Tapwater Exposures, Effects Potential, and Residential Risk Management in Northern Plains Nations

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ABSTRACT: In the United States (US), private-supply tapwater (TW) is rarely monitored. This data gap undermines individual/community risk-management decision-making, leading to an increased probability of unrecognized contaminant exposures in rural and remote locations that rely on private wells. We assessed point-of-use (POU) TW in three northern plains Tribal Nations, where ongoing TW arsenic (As) interventions include expansion of small community water systems and POU adsorptive-media treatment for Strong Heart Water Study participants. Samples from 34 private-well and 22 public-supply sites were analyzed for 476 organics, 34 inorganics, and 3 in vitro bioactivities. 63 organics and 30 inorganics were detected. Arsenic, uranium (U), and lead (Pb) were detected in 54%, 43%, and 20% of samples, respectively. Concentrations equivalent to public-supply maximum contaminant level(s) (MCL) were exceeded only in untreated private-well samples (As 47%, U 3%). Precautionary health-based screening levels were exceeded frequently, due to inorganics in private supplies and chlorine-based disinfection byproducts in public supplies. The results indicate that simultaneous exposures to co-occurring TW contaminants are common, warranting consideration of expanded source, point-of-entry, or POU treatment(s). This study illustrates the importance of increased monitoring of private-well TW, employing a broad, environmentally informative analytical scope, to reduce the risks of unrecognized contaminant exposures.

KEYWORDS: tapwater, arsenic, organics, inorganics, human health, private wells, underserved communities

1. INTRODUCTION

Water is life (Mní wíčhóni in Lakota). The quality and sustainability of drinking water are growing challenges in the United States (US) and world wide due to, among other reasons, increasing water demands and drinking-water source contamination. US public, private, and bottled drinking-water supplies share many anthropogenic-contaminant (i.e., human-generated/-driven) concerns, because most of the 350,000 chemicals estimated to be in commercial use globally and, by extension, potentially in drinking-water source waters are not currently regulated or systematically monitored in public-supply tapwater (TW) or in bottled drinking water. Note, the U.S. Environmental Protection Agency (EPA) does not regulate private wells nor does it provide recommended criteria or standards for individual wells. In contrast, many water-borne pathogens (e.g., Cryptosporidium) and naturally occurring contaminants (e.g., arsenic, As) are actively regulated in US public and bottled-water supplies.

The potential for unrecognized contaminant exposures and adverse health effects is notably elevated for private and small community drinking-water supplies in rural and remote areas, due to differences in regulation, technical expertise, natural/economic resources, and associated risk-management options. Although some geogenic groundwater contaminants, such as As, exhibit broadly predictive geospatial patterns, individual point-of-use (POU) TW concentrations reflect multiple factors including well-screen/open-hole depth, geologic stratigraphy, and spatial/temporal variability in water levels and redox conditions and, consequently, can differ...
substantially and unpredictably from well to well. Further, As and several other contaminants are imperceptible (tasteless and odorless) without TW testing.

Prior studies have documented a range of contaminant concerns in unregulated drinking water. Due to high analytical costs, common-place conflation of organoleptic quality with safety, and other socioeconomic factors, private-well water-quality data remain scarce and, where available, are typically limited to a few targeted contaminants. Similarly, small rural water systems are often concerns for various socioeconomic reasons, including financial limitations of smaller and lower-income populations. The elevated probability of unrecognized exposures has prompted calls for universal private-well As testing, but, acknowledging the increasingly human-impacted water cycle, broader characterization of private-well and rural-water-system contaminant exposures is needed.

The Strong Heart Study (SHS) is an ongoing population-based prospective-cohort study of cardiovascular disease and associated risk factors among American Indian (AI) adults in participating Tribal Nations in Arizona, North Dakota, Oklahoma, and South Dakota. Groundwater As varies regionally across the US, with elevated concentrations predicted and observed throughout SHS areas. SHS research has associated low to moderate drinking-water As exposures with lung, prostate, and pancreatic cancer, cardiovascular disease, kidney disease, lung disease, and type-2 diabetes outcomes. Efforts to manage As-related health risks in SHS-area TW include the development/expansion of rural water systems and the Strong Heart Water Study (SHWS), a participatory randomized controlled intervention to reduce As exposures in remote residences in North and South Dakota using undersink adsorptive-media POU treatment.

The U.S. Geological Survey (USGS) collaborates with EPA, the National Institute of Environmental Health Science (NIEHS), Food and Drug Administration (FDA), Tribal Nations, universities, utilities, communities, and others to inform drinking-water exposure and water-supply data gaps by assessing TW inorganic/organic contaminant mixtures and associated distal (e.g., ambient source water) and proximal (e.g., premise plumbing and POU treatment) drivers in a range of socioeconomic and source-water vulnerability settings across the US. As part of that ongoing effort, we assessed exposures to a broad suite of potential inorganic and organic TW contaminants in 56 homes in three areas of North Dakota and South Dakota in 2019 to provide insight into cumulative contaminant risk to human health of private-well and small...
community public-supply TW in this region, to assess the utility of broader TW contaminant assessments for identifying additional risk management efficiencies in areas undergoing drinking-water interventions for As, and to expand the national perspective on inorganic and organic contaminant exposures at the TW point of use by maintaining the same general sampling protocol and analytical toolbox employed in previous studies. For this study, TW exposure was operationally represented as concentrations of 476 organics, 34 inorganics, and 3 bioactivity indicators in residential and community POU TW samples. Potential human-health risks of individual and aggregate TW exposures were explored based on cumulative detections/concentrations of designed-bioactive chemicals (e.g., pesticides and pharmaceuticals), as well as the cumulative exposure-activity ratio(s) (ΣEAR) and hazard indices (HI) of cumulative benchmark-based toxicity quotient(s) (ΣTQ). In line with previous results by this research group and others, simultaneous TW exposures to multiple inorganic and organic constituents of potential human-health interest were hypothesized to occur in both private- and public-supply samples.

2. METHODS

2.1. Site Selection and Sample Collection. Sample locations were selected from community volunteers to provide broad spatial coverage of private-/public-supply TW in three Tribal areas in North Dakota and South Dakota, with 16
private; 10 private/10 public; and 8 private/12 public TW locations from communities A, B, and C, respectively (Figures 1 and S1). All community A locations were SHWS participants, for which the inclusion criterion was greater than maximum contaminant level(s) (MCL) baseline TW As concentrations. In this study, all private-supply and 15 public-supply TW samples were groundwater sourced. In community B, three and seven public-supply sample locations were connected to groundwater-sourced and surface-water-sourced (Missouri River) water systems, respectively. Community C public-supply samples were groundwater sourced, with 11 samples from the primary, multiwell water system and one sample from a small (65 people) system. In general, TW samples were collected from untreated kitchen faucets, except for four (three private, one public) community B samples collected from POU-treatment taps (denoted POU-AF in Supporting Information Tables) at the participants’ request. One other TW-sample location (community B) had a point-of-entry water-softener system (POE-S in Supporting Information Tables).

Taps (cold water) were sampled once each from September to November 2019. Samples were collected at the participant’s convenience throughout the day, without precleaning, screen removal, or Lead and Copper Rule stagnant-sample protocols. Complete sampling details are provided elsewhere.

2.2. Methods and Quality Assurance. Briefly, TW samples were analyzed by USGS using seven organic (6 classes; 476 total/468 unique analytes), five inorganic (34 ions/trace elements), and two field (3 parameters) methods (Table S2) and by USEPA using three in vitro bioassay (ER, AR, and GR) methods, as discussed and described in detail previously. Organic analytes included cyanotoxin, disinfection byproduct(s) (DBP), pesticide, per/polyfluoroalkyl substance(s) (PFAS), volatile organic compound(s) (VOC), and pharmaceutical classes; additional method details are in the

Figure 3. Detected concentrations (μg L⁻¹) and the number of sites (right axis) for 63 organic analytes (left axis, in order of decreasing total detections) detected in TW samples collected during 2019 in North Dakota and South Dakota. Circles are data for individual samples. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively.
Differences between TW-sample groups were assessed by nonparametric one-way PERMANOVA (Paleontological Statistics, PAST, vers. 4.03) and permuted (\(\rho\)) results, ToxCast exclusions, and health-based benchmarks are summarized in Tables S9–S13 (additional details in Supporting Information).

3. RESULTS AND DISCUSSION

Regulated and unregulated chemicals (inorganic, organic) were detected in TW samples in all three study areas (Tables 1, S3, and S4; Figures 1–4), with two or more detections of human-health interest commonly observed per sample. 63 (14%) organic and 30 (91%) inorganic analytes were detected. In this discussion, the enforceable EPA MCL or, for Pb, action level (AL) for technology treatment is provided from a regulatory perspective, but the organ/organism-level human-health effects of individual contaminant exposures are contextualized based on MCLG and human-health advisories, for three reasons. First, EPA MCL and AL are enforceable in public supplies but not in private supplies. Second, MCL and AL are set as close to MCLG values as feasible but are often higher to reflect technical and financial constraints of drinking-water monitoring and treatment. Last, MCLG and health advisory values generally include a margin of exposure to provide a safety threshold, in the case of MCLG defined as the concentration below which there is no known risk to the health of presumptive “most vulnerable” (e.g., infants, children, pregnant women, elderly, and immune-compromised) subpopulations.

3.1. TW Arsenic, Uranium, and Lead

Consistent with previous reports, TW exposures to As, U, and Pb, which have no known safe level of drinking-water exposure for vulnerable sub-populations (MCLG zero), were widely observed (54, 43, and 20% of samples, respectively) in the three study areas in private- and public-supply locations (Figure 2).

In line with earlier SHWS findings, the redox-reactive geogenic contaminant As was consistently detected (MCLG exceedance) in communities A and C (94 and 75% of samples, respectively), but not in community B. Consistent with the SHWS inclusion criterion, As was detected in all but one community A sample, near (9 \(\mu g\) L\(^{-1}\) in three samples) or above (11 samples) MCL-equivalent concentrations in 88% (14/16) of samples. In community C, As was detected in 50% (4/8) and...
Table 1. Number of Exceedances of Maximum Contaminant Level (MCL) Concentrations (MCL-Equivalent for Private Well Locations) or Listed Health GVs Observed in TW Samples

| class    | constituent       | public supply | private wells |
|----------|-------------------|---------------|---------------|
|          |                   | community B   | community C   | community A | community B | community C |
|          |                   | (N = 10)      | (N = 12)      | (N = 16)    | (N = 10)    | (N = 8)     |
|          |                   | value         |              |            |            |             |
| inorganic| arsenic           | MCL           | 10 μg/L      | 0           | 0           | 11           |
|          |                   | MCLG          | 0 μg/L       | 0           | 11          | 0            |
|          | lead              | AL            | 15 μg/L      | 0           | 0           | 0            |
|          | manganese         | DWHA          | 300 μg/L     | 0           | 0           | 0            |
|          | nitrate           | MCL(MCLG)     | 10 mg/L      | 0           | 0           | 0            |
|          | selenium          | MCL(MCLG)     | 50 μg/L      | 0           | 0           | 0            |
|          | uranium           | MCL           | 30 μg/L      | 0           | 0           | 0            |
|          |                   | MCLG          | 0 μg/L       | 2           | 0           | 15           |
| organic  | atrazine          | MCL(MCLG)     | 3 μg/L       | 0           | 0           | 0            |
|          | benzenne          | MCLG          | 0 μg/L       | 0           | 0           | 1            |
|          | bromodichloromethane | MCLG       | 0 μg/L       | 9           | 12          | 0            |
|          | dichloromethane   | MCLG          | 0 μg/L       | 2           | 0           | 0            |
|          | 1,2-dichloropropane | MCLG      | 0 μg/L       | 0           | 0           | 0            |
|          | tribromomethane   | MCLG          | 0 μg/L       | 0           | 9           | 0            |
|          | TCE               | MCLG          | 0 μg/L       | 0           | 0           | 0            |
|          | vinyl chloride    | MCLG          | 0 μg/L       | 1           | 0           | 0            |

"MCL, maximum contaminant level; MCLG, maximum contaminant level goal; AL, technology treatment action level; DWHA, drinking water health advisory (lifetime); EU Directive, European Union Directive. "MCL(MCLG)" indicates the same value for both.

92% (11/12) of private- and public-supply samples, respectively, but MCL-equivalent exceedences occurred only in three private-well locations. Overall, the results support ongoing expansions/connections to public supplies as an effective approach to limit TW As-exposures to <MCL concentrations in these communities and POU/POE treatment. 4,1,2 in private-supply locations where a public-supply connection is not feasible. The results emphasize the potential for unrecognized exposures to contaminants, including contaminants of human-health concern, in unregulated/unmonitored private supplies and support private-well As monitoring. The results also support the potential use of POU/POE treatment at public-supply locations with detectable As, as an additional As removal step. While As-associated Safe Drinking Water Information System (SDWIS) violations, As concentrations, and urinary As levels have been detected and were moderately positively correlated since the MCL was lowered, no safe level of TW As exposure is recognized for vulnerable subpopulations. Drinking water As exposure is associated with various cancers, organ-system toxicity, cardiovascular diseases, adverse pregnancy outcomes, and mortality. Adverse health associations with <MCL As exposures have prompted a 5 μg L⁻¹ MCL in some US states (e.g., New Jersey and New Hampshire). Every private-well sample with detectable As and 92% of community C public-supply samples exceeded 5 μg L⁻¹.

Also, consistent with previous findings, the redox-reactive geogenic radionuclide U was detected (MCLG exceedance) in all three communities (A: 94%, B: 25%, and C: 20%). Drinking-water U is associated with nephotoxicity and osteotoxicity in humans, inhibition of DNA-repair mechanisms in human embryonic kidney 293 (HEK293) cells, and estrogen-receptor effects in mice. The MCL-equivalent concentration was exceeded only in one private-well location. Community C U exposures differed (PERMANOVA, p = 0.013) between private- (4 detections) and public-supply (no detections) locations. No difference was apparent in community B (p = 0.93), with 2–3 detections (≤6 μg L⁻¹) each in private-well and public-supply samples. Other widely documented, drinking-water radionuclides (e.g., radium and radon) not assessed herein should be included in future assessments.

As and U co-occurred in 16 (42%) of the 38 samples in which either was detected and were moderately positively correlated (Spearman ρ = 0.48, permutation [n = 9999] p = 0.0002). Because groundwater As and U are favored under reducing and oxidizing conditions, respectively, frequent co-occurrence in SHWS well water suggests redox heterogeneity is common or redox-independent mechanisms (e.g., pH/alkalinity-driven solubility) are important. Elevated iron (Fe) and manganese (Mn) concentrations in oxic TW herein support the former. A moderate correlation (ρ ≥ 0.42; p < 0.0001) between U and nitrate (NO₃⁻) was reported for the High Plains aquifer, the northern extension of which underlies community A; a weaker correlation (ρ ≥ 0.27; p < 0.042) was observed herein.

Pb was detected sporadically (20%) in private- and public-supply locations in all communities but did not exceed the AL-equivalent concentration. Elevated drinking-water Pb-exposures primarily are associated with neurocognitive impairment in infants and children. The American Academy of Pediatrics recommends that drinking-water Pb not exceed 1 μg L⁻¹, a common MDL for US public-supply compliance monitoring. Drinking-water Pb is attributed primarily to premise-plumbing and distribution-infrastructure materials that predate the 1986 SDWA Amendments. In this study, no difference in Pb detections (p ≥ 0.11) between private- and public-supplies and no systematic Pb detections within a given public-supply system support premise plumbing as the probable source. Importantly, the current results likely underestimate TW Pb occurrence and concentrations in the study area, because flushing effectively decreases plumbing-derived contaminant...
concentrations, and same-day prior TW use was common in this study.

3.2. TW Nitrate. TW nitrate−nitrogen (NO$_3^-$−N) concentrations were generally low (median: 0.4 mg L$^{-1}$) in the study area, with elevated (>2 mg L$^{-1}$) concentrations, including one MCL-equivalent exceedance (Table 1), observed infrequently (4 samples) and only in private-well locations. No co-contaminants (e.g., human-use pharmaceuticals) indicative of human-waste sources (e.g., septic systems) were detected in elevated NO$_3^-$−N samples, indicating other sources, such as inorganic/organic crop fertilizers or animal wastes, as possible contributors to elevated TW NO$_3^-$−N concentrations; the lack of detectable pesticides in the four TW samples with >2 mg L$^{-1}$ NO$_3^-$−N points toward the latter. The NO$_3^-$−N MCLG was established to protect against bottle-fed infant (<6 months) methemoglobinemia. Emerging evidence associates <MCL NO$_3^-$−N concentrations with other adverse health outcomes, including cancer, thyroid disease, and neural tube defects.

3.3. TW Manganese. No Mn MCL (or WHO GV) currently exists, but USEPA maintains a 300 µg L$^{-1}$ lifetime drinking-water health advisory (DWHA; assumes 100% exposure from drinking water). Approximately 32% (18/56) of the samples in this study (75% in community C) exceeded or equaled the USEPA DWHA, raising concerns about prolonged exposures. More concerning, a Mn concentration greater than the 1 day acute exposure level of 1 mg L$^{-1}$ for small (≤10 kg) children co-occurred in a private-well TW sample with a greater than MCL-equivalent U concentration, again emphasizing the elevated risk of unrecognized exposures in private-well TW. Community B Mn concentrations differed by an order of magnitude (p = 0.0002) between surface-water-sourced public-supply (median: 2 µg L$^{-1}$) and groundwater-sourced (private-/public-supply median: 23 µg L$^{-1}$) samples. Median Mn concentrations were more than an order of magnitude higher in community C samples (all groundwater-sourced), with no difference (p = 0.21) between private- and public-supply locations (medians 575 and 554 µg L$^{-1}$, respectively). However, the highest Mn concentration in this study (2880 µg L$^{-1}$) was observed in a private-well TW sample in community C, which also had the study’s highest dissolved Fe (4640 µg L$^{-1}$) and only >MCL-equivalent U concentration (34 µg L$^{-1}$). As noted above, frequent co-occurrence in groundwater-sourced TW samples of redox-reactive inorganics, including those (e.g., As and U) mobilized under different redox conditions, is consistent with widespread well-water redox heterogeneity.

Across the US, approximately 6.9% of drinking-water-aquifer samples (n = 3662) exceeded 300 µg L$^{-1}$ Mn, an exceedance rate comparable to those for MCL-equivalent concentrations of NO$_3^-$−N (4.1%) and As (6.7%) in the same wells. Groundwater Mn concentrations in excess of 300 µg L$^{-1}$ were associated with proximity to surface waters and organic-rich soils, consistent with the elevated Mn concentrations observed in community C, near a large regional lake. Growing concerns for cognitive, neurodevelopmental, and behavioral effects of long-term exposures in children have prompted calls to re-evaluate the regulation/monitoring of drinking-water Mn. To protect against neurological effects in bottle-fed infants, WHO recently released a provisional Mn GV of 80 µg L$^{-1}$, a value

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Figure 5. Cumulative concentrations (circles, ●) of all organics (plot A) and select organic classes (plots B–D) detected during 2019 in North Dakota and South Dakota in public-supply (shaded) and private-supply (unshaded) TW samples within each study area. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. Numbers above each boxplot pair indicate the permuted probability that the centroids and dispersions are the same (PERMANOVA; 9999 permutations). "nd" indicates not detected.

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1778
exceeded by 39% (22/56) of samples in the current study (85% of community C).

### 3.4. TW Selenium

Elevated drinking-water Se has been proposed as a risk factor for adverse health outcomes, including amyotrophic lateral sclerosis (ALS), Parkinson’s disease, neurotoxicity, and skin cancer. Elevated serum Se concentrations have been associated with diabetes and elevated fasting glucose. While the USEPA Se MCLG is currently 50 μg L$^{-1}$, growing concerns prompted a recent 20 μg L$^{-1}$ European Commission parametric value for Se. Based on a comparative cohort (exposed, unexposed) study of long-term exposure to drinking-water Se in the range of 7–10 μg L$^{-1}$ in northern Italy, a drinking-water limit of 1 μg L$^{-1}$ was proposed to decrease the risk of adverse health effects, including neoplasms and endocrine and neurological diseases. In the current study, Se was detected in excess of 1 μg L$^{-1}$ in 26% (9/34) of private-well TW samples (8/14 community A), but not in any public-supply samples.

### 3.5. TW Fluoride

Detected F concentrations (Figure S1, Table S3) were well below the USEPA MCL established to prevent dental caries (Figure S1), consistent with concentration addition. Both approaches are limited to underestimate of the contaminant exposures documented in drinking-water sources. Likewise, both approaches are limited to underestimate of the contaminant exposures documented in drinking-water sources. Likewise, both approaches are limited to underestimate of the contaminant exposures documented in drinking-water sources.

### 3.6. TW Organics

TW samples were screened for 4 cyanotoxins, 22 DBP, 218 pesticide, 34 PFAS, 78 VOC, and 112 pharmaceutical analytes. Among the 63 organic analytes detected at least once, 59% (38) were detected in 5% (≤3) or fewer samples, with 20 (31%) detected only once. At least one organic analyte was detected in 79% (44/56) of the TW sample locations, with more than one detected in 59% (33/56) of locations. Higher numbers and cumulative concentrations of detected organics were observed in public-supply TW samples than in private supply in communities B and C (p < 0.0001), attributable primarily to DBP. In general, few organics were detected in private-well samples (Figures 4 and 5), with 35% (12/34) having no organic detections; a median detection of 1 β-Dihydrotestosterone equiv L$^{-1}$ was detected above its bioassay MDC (Table S8). No detected estrogenic activity (estrogen or androgen activity) exceeded respective benchmarks, respectively) and assume cumulative effects are reasonably approximated by concentration addition. The co-occurrence of multiple petroleum-hydrocarbon contaminants in two remote rural, private-well TW locations is consistent with groundwater contamination from farm-related refueling activities. VOC remained a frequently detected class in public-supply TW locations, with predominantly xylene observed in community C and xylene and the fuel-oxygenate, t-butyl alcohol, systematically detected in community B. However, consistent with previous findings, DBP dominated public supply organics, representing on average (median) 58% of detections and 92% of cumulative concentrations. Cumulative DBP concentrations were more than an order of magnitude higher (p < 0.0001) in surface-water-sourced public-supply TW samples (community B only; median: 24.2 μg L$^{-1}$) than in groundwater-sourced public-supply locations (median: 2.0 μg L$^{-1}$) in communities B and C. Consistent with widespread agricultural use within Corn Belt drainage basins, including the Missouri River basin, pesticides (median: 6) were detected (concentrations ≤ 0.33 μg L$^{-1}$) in every surface-water-sourced public-supply sample but were rarely detected in any groundwater-supplied location in this study. Other notable, albeit less frequent, organic detections of growing human-health concerns included PFAS compounds (PFBA, one private supply, 83.7 ng L$^{-1}$; PFBS, two private supplies, maximum 13.2 ng L$^{-1}$) and cyanotoxins (cylindrospermopsin, one public supply, 90 ng L$^{-1}$; saxitoxins, two private supplies, both 30 ng L$^{-1}$), all below current lowest state drinking-water ALs or advisories for PFBA (7000 ng L$^{-1}$), PFBS (345 ng L$^{-1}$) cylindrospermopsin (700 ng L$^{-1}$), and saxitoxins (300 ng L$^{-1}$).

Among the 63 detected organics, 16 have MCLG; among these 12 have individual MCL and 4 are addressed as a class by the trihalomethane (THM) MCL. No MCL or MCL-equivalent concentration was exceeded in public- or private-supply samples, respectively. However, seven detected analytes have an MCLG of zero. Among these MCLG exceedances, only bromodichloromethane, tribromomethane, and dichloromethane were detected in more than one sample and only in treated public supplies. The remaining MCLG (zero) exceedances were single detections each of 1,2-dichloropropane, benzene, trichloroethylene (TCE), and vinyl chloride.

### 3.7. TW In Vitro ER, AR, and GR Bioactivity

While estrogenic activity was detected in five samples above the T47D-KBluc minimum detectable concentration [MDC; 0.0683 ng 17β-estradiol equivalents (E2Eq) L$^{-1}$], androgenic activity was detected in one sample above the CV1-chAR MDC (0.9 ng dihydrotestosterone equiv L$^{-1}$), glucocorticoid activity was not detected above its bioassay MDC (Table S8). No detected activity (estrogen or androgen activity) exceeded respective drinking water effect-based trigger values (indicative of adverse health effects) previously developed for similar molecular-endpoint bioassays.

### 3.8. TW Aggregated Screening Assessment: $Σ_{EAB}$ and $Σ_{TQ}$

We screened for TW cumulative-exposure effects of potential human-health interest using two analogous bioactivity-weighted approaches ($Σ_{EAB}$, $Σ_{TQ}$) with distinct strengths and limitations. Both are based on detected TW constituents and constrained by the analytical scope (468 organics and 33 inorganics), which, while extensive, is an orders-of-magnitude underestimate of the contaminant exposures documented in drinking-water sources. Likewise, both approaches are limited to available weighting factors (ToxCast ACC and human-health benchmarks, respectively) and assume cumulative effects are reasonably approximated by concentration addition. The $Σ_{EAB}$ approach leverages high-throughput exposure-effects data for the 10,000 + organics and approximately 1000 vertebrate-cell-line molecular endpoints in the invivo
troDBv3.2 release to estimate potential cumulative activity at sensitive and possibly more protective sublethal molecular endpoints but has limited to no coverage of inorganic contaminants and unknown transferability to organ/organism scales. Importantly, the approach employed here aggregates contaminant bioactivity ratios across all endpoints without restriction to recognized modes of action as a precautionary screening for further investigation of potential effects but may not accurately reflect the apical effects that typically drive regulatory risk assessments. In contrast, the ΣTQ HI approach provides insight into potential effects of simultaneous inorganic and organic exposures and is targeted at apical human-health effects, but it is notably constrained to available regulatory risk determinations.

Only about half (32) of the 63 organics detected in TW in this study and only 5 of 12 detected DBP had exact Chemical Abstract Services (CAS) number matches in the ToxCast invitroDBv3.2 database (Figure S2; Table S10). Consistent with the presence of DBP in public supply and the generally infrequent and low-concentration detections of organics in private supplies, site-specific ΣEAR was higher (p = 0.0001) in public-supply TW (median: 0.0412) than in private supply (median: <0.00001) (Figure 6; Table S10). However, the highest EAR (and ΣEAR) in this study was observed in a private-well TW sample from community A with a concentration of 1-butanol more than 10 times that (ACC) shown to modulate molecular targets in vitro (i.e., solid red ΣEAR = 1 line). Individual EAR or ΣEAR near or above 0.1 in the seven surface-water-sourced TW samples from community B indicated an elevated probability of effects, driven primarily by the DBP, chlorodibromomethane. Exceedance of ΣEAR = 0.001 (precautionary screening-level threshold of interest) in all public-supply and five private-supply samples indicated that further investigation of the cumulative biological activity from SHWS area TW exposures is warranted, even when considering only the organic contaminants detected in this study.

Every TW sample exceeded the ΣTQ = 0.1 HI screening threshold of concern and all, but four, private-well TW samples exceeded ΣTQ = 1 (Table S12). These ΣTQ results indicate high probabilities of aggregated risks in SHWS private- and public-supply TW samples when considering exposures to both organic and inorganic chemicals (Figures 6 and S3; Table S13). ΣTQ was

Figure 6. Top. Individual EAR values (circles, ●) and cumulative EAR (ΣEAR, sum of all detected; red triangles, ▲) across all assays for 32 organic analytes listed in ToxCast and detected in public-supply (shaded) and private-supply (unshaded) TW samples collected during 2019 in North Dakota and South Dakota. Solid and dashed red lines indicate concentrations shown to modulate effects in vitro and effects-screening-level thresholds (EAR = 0.001), respectively. Bottom. Human health benchmark-based individual TQ values (circles, ●) and cumulative TQ (ΣTQ, sum of all detected; red triangles, ▲) for inorganic and organic analytes listed in Table S12 and detected in treated public-supply (shaded) and untreated private-supply (unshaded) TW samples. Solid and dashed red lines indicate benchmark equivalent concentrations and effects-screening-level threshold of concern (TQ = 0.1), respectively. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively, for both plots.
driven primarily by inorganics (As, Mn, Pb, and U) in private-well TW samples and by organics (DBP) and inorganics (As, Mn, Pb, and U) in public-supply TW samples. Site-specific HI were higher \( (p = 0.0009) \) in public-supply (median: 30.6) than in private-supply (median: 20.3) TW (Figure 7), with only modest differences \( (p = 0.0301) \) in community B public-supply (median: 89.6) versus private-supply (median: 80.2) samples. Common-place DBP-driven exceedance of HI screening-levels of concern in public-supply TW, in this study and previously,\(^\text{19,30,43,44}\) reemphasize the public-health tradeoff of chlorine disinfection.\(^\text{152,153}\) The importance of better understanding of the cumulative DBP health risks,\(^\text{152,154}\) and the need for improved DBP-precursor \( (\text{e.g., natural organic matter}) \) removal prior to disinfection.\(^\text{155,156}\) Likewise, frequent exceedances of the \( \Sigma_{\text{TQ}} \) HI screening level of 0.1 in unregulated and generally unmonitored private-supply TW in this and previous studies\(^\text{19,30,44}\) reiterate the inherent human-health challenge of unmonitored TW.\(^\text{6,12,21–23}\) Simultaneous co-occurring inorganic and organic exposures and corresponding potentials for cumulative effects add weight to previous recommendations for systematic private-supply monitoring,\(^\text{23}\) with an analytical scope that more realistically reflects the breadth of inorganic and organic environmental contamination.\(^\text{5,157}\)

### 3.9. Implications for Drinking-Water Treatment and TW Exposure Mitigation

The results indicate effective treatment of regulated contaminant exposures to below MCL levels in all public-supply TW samples in this study. Considering the multiple exceedances of health-only MCL\(^\text{G},7,9,23\) however, complete communication of public-supply TW monitoring results, including exposures below current MCL, is needed to support consumer POU-treatment decision-making. Likewise, the ongoing SHWS As intervention has documented an effective reduction of TW As exposures in private-well locations in the study area using POU adsorptive media.\(^\text{41}\) In light of growing evidence for human-health effects of exposures to currently unregulated TW contaminants \( (\text{e.g., unregulated DBP}^{154} \text{ and PFAS}^{158}) \) or to regulated contaminants at <MCL concentrations \( (\text{e.g., As}^{98} \text{ and NO}_3^{116}) \), common co-occurrences of multiple analytes with human-health implications in both private- and public-supply samples, including co-occurring exceedances of MCLG and \( \Sigma_{\text{TQ}} > 1 \), may reasonably raise consumer concerns\(^\text{159,160}\) and corresponding interest in POU/PF treatment.\(^\text{159}\) The median per sample number of health-benchmark exceedances in this study was two \( (\text{range: 0–5}) \), illustrating the importance of identifying stand-alone POU/PO treatment options for unregulated private-well TW, which are effective against multiple contaminants,\(^\text{159,160}\) and highlighting the potential value of POU treatment of public-supply TW for additional contaminant removal, including DBP.\(^\text{159}\)

Several POE/POU treatment technologies are effective in reducing TW exposures to the contaminants identified in this study.\(^\text{159}\) The protective-ness of POE/POU approaches depends on the selection of appropriate filtration technologies for exposures of concern, timely and effective maintenance, and monitoring to confirm acceptable performance. For locations in the study area where geogenic contaminants like As and U are the only exposures of apparent concern, single-stage configurations of multiple treatment technologies are appropriate, including solid-block activated carbon, ion exchange media, redox media, and reverse osmosis (RO).\(^\text{159,160}\) However, broadly effective single-stage treatment technologies, such as RO, or multistage/multifiltration systems \( (\text{sediment filter, redox media, activated carbon, ion exchange, RO, and UV disinfection}) \) may be more appropriate for those locations...
with mixtures of inorganic and organic contaminants or unknown contaminant-exposure profiles (i.e., unmonitored private wells).

4. CONCLUSIONS

Assessment and communication of TW contaminant exposures are essential to contaminant-risk-management and public-health decision-making at household and community scales. The perceived risks of and resultant resource commitments to drinking-water contaminant exposures are highly variable at both scales due to differences in availability of actionable drinking-water contaminant exposure/risk information, risk acceptability/tolerance thresholds, and overall exposure/risk portfolios (exposome). In the US, SDWA-stipulated annual public-supply consumer confidence reports support community and household-level decision-making, but decisions concerning additional community- or household-level treatment of public-supply TW are constrained by limited information on unregulated contaminants and on <MCL (or <AL) concentrations of regulated contaminants. Limited financial resources, water-quality expertise, and contaminant exposure data at the household scale fundamentally constrain private-supply decision-making and risk-mitigation options. Analytically extensive datasets like this study, which are intended to inform scientific and public-health understanding of the role of drinking water as a vector for human contaminant exposures and associated human-health outcomes, remain limited because broad assessment of regulated and unregulated contaminants are not generally conducted at the TW point of exposure in the US or worldwide.

These results indicate that simultaneous exposures to contaminants of human-health interest are common in both public- and private-supply TW locations across the study area. The bioactivity-weighted screening ($\Sigma_{EAR}$ and $\Sigma_{TO}$) results (Tables S10 and S13) indicate that exposures to DBP and inorganics at <MCL concentrations are the primary drivers of human-health interest in public-supply TW in communities B and C. These public-supply results align with the previous finding and support the need for better understanding of exposure-effect relations and cumulative health risks of regulated/unregulated DBP and for improved source-water pretreatment technologies to address DBP precursors, such as surface-water natural organic matter. Exposures to As and U in groundwater-sourced drinking-water supplies have been reported previously in the study area and the concentrations observed in public-supply TW herein were below corresponding NPDRW MCL. However, because there is no known safe level of exposure for either compound (i.e., MCLG zero), community and individual interests in improved drinking-water facility processes and household treatment options are reasonable. The benchmark-weighted screening ($\Sigma_{TO}$) results (Table S13) also indicate that exposures to inorganics often at concentrations above NPDRW MCL-equivalent concentrations are frequent drivers of potential human-health concerns for private-supply TW across the study area, along with more sporadic detections of Pb and other anthropogenic contaminants.

Thus, these results substantiate continued expanded and connection of public-supply systems to limit contaminant exposures to <MCL concentrations and incorporation of well-maintained POE/POU treatment as an integral complementary line of consumer protection for public-supply TW during normal and outbreak conditions and as prudent protection against unrecognized simultaneous exposures to multiple contaminants in private-supply homes. These results emphasize the importance of continued characterization of POU TW exposures, especially in unregulated and unmonitored private supplies and small community water supplies, using an analytical coverage that serves as a realistic indicator of the breadth and complexity of inorganic and organic contaminant mixtures known to occur in ambient source waters to support models of TW contaminant exposures and related risks. Increased availability of such health-based monitoring data, including results below current, technically/ economically constrained enforceable standards (e.g., MCL), is important to support public engagement in source-water protection and drinking-water treatment and to inform consumer POE/POU treatment decisions in these Tribal communities and throughout the US.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsestwater.2c00293.

Site information; compound information for analyses performed by various laboratories for the USGS; parameters and concentrations of analyzed major anions and cations; detected organic compounds; inorganic analyte detections; concentrations of the analytes detected in organic analyte quality assurance field blanks; surrogate recovery or internal dilution standard summary statistics; mammalian bioactivities; endpoint combinations excluded from ToxCast evaluation; site-specific EAR; and human-health-based benchmarks; and site-specific TQ (XLSX).

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

(1) Pierce, G.; Gonzalez, S. Mistrust at the tap? Factors contributing to public drinking water (mis) perception across US households. Water Pol. 2017, 19, 1–12.
(2) Doria, M. D. F. Factors influencing public perception of drinking water quality. Water Pol. 2010, 12, 1–19.
(3) Villanueva, C. M.; Kogevasins, M.; Cordier, S.; Templeton, M. R.; Vermeulen, R.; Nuckols, J. R.; Nieuwenhuijzen, M. J.; Levallois, P. Assessing exposure and health consequences of chemicals in drinking water: current state of knowledge and research needs. Environ. Health Perspect. 2014, 122, 213.
(4) Wang, Z.; Walker, G. W.; Muir, D. C. G.; Nagatani-Yoshida, K. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environ. Sci. Technol.* 2020, 54, 2575.

(5) Bradley, P. M.; Journey, C.; Romanok, K.; Barber, L.; Buxton, H. T.; Foreman, W. T.; Furlong, E. T.; Glassmeyer, S.; Hladik, M.; Iwanowicz, L. R.; Jones, D.; Kolpin, D.; Kuivila, K.; Loftin, K.; Mills, M.; Meyer, M.; Orlando, J.; Reilly, T.; Smalling, K.; Villeneuve, D. Expanded Target-Chemical Analysis Reveals Extensive Mixed-Organic-Contaminant Exposure in U.S. Streams. *Environ. Sci. Technol.* 2017, 51, 4792–4802.

(6) DeSimone, L. A.; McMahon, P. B.; Rosen, M. R. The quality of our Nation’s waters: water quality in Principal Aquifers of the United States, 1997–2010. USGS: Reston, VA, 2015; Vol. 1360, p 161.

(7) U.S. Environmental Protection Agency. *National Primary Drinking Water Regulations*, 2021. https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations (July 11, 2021).

(8) U.S. Environmental Protection Agency. 141: National Primary Drinking Water Regulations; U.S. Environmental Protection Agency: Washington, DC, 2021. 40 C.F.R.. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=339dba0247882184124429266bd34&ty=HTML$h=k&mc=true&pl=pt40.25.141&rt=PART#_top.

(9) U.S. Food & Drug Administration. *Bottled water*: Washington, DC, 2021; 21 C.F.R. § 165.110In 21 C.F.R.. https://www.ecfr.gov/current/title-21/part-165/subpart-B-section-165.110#page-top.

(10) U.S. Environmental Protection Agency Private drinking water wells, 2021. https://www.epa.gov/privatewells/ (March 30, 2021).

(11) Committee on Environmental Health and Committee on Infectious Diseases. Drinking water from private wells and risks to children. *Pediatrics* 2009, 123, 1599–1605 American Academy of Pediatrics.

(12) Rogan, W. J.; Brady, M. T. Drinking water from private wells and risks to children. *Pediatrics* 2009, 123, e1123–e1137.

(13) Zheng, Y. Lessons Learned from Arsenic Mitigation among Private Well Households. *Curr. Environ. Health Rep.* 2017, 4, 373–382.

(14) Wescoat, J. L.; Headington, L.; Theobald, R. Water and poverty in the United States. *Geosforum* 2007, 38, 801–814.

(15) Nigra, A. E. Environmental racism and the need for private well protections. *Proc. Natl. Acad. Sci. U.S.A.* 2020, 117, 17476–17478.

(16) Ayotte, J. D.; Medalie, L.; Qi, S. L.; Backer, L. C.; Nolan, B. T. Estimating the high-arsenic domestic-well population in the conterminous United States. *Environ. Sci. Technol.* 2017, 51, 12443–12454.

(17) Lombard, M. A.; Scannell Bryan, M.; Jones, D. K.; Bulka, C.; Bradley, P.; Backer, L.; Focazio, M.; Silverman, D.; Toccalino, P.; Argos, M.; Gribble, M.; Ayotte, J. D. Machine learning models of arsenic in private wells throughout the conterminous United States as a tool for exposure assessment in human health studies. *Environ. Sci. Technol.* 2021, 55, S012.

(18) Ayotte, J. D.; Belaval, M.; Olson, S. A.; Burow, K. R.; Flanagan, S. M.; Hinkle, S. R.; Lindsey, B. D. Factors affecting temporal variability of arsenic in groundwater used for drinking water supply in the United States. *Sci. Total Environ.* 2015, 505, 1370–1379.

(19) Lombard, M. A.; Daniel, J.; Jeddy, Z.; Hay, L. E.; Ayotte, J. D. Assessing the impact of drought on arsenic exposure from private domestic wells in the conterminous United States. *Environ. Sci. Technol.* 2021, 55, 1822–1831.

(20) Postma, J.; Butterfield, P. W.; Odom-Mayron, T.; Hill, W.; Butterfield, P. G. Rural children’s exposure to well water contaminants: Implications in light of the American Academy of Pediatrics’ recent policy statement. *J. Am. Acad. Nurse Pract.* 2011, 23, 258–265.

(21) Focazio, M. J.; Tipton, D.; Dunkle Shapiro, S. S.; Geiger, L. H. The chemical quality of self-supplied domestic well water in the United States. *Ground Water Monit. Remed.* 2006, 26, 92–104.

(22) MacDonald Gibson, J.; Pieper, K. Strategies to improve private-well water quality: A North Carolina perspective. *Environ. Health Perspect.* 2017, 125, 076001.
(38) Powers, M.; Sanchez, T. R.; Grau-Perez, M.; Yeh, F.; Francesconi, K. A.; Goessler, W.; George, C. M.; Heaney, C.; Best, L. G.; Uman, J. G.; Brown, R. H.; Navas-Acien, A. Low-moderate arsenic exposure and respiratory in American Indian communities in the Strong Heart Study. *Environ. Health Perspect.* 2019, 118, 104.

(39) Tinkel, N. E.; Spratlen, M. J.; Domingo-Relloso, A.; Tellez-Plaza, M.; Grau-Perez, M.; Francesconi, K. A.; Goessler, W.; Howard, B. V.; MacCluer, J.; North, K. E.; Uman, J. G.; Factor-Litvak, P.; Cole, S. A.; Navas-Acien, A. Associations of maternal arsenic exposure with adult fasting glucose and insulin resistance in the Strong Heart Study and Strong Heart Family Study. *Environ. Int.* 2020, 137, 105531.

(40) Grau-Perez, M.; Kuo, C.-C.; Gribble, M. O.; Balakrishnan, P.; Jones Spratlen, M. J.; Vaidya, D.; Francesconi, K. A.; Goessler, W.; Guallar, E.; Silbergeld, E. K.; Uman, J. G.; Best, L. G.; Lee, E. T.; Howard, B. V.; Cole, S. A.; Navas-Acien, A. Association of low-moderate arsenic exposure and arsenic metabolism with incident diabetes and insulin resistance in the Strong Heart Family Study. *Environ. Health Perspect.* 2017, 125, 127004.

(41) Powers, M.; Yracheta, J.; Harvey, D.; O’Leary, M.; Best, L. G.; Black Bear, A.; MacDonald, L.; Susan, J.; Hasan, K.; Thomas, E.; Morgan, C.; Olmedo, C.; Chen, R.; Rule, A.; Schwab, K.; Navas-Acien, A.; George, C. M. Arsenic in groundwater in private wells in rural North Dakota and South Dakota: Water quality assessment for an intervention trial. *Environ. Res.* 2019, 186, 41–47.

(42) Thomas, E. D.; Gittelsohn, J.; Yracheta, J.; Powers, M.; O’Leary, M.; Harvey, D. E.; Red Cloud, R.; Best, L. G.; Black Bear, A.; Navas-Acien, A.; George, C. M. The Strong Heart Water Study: Informing and designing a multi-level intervention to reduce arsenic exposure among private well users in Great Plains Indian Nations. *Sci. Total Environ.* 2019, 650, 3120–3133.

(43) Bradley, P. M.; Argos, M.; Kolpin, D. W.; Meppelink, S. M.; Romanok, K. M.; Smilling, K. L.; Focazio, M. J.; Allen, J. M.; Dietze, J. E.; Devito, M. J.; Donovan, A. R.; Evans, N.; Givens, C. E.; Gray, J. L.; Higgins, C. P.; Hladik, M. L.; Iwanowicz, L. R.; Journey, C. A.; Lane, R. F.; Laughery, Z. R.; Loftin, K. A.; McCleskey, R. B.; McDonough, C. A.; Medlock-Kakaley, E.; Meyer, M. T.; Putz, A. R.; Richardson, S. D.; Stark, A. E.; Weis, C. P.; Wilson, V. S.; Zehraoui, A. Mixed organic and inorganic tapwater exposures and potential effects in greater Chicago area, USA. *Sci. Total Environ.* 2020, 719, 137236.

(44) Bradley, P. M.; Padilla, I. Y.; Romanok, K. M.; Smilling, K. L.; Focazio, M. J.; Breitmeyer, S. E.; Cardon, M. C.; Conley, J. M.; Evans, N.; Givens, C. E.; Gray, J. L.; Gray, L.; Hartig, P. C.; Higgins, C. P.; Hladik, M. L.; Iwanowicz, L. R.; Lane, R. F.; Loftin, K. A.; McCleskey, R. B.; McDonough, C. A.; Medlock-Kakaley, E.; Merpelink, S.; Weis, C. P.; Wilson, V. S. Pilot-scale expanded assessment of inorganic and organic tapwater exposures and predicted effects in Puerto Rico, USA. *Sci. Total Environ.* 2021, 788, 147721.

(45) Moretto, A.; Bachman, A.; Boobis, A.; Solomon, K. R.; Pastoor, T. P.; Wilks, M. F.; Embry, M. R. A framework for cumulative risk assessment in the 21st century. *Crit. Rev. Toxicol.* 2017, 47, 85–97.

(46) Norton, S. B.; Rodier, D. J.; van der Schalie, W. H.; Wood, W. P.; Blackwell, B. R.; Ankley, G. T.; Corsi, S. R.; DeCicco, L. A.; Judson, K. A.; Li, R. S.; Martin, S.; Murphy, T. M.; Schroeder, E.; Smith, A.; Swintek, J.; Villeneuve, D. L. An “EAR” on environmental surveillance and monitoring: A case study on the use of exposure-activity ratios (EARs) to prioritize sites, chemicals, and bioactivities of concern in Great Lakes waters. *Environ. Sci. Technol.* 2017, 51, 8713–8724.

(47) Romanok, K. M.; Bradley, P. M.; McCleskey, R. B. Inorganic Concentration Results for Assessment of Mixed-Organic/Inorganic Chemical and Biological Exposures in North Dakota and South Dakota Tapwater. U.S. Geological Survey data release, 2019.

(48) Moretto, A.; Bachman, A.; Boobis, A.; Solomon, K. R.; Pastoor, T. P.; Wilks, M. F.; Embry, M. R. A framework for cumulative risk assessment in the 21st century. *Crit. Rev. Toxicol.* 2017, 47, 85–97.

(49) Norton, S. B.; Rodier, D. J.; van der Schalie, W. H.; Wood, W. P.; Slimak, M. W.; Gentile, J. H. A framework for ecological risk assessment (EAR) at the EPA. *Environ. Toxicol. Chem.* 1992, 11, 1663–1672.

(50) Hladik, M. L.; Focazio, M. J.; Engle, M. Discharges of produced waters from oil and gas extraction via wastewater treatment plants are sources of disinfection by-products to receiving streams. *Sci. Total Environ.* 2014, 466–467, 1085–1093.

(51) Furlong, E.; Noriega, M.; Kanagy, C.; Kanagy, L.; Coffey, L.; Burkhardt, M. Methods of the National Water Quality Laboratory. Chapter B10. Determination of human-use pharmaceuticals in filtered water by direct aqueous-injection high-performance liquid chromatography/tandem mass spectrometry. *U.S. Geological Survey Techniques and Methods. Book 5, Laboratory Analysis, 2015*; p 73.

(52) Fishman, M. J.; Friedman, L. C. Methods for determination of inorganic substances in water and fluvial sediments. *Methods of the National Water Quality Laboratory. Chapter B10, p 49*..

(53) Hoffman, G. L.; Fishman, M. J.; Garbarino, J. R. Methods of Analysis by the US Geological Survey National Water Quality Monitoring Laboratory: In-bottle Acid Digestion of Whole-water Samples. *U.S. Geological Survey Techniques and Methods. Book 5, Laboratory Analysis, 2015*; p 73.

(54) Hladik, M. L.; Focazio, M. J.; Engle, M. Discharges of produced waters from oil and gas extraction via wastewater treatment plants are sources of disinfection by-products to receiving streams. *Sci. Total Environ.* 2014, 466–467, 1085–1093.

(55) U.S. Environmental Protection Agency. *Lead and Copper Rule: A Quick Reference Guide*, 2008, (March 3, 2022).

(56) U.S. Environmental Protection Agency. *National Primary Drinking Water Regulations: Lead and Copper Rule Revisions - Pre-publication Version*; U.S. Environmental Protection Agency: Washington, DC, 2020; 40 C.F.R. § 141 and § 1420 C.F.R. § 141/142.

(57) Rose, D.; Sandstrom, M.; Murtagh, L. Methods of the National Water Quality Laboratory. Chapter B12. Determination of heat purgeable and ambient purgeable volatile organic compounds in water by gas chromatography/mass spectrometry. *U.S. Geological Survey Techniques and Methods. Book 5, Laboratory Analysis, 2016*; p 61.

(58) Sandstrom, M. W.; Kanagy, L. K.; Anderson, C. A.; Kanagy, C. J. Methods of the National Water Quality Laboratory. Chapter B11. Determination of pesticides and pesticide degradation products in filtered water by direct aqueous-injection liquid chromatography-tandem mass spectrometry. *U.S. Geological Survey Techniques and Methods. Book 5, Laboratory Analysis, 2015*; p 73.

(59) Graham, J. L.; Loftin, K. A.; Meyer, M. T.; Ziegler, A. Cyanotoxin mixtures and taste-and-odor compounds in cyanobacterial blooms from the Midwestern United States. *Environ. Sci. Technol.* 2010, 44, 7361–7368.
(65) Pfaff, J. D. Method 300.0. Determination of Inorganic Anions by Ion Chromatography. U.S. Environmental Protection Agency, 1993; p 30.
Revision 2.1; USEPA Method 300.0.
(66) Ball, J. W.; McCleskey, R. B. A new cation-exchange method for accurate field speciation of hexavalent chromium. Talanta 2003, 61, 305–313.
(67) Hergenreder, R. L. Trace Metals in Waters by GFAAS. In According with U.S. EPA and Health Canada Requirements; PerkinElmer, Inc.: Waltham, MA, 2011; p 5. https://www.perkinelmer.com/lab-solutions/resources/docs/PinAAcleTraceMetalsinWaterbyGFAAApNote.pdf.
(68) U.S. Environmental Protection Agency. Inductively Coupled Plasma-Optical Emission Spectrometry, 2014; p 35. Method 6010D; EPA SW-846 Update V, accessed November 2, 2017. https://www.epa.gov/sites/production/files/2015-12/documents/6010d.pdf.
(69) Wilson, V. S.; Bobseine, K.; Gray, L. E. Development and characterization of a cell line that stably expresses an estrogen-responsive luciferase reporter for the detection of estrogen receptor agonist and antagonists. Toxicol. Sci. 2004, 81, 69–77.
(70) Wilson, V. S.; Bobseine, K.; Lambright, C. R.; Gray, L. E., Jr. A novel cell line, MDA-kb2, that stably expresses an androgen- and glucocorticoid-responsive reporter for the detection of hormone receptor agonists and antagonists. Toxicol. Sci. 2002, 66, 69–81.
(71) Hartig, P. C.; Bobseine, K. L.; Britt, B. H.; Cardon, M. C.; Lambright, C. R.; Wilson, V. S.; Gray, L. E. Jr. Development of two androgen receptor assays using adenoviral transduction of MMTV-Luc reporter and/or hAR for endothrine screening. Toxicol. Sci. 2002, 66, 82–90.
(72) Hartig, P. C.; Cardon, M. C.; Lambright, C. R.; Bobseine, K. L.; Gray, L. E.; Wilson, V. S. Substitution of synthetic chimpanzee androgen receptor for human androgen receptor in competitive binding and transcriptional activation assays for EDC screening. Toxicol. Lett. 2007, 174, 89–97.
(73) Conley, J.; Evans, N.; Cardon, M.; Rosenthal, L.; Iwanowicz, L.; Hartig, P.; Schenck, K.; Bradley, P.; Wilson, V. Occurrence and in vitro bioactivity of estrogen, androgen, and glucocorticoid compounds in a nationwide screen of United States stream waters. Environ. Sci. Technol. 2017, 51, 4781–4791.
(74) Kolpin, D. W.; Hubbard, L. E.; Cwiertny, D. M.; Meppelink, S. M.; Thompson, D. A.; Gray, J. L. A comprehensive statewide spatiotemporal stream assessment of per- and polyfluoralkyl substances (PFAS) in an agricultural region of the United States. Environ. Sci. Technol. Lett. 2021, 8, 981−988.
(75) Childress, C.; Foreman, W.; Conner, B.; Maloney, T. New reporting procedures based on long-term method detection levels and some considerations for interpretations of water-quality data provided by the U.S. Geological Survey National Water Quality Laboratory. U.S. Geological Survey Open-File Report 99–193, 1999; p 19.
(76) U.S. Environmental Protection Agency. Guidelines Establishing Test Procedures for the Analysis of Pollutants; U.S. Environmental Protection Agency: Washington, DC, 2020; pp 319–322. 40 C.F.R. § 136In 40 C.F.R. § 136. http://www.ecfr.gov/cgi-bin/text-idx?SID=3c7868c6952ebe97926e8429ed9b8bad&mc=true&node=pt40.23.136&rgn=div5.
(77) Mueller, D. K.; Schertz, T. L.; Martin, J. D.; Sandstrom, M. W. Design, analysis, and interpretation of field quality-control data for water-sampling projects. U.S. Geological Survey Techniques and Methods Book 4, 2015; Chapter C4, p 54. DOI: 10.3133/tm4c4.
(78) Foreman, W. T.; Williams, T. L.; Furlong, E. T.; Hemmerle, D. M.; Stetson, S. J.; Jha, V. K.; Noriega, M. C.; Decess, J. A.; Reed-Parker, C.; Sandstrom, M. W. Comparison of detection limits estimated using single- and multi-concentration spike-based and blank-based procedures. Talanta 2011, 228, 122139.
(79) Hammer, Ō.; Harper, D. A.; Ryan, P. D. PAST: paleontological statistics software package for education and data analysis. Palaeontol. Electrorn. 2001, 4, 9.
(80) U.S. Environmental Protection Agency. Sustainable Futures/Pollution Prevention (P2) Framework Manual; U.S. Environmental Protection Agency: Washington, D.C., 2012; p 326. EPA-748-B12-001. https://www.epa.gov/sustainable-futures/sustainable-futures-p2-framework-manual.
(81) De Cicco, L.; Corsi, S. R.; Villeneuve, D.; Blackwell, B. R.; Ankley, G. T. toxExcel: Evaluation of Measured Concentration Data Using the ToxCast High-Throughput Screening Database or a User-Defined Set of Concentration Benchmarks. R package version 1.0.0, 2018, (May 1, 2018)
(82) R Development Core Team. R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing: Vienna, Austria, 2019. Version 3.5.2.
(83) Cedergreen, N.; Christensen, A. M.; Kamper, A.; Kudsk, P.; Mathiassen, S. K.; Streibig, J. C.; Sørensen, H. A review of independent action compared to concentration addition as reference models for mixtures of compounds with different molecular target sites. Environ. Toxicol. Chem. 2008, 27, 1621–1632.
(84) Altenburger, R.; Scholze, M.; Busch, W.; Escher, B. I.; Jakobs, G.; Krauss, M.; Krüger, J.; Neale, P. A.; Ait-Aissa, S.; Almeida, A. C.; Seiler, T.-B.; Brion, F.; Hilscherová, K.; Hollett, H.; Novák, J.; Schlichting, R.; Serra, H.; Shao, Y.; Tindall, A.; Tollesén, K. E.; Umbuzeiro, G.; Williams, T. D.; Kortenkamp, A. Mixture effects in samples of multiple contaminants - An inter-laboratory study with manifold bioassays. Environ. Int. 2018, 114, 95–106.
(85) Stalter, D.; O’Malley, E.; von Gunten, U.; Escher, B. I. Mixture effects of drinking water disinfection by-products: implications for risk assessment. Environ. Sci.: Water Res. Technol. 2020, 6, 2341.
(86) U.S. Environmental Protection Agency. EPA’s National Center for Computational Toxicology: ToxCast Database (invitroDB) Vers. S.0, 2020, accessed at https://doi.org/10.23645/epacomptox.6062623.v5.
(87) U.S. Environmental Protection Agency. ToxCast & Tox21 Summary Files from InvitroDB_v3, 2019, accessed at https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttmd.
(88) U.S. Environmental Protection Agency. Water Quality Standards; U.S. Environmental Protection Agency: Washington, DC, 2017; 40 C.F.R. § 131In 40 C.F.R. § 131.
(89) World Health Organization (WHO). Guidelines for Drinking-Water Quality, 2011; p 631. Fourth edition incorporating the first addendum. https://apps.who.int/iris/rest/bitstreams/1080656/retrieve.
(90) Norman, J. E.; Toccalino, P. L.; Morman, S. A. Health-Based Screening Levels for Evaluating Water-Quality Data, 2nd ed.; U.S. Geological Survey, 2018, (February 10, 2020)
(91) U.S. Environmental Protection Agency. How EPA Regulates Drinking Water Contaminants, 2021; https://www.epa.gov/dwregdev/how-epa-regulates-drinking-water-contaminants (July 11, 2021).
(92) Lapheah, B.; Lowry, J.; Ahdoot, S.; Baum, C.; Bernstein, A.; Bole, A.; Brumburg, H.; Campbell, C.; Pacheco, S.; Spanier, A.; Trasande, L.; Osterhoudt, K.; Paulson, J.; Sandel, M.; Rogers, P. Prevention of Childhood Lead Toxicity. Pediatrics 2016, 138, No. e20161493.
(93) Swift Bird, K.; Navarre-Stitchler, A.; Singh, K. Hydrogeological controls of arsenic and uranium dissolution into groundwater of the Pine Ridge Reservation, South Dakota. Appl. Geochem. 2020, 114, 104522.
(94) Foster, S. A.; Pennino, M. J.; Compton, J. E.; Leibowitz, S. G.; Kile, M. L. Arsenic drinking water violations decreased across the United States following revision of the maximum contaminant level. Environ. Sci. Technol. 2019, 53, 11478−11485.
(95) Nigra, A. E.; Sanchez, T. R.; Nachman, K. E.; Harvey, D. E.; Chillrud, S. N.; Graziano, J. H.; Navas-Acien, A. The effect of the Environmental Protection Agency maximum contaminant level on arsenic exposure in the USA from 2003 to 2014: an analysis of the National Health and Nutrition Examinations Survey (NHANES). Lancet Public Health 2017, 2, e513–e521.
(96) Welch, B.; Smit, E.; Cardenas, A.; Hystad, P.; Kile, M. L. Trends in urinary arsenic among the U.S. population by drinking water source: Results from the National Health and Nutritional Examinations Survey 2003–2014. Environ. Res. 2018, 162, 8–17.
(97) U.S. Environmental Protection Agency. 2018 Edition of the Drinking Water Standards and Health Advisories, 2018; p 20. EPA 822-F-
(116) Ward, M. H.; Jones, R. R.; Brender, J. D.; de Kok, T. M.; Weyer, P. J.; Nolan, B. T.; Villanueva, C. M.; van Breda, S. G. Drinking water nitrate and human health: an updated review. *Int. J. Environ. Res. Publ. Health* 2018, 15, 1557.

(117) Jones, R. R.; Weyer, P. J.; DellaValle, C. T.; Inoue-Choi, M.; Anderson, K. E.; Cantor, K. P.; Krasner, S.; Robien, K.; Freeman, L. E.; Silverman, D. T.; Ward, M. H. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. *Environ. Health Perspect.* 2016, 124, 1751–1758.

(118) Aschebrooke-Kilfoy, B.; Heltshle, S. L.; Nuckols, J. R.; Sabra, M. M.; Shuldiner, A. R.; Mitchell, B. D.; Airola, M.; Holford, T. R.; Zhang, Y.; Ward, M. H. Modeled nitrate levels in well water supplies and prevalence of abnormal thyroid conditions among the Old Order Amish in Pennsylvania. *Environ. Health* 2012, 11, 6.

(119) Brender, J. D.; Weyer, P. J.; Romitti, P. A.; Mohanty, B. P.; Shinde, M. U.; Vuong, A. M.; Sharkey, J. R.; Dwivedi, D.; Horel, S. A.; Kantomneni, J.; Huber, J. C.; Zheng, Q.; Werler, M. M.; Kelley, K. E.; Griesenbeck, J. S.; Zhan, F. B.; Langlois, P. H.; Suares, L.; Canfield, M. A. Prenatal nitrate intake from drinking water and selected birth defects in offspring of participants in the National Birth Defects Prevention Study. *Environ. Health Perspect.* 2013, 121, 1083–1089.

(120) McMahon, P. B.; Belitz, K.; Reddy, J. E.; Johnson, T. D. Elevated manganese concentrations in United States groundwater, role of land surface—soil—aquifer connections. *Environ. Sci. Technol.* 2019, 53, 29–38.

(121) Iyare, P. U. The effects of manganese exposure from drinking water on school-age children: A systematic review. *Neurotoxicology* 2019, 73, 1–7.

(122) Ramachandran, M.; Schwabe, K. A.; Ying, S. C. Shallow groundwater manganese merits deeper consideration. *Environ. Sci. Technol.* 2021, 55, 3465–3466.

(123) World Health Organization. *Manganese in Drinking-Water: Background Document for Development of WHO Guidelines for Drinking-Water Quality*, 2020; p 55. Version for public review. https://www.who.int/docs/default-source/wash-documents/wash-chemicals/gdwq-manganese-background-document-for-public-review.pdf?sfvrsn=9296741f_5

(124) Frébie, S. H.; Mitchell, E. J.; Sarkar, B. Urgent need to reevaluate the latest World Health Organization guidelines for toxic inorganic substances in drinking water. *Environ. Health* 2015, 14, 63.

(125) Vinceti, M.; Bonvicini, F.; Rothman, K. J.; Vescovi, L.; Wang, F. The relation between amyotrophic lateral sclerosis and inorganic selenium in drinking water: a population-based case-control study. *Environ. Health* 2010, 9, 77.

(126) Naderi, M.; Paar, P.; Zonouzi-Marand, M.; Chivers, D. P.; Niyoji, S.; Kwong, R. W. M. A comprehensive review on the neuropathophysiology of selenium. *Sci. Total Environ.* 2021, 767, 144329.

(127) Vinceti, M.; Crespi, C. M.; Malagoli, C.; Bottecchi, I.; Ferrari, A.; Sieri, S.; Krogh, V.; Alber, D.; Bergomi, M.; Seidenari, S.; Pellicani, G. A case-control study of the risk of cutaneous melanoma associated with three selenium exposure indicators. *Tumori J.* 2012, 98, 287–295.

(128) Laclaustra, M.; Navas-Acien, A.; Stranges, S.; Or dovás, J. M.; Guaraldi, E. Serum selenium concentrations and diabetes in U.S. adults. *National Health and Nutrition Examination Survey (NHANES) 2003-2004. Environ. Health Perspect.* 2009, 117, 1409–1413.

(129) Bleys, J.; Navas-Acien, A.; Guaraldi, E. Serum selenium and diabetes in U.S. adults. *Diabetes Care* 2007, 30, 829–834.

(130) Canadian Health. *Guidelines for Canadian Drinking Water Quality*, 2020; p 28. Summary Table. https://www.canada.ca/content/dam/hc-sc/migration/htc-sc/ewh-sgmt/alt_formats/pdf/pubs/water-ewau/sum_guide_res_recom/summary-table-EN-2020-02-11.pdf

(131) Directive (EU) 2020/2184, Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the Quality of Water Intended for Human Consumption. Directive (EU) 2020/2184; Council of the European Union, 2020; p 62. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020L2184&from=EN.
