable organics were attributable to pesticide-related (parent or transformation product) contaminants, and maximum cumulative pesticide detections and concentrations were more than an order of magnitude higher than observed in public- or private-supply TW samples in previous studies by this group, using the same pesticide analytical method (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b).

TW samples contained on average 8 pesticides (IQR: 1–10; range: 0–21), with median cumulative concentrations of $0.56 \mu\text{g L}^{-1}$ (IQR: not detected (nd)– $3.9 \mu\text{g L}^{-1}$; range: nd– $14.6 \mu\text{g L}^{-1}$). In general, the most frequently detected organic analytes were herbicide-related (e.g., acetochlor, atrazine, metolachlor) and primarily transformation products, consistent with previous findings for groundwater samples in Iowa (Kolpin et al., 2000). Three neonicotinoid insecticides (clothianidin, imidacloprid, thiamethoxam) also were detected in > 5 % of the TW samples, with clothianidin observed in more than half. Frequent TW exposures to neonicotinoid insecticides are emerging human-health concerns (Cimino et al., 2017; Thompson et al., 2020), driven by widespread adoption of neonicotinoid seed treatment for crop-pest management (Douglas and Tooker, 2015; Tooker et al., 2017). Other frequently detected organics included the pharmaceutical nicotine, the phytoestrogen genistein, and the PFAS compound perfluorobutanoate (PFBA), detected in 38 %, 21 %, and 13 % of samples, respectively.

Among the 51 detected organics, only 4 have EPA promulgated MCLG and none were exceeded. No differences ($p \geq 0.264$) in cumulative concentrations of organics or organics sub-classes were observed between alluvial and karst TW sources (Figs. 1 and S3). Consistent with predominant herbicide-intensive corn/soybean crop agriculture across the study area, PCA (Fig. S4) revealed central clustering and no apparent differences ($\alpha = 0.05$) for multivariate concentration profiles, except for two sites distinguished by co-occurring estrogenic-organic detections and almost two orders of magnitude higher detected metolachlor concentration (AHS 012) and by the highest concentrations and simultaneous detections of three neonicotinoid analytes (AHS 031). Frequent and simultaneous detections of multiple pesticides in TW samples raise concerns for potential adverse human-health effects and demonstrate the need for improved understanding of the implications of long-term TW exposures to mixtures of pesticides and other commonly co-occurring organic contaminants.

3.3. TW exposure-benchmark comparisons - microbial

Elevated ($> 100 \text{ CFU } 100 \text{ mL}^{-1}$) heterotrophic bacteria plate counts (HPC) were common in this study, exceeding the quantitation limit (“too numerous to count” $> 2400 \text{ CFU } 100 \text{ mL}^{-1}$) in 23 % of samples (Table S5a). HPC bacteria occur naturally in the environment, are commonly detected in private-well TW, and are not an intrinsic health concern, but do provide a useful indication of system maintenance (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023), which for private wells would include regular disinfection (U.S. Environmental Protection Agency, 2021c). Common detection of total coliform bacteria (28 %) and frequent detection of growth on at least one putative-pathogen selective media across all TW samples raise concerns for human health. The MCLG for total coliforms in TW is zero (U.S. Environmental Protection Agency, 2018; U.S. Environmental Protection Agency, 2023). Two TW samples were positive for total coliform bacteria and *Escherichia coli* (*E. coli*; fecal indicator bacteria), a result which, if confirmed, would represent a MCL violation in a public-supply setting. Detections of *Salmonella* (12 samples) and *Campylobacter* (1 sample) spp., common causes of foodborne bacterial diarrheal diseases (Eng et al., 2015; Silva et al., 2011), support concerns for adverse TW microbial exposures in this agriculturally-intensive area. Widespread (24 % of samples) growth on oxacillin-resistant staphylococci selective media, including “too numerous to count” (10 % of samples), indicates the presence of antibiotic-resistant microorganisms, a growing public-health (Laxminarayan et al., 2013) and drinking-water quality concern (Ashbolt et al., 2013). Total coliform bacteria, *E. coli*, *Salmonella* spp., *Campylobacter* spp., staphylococci, and antibiotic-resistant staphylococci are well-documented in livestock and poultry wastes (U.S. Environmental Protection Agency, 2013) and are acknowledged human-exposure concerns in nearby groundwater drinking-water supplies, especially unmonitored private wells (Borchardt et al., 2021; Burch et al., 2021), due to infiltration from waste storage lagoons (Chee-Sanford et al., 2001) and agricultural land applications (Givens et al., 2016). These results reiterate the inherent human-health challenge of unmonitored TW (DeSimone et al., 2015; Focazio et al., 2006; MacDonald Gibson and Pieper, 2017; Rogan and Brady, 2009) and support previous calls for systematic private-well monitoring (Zheng and Flanagan, 2017), including for microbial contamination.

3.4. TW in vitro bioactivities

Net biological activities were observed by NCI and EPA in some TW samples using distinct in vitro methodologies. For NCI bioassays (Table S6a), 5 of the 47 (11 %) TW samples exhibited significant ($p < 0.05$) receptor bioactivity, with AhR and AR bioactivities in 3 samples each (co-occurring in 2 samples) and ER bioactivity in another. Results for 2 other samples indicated borderline ($0.05 \leq p \leq 0.1$) AR and GR bioactivity. For EPA bioassays (Table S6b), ER activity was detected in 6 (13 %) samples above the T47D-KBluc minimum detectable concentration (MDC; $0.0164 \text{ ng } 17\text{-Estradiol Equivalents (E2Eq) L}^{-1}$); detected ER

activity did not exceed a previously developed drinking water effects-based trigger value (1 ng E2Eq L^{-1}) for adverse effects (Brand et al., 2013). No AR or GR bioactivities were detected above corresponding bioassay MDC. The results indicated the potential for net biological effects of some TW exposures in this agriculturally-intensive area and the need for further investigation of potential contaminant drivers of the observed activities.

3.5. TW aggregated screening assessments

Cumulative-exposure effects of potential human-health interest were screened using two bioactivity-weighted approaches (Σ_{EAR} , Σ_{TQ}) based on detected TW analytes. Both approaches 1) are constrained by the analytical scope (437 organics, 32 inorganics), which, while extensive, is an orders-of-magnitude underestimate of the organic chemicals in commercial use and by extension in the environment (Wang et al., 2020), 2) are limited to available weighting-factors (ToxCast ACC and human-health benchmarks, respectively), and 3) assume cumulative effects are reasonably approximated by concentration addition (Backhaus, 2016; Cedergreen et al., 2008; Ermler et al., 2011; Medlock-Kakaley et al., 2018; Sigurnjak Bureš et al., 2021; Stalter et al., 2020). The Σ_{EAR} approach (Blackwell et al., 2017; Bradley et al., 2021a) leverages ToxCast high-throughput exposure-effects data (Filer et al., 2017; Richard et al., 2016) to estimate potential cumulative activity of organics at sensitive molecular endpoints, but not all predicted pathway responses are necessarily adverse at organ/organism scales and ToxCast has no coverage of inorganic contaminants (Schroeder et al., 2016). We aggregated contaminant bioactivity ratios across all endpoints without restriction to recognized modes of action as a precautionary screening for further investigation of potential effects

(Bradley et al., 2021a; Bradley et al., 2021b) (i.e., as a lower bound estimate of in vivo adverse effect levels (Paul Friedman et al., 2020)), but this approach may not accurately reflect apical effects (Blackwell et al., 2017; Schroeder et al., 2016). The Σ_{TQ} approach assesses effects of simultaneous inorganic and organic exposures, is targeted at apical human-health effects, but is limited to existing health benchmarks.

Approximately half (30) of the 51 detected organic compounds had exact Chemical Abstract Services (CAS) number matches in the ToxCast invitroDBv3.2 database (Table S7b). However, the highest EAR (0.55) and the only Σ_{EAR} exceeding the level expected to modulate molecular targets in vitro (i.e., solid red $\Sigma_{\text{EAR}} = 1$ line, Fig. 5) in this study was for a TW sample (AHS 012) containing $5.23 \mu\text{g L}^{-1}$ metolachlor, and co-occurring detections of EE2 and equilin. Exceedance of $\Sigma_{\text{EAR}} = 0.001$ (precautionary screening-level threshold of interest) in more than half (26/47) of the samples indicated that further investigation of the cumulative biological activity of TW exposures in this agriculturally-intensive area is warranted.

Approximately 83 % (39/47) of the TW samples in this study exceeded the $\Sigma_{\text{TQ}} = 0.1$ HI screening threshold of potential concern and 47 % (22/47) exceeded $\Sigma_{\text{TQ}} = 1$ (Fig. 5; Table S8b). These Σ_{TQ} results indicate high probabilities of aggregated risks in private-well TW samples in this agriculturally-intensive area, when considering exposures to both organic and inorganic contaminants. Consistent with the above discussion of individual contaminant benchmark comparisons and the lack of human-health benchmarks for most of the organic contaminants detected in TW in this study, Σ_{TQ} was driven primarily by inorganics, notably by $\text{NO}_3\text{-N}$, which exceeded the MCLG (MCL) in 32 % (15/47) of collected TW samples, and less frequently (4/47) by U, for which there is no known safe level of exposure to vulnerable subpopulations (MCLG zero (U.S. Environmental

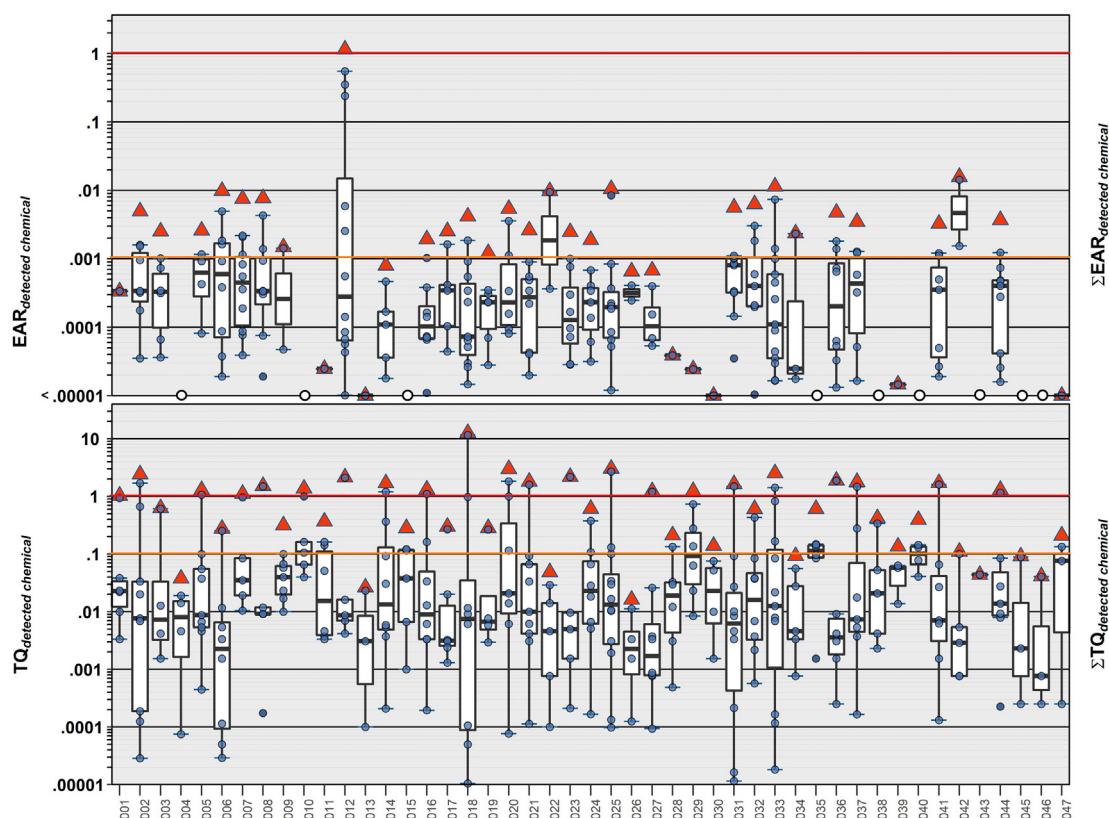


Fig. 5. Top. Individual EAR values (circles, ●) and cumulative EAR (Σ_{EAR} , sum of all detected; red triangles, ▲) across all assays for 43 organic analytes detected in samples of private-supply tapwater collected during 2018–19 in northeast Iowa. Red and orange lines indicate concentrations shown to modulate effects in vitro ($\text{EAR} = 1$) and effects-screening-level thresholds ($\text{EAR} = 0.001$), respectively. **Bottom.** Human health benchmark-based individual TQ values (circles) and cumulative TQ (Σ_{TQ} , sum of all detected; red triangles, ▲) for inorganic and organic analytes listed in Table S11 and detected in samples of private-supply tapwater. Red and orange lines indicate benchmark equivalent concentrations ($\text{TQ} = 1$) and effects-screening-level threshold of concern ($\text{TQ} = 0.1$), respectively. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively, for both plots.

Protection Agency, 2018)). Other notable Σ_{TQ} results included the elevated alachlor exposure in a single sample and common-place simultaneous exposures to multiple pesticides. The results of this and previous (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b) studies by this group reiterate the inherent human-health challenge of unmonitored TW (DeSimone et al., 2015; Focazio et al., 2006; MacDonald Gibson and Pieper, 2017; Rogan and Brady, 2009; Zheng and Flanagan, 2017) and the potential importance of systematic private-supply monitoring (Zheng and Flanagan, 2017), with an analytical scope that reflects the breadth of inorganic and organic environmental contamination (Bradley et al., 2017; Glassmeyer et al., 2017; Moschet et al., 2014; Schaidler et al., 2016; Schaidler et al., 2014).

4. Conclusions

Improved understandings of TW contaminant exposures based on more environmentally realistic and directly comparable POU exposure characterizations like this and others by this group (Bradley et al., 2020; Bradley et al., 2018; Bradley et al., 2021a; Bradley et al., 2021b; Bradley et al., 2022), in a range of source-water vulnerability settings, are essential to public health, because drinking-water is a biological necessity and, consequently, a high-vulnerability vector for human contaminant exposures (Dai et al., 2017). The paucity of information on private-well contaminant exposures is a recognized public-health data gap and a fundamental obstacle to private-supply risk-management and decision-making (Bradley et al., 2021a; Bradley et al., 2021b; Zheng and Flanagan, 2017). The current results address a critical lack of directly comparable data on broad contaminant exposures in TW in agriculturally-developed settings and document commonplace simultaneous exposures to inorganic, organic, and microbial contaminants of human-health concern. Based on these one-time spatial synoptic results, further spatial coverage and, importantly, assessment of temporal variability are warranted to more fully characterize POU exposures. The results indicate that incorporation of well-maintained, residential treatment systems could substantially protect against unrecognized contaminant exposures in private-well homes, including in agriculturally developed areas. Several POU (and point-of-entry) treatment technologies are effective in reducing TW exposures to many of the contaminants identified in this study (Wu et al., 2021). However, given the common-place simultaneous exposures to multiple inorganic, organic, and microbial contaminants in the study area, broadly effective single-stage treatment technologies, such as RO, or multi-stage/multi-filtration systems (sediment filter, redox media, activated carbon, ion exchange, RO, UV disinfection, etc) warrant consideration. More broadly, the results corroborate the importance of continued systematic, quantitative assessments of contaminant exposures and associated bioactivities in TW, especially in unregulated and unmonitored locations (Baken et al., 2018; Braun and Gray, 2017; Gross and Birnbaum, 2017; Lanphear, 2017; Schriks et al., 2010), to support models of drinking-water contaminant exposures and related risks at the point of use.

CRediT authorship contribution statement

Paul M. Bradley: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Dana W. Kolpin:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Darrin A. Thompson:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Kristin M. Romanok:** Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. **Kelly L. Smalling:** Formal analysis, Visualization, Writing – review & editing. **Sara E. Breitmeyer:** Visualization. **Mary C. Cardon:** Investigation. **David M. Cwiertny:** Writing – review & editing. **Nicola Evans:** Investigation, Writing – review & editing. **R. William Field:** Writing – review & editing. **Michael J. Focazio:** Writing – review & editing. **Laura E. Beane Freeman:** Writing – review & editing. **Carrie E. Givens:** Investigation, Writing – review & editing. **James L. Gray:** Investigation, Writing – review

& editing. **Gordon L. Hager:** Writing – review & editing. **Michelle L. Hladik:** Investigation, Writing – review & editing. **Jonathan N. Hofmann:** Writing – review & editing. **Rena R. Jones:** Writing – review & editing. **Leslie K. Kanagy:** Investigation. **Rachael F. Lane:** Investigation, Writing – review & editing. **R. Blaine McCleskey:** Investigation, Writing – review & editing. **Danielle Medgyesi:** Writing – review & editing. **Elizabeth K. Medlock-Kakaley:** Formal analysis, Investigation, Writing – review & editing. **Shannon M. Meppelink:** Data curation, Investigation, Writing – review & editing. **Michael T. Meyer:** Investigation. **Diana A. Stavreva:** Investigation, Writing – review & editing. **Mary H. Ward:** Writing – review & editing.

Data availability

Data are available in Supplementary Material and at <https://doi.org/10.5066/P9IYT37H>

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2023.161672>.

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