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Tapwater exposures, residential risk, and mitigation in a PFAS-impacted-groundwater community†

Paul M. Bradley, [*a] Kristin M. Romanok, [b] Kelly L. Smalling, [b] Lee Donahue,[c] Mark P. Gaikowski, [d] Randy K. Hines, [d] Sara E. Breitmeyer, [e] Stephanie E. Gordon, [f] Keith A. Loftin, [g] Richard Blaine McCleskey, [h] Shannon M. Meppelink [i] and Molly L. Schreiner [b]

Tapwater (TW) safety and sustainability are priorities in the United States. Per/polyfluoroalkyl substance(s) (PFAS) contamination is a growing public-health concern due to prolific use, widespread TW exposures, and mounting human-health concerns. Historically-rural, actively-urbanizing communities that rely on surficial-aquifer private wells incur elevated risks of unrecognized TW exposures, including PFAS, due to limited private-well monitoring and contaminant-source proliferation in urbanizing landscapes. Here, a broad-analytical-scope TW-assessment was conducted in a hydrologically-vulnerable, Mississippi River alluvial-island community, where PFAS contamination of the shallow-alluvial drinking-water aquifer has been documented, but more comprehensive contaminant characterization to inform decision-making is currently lacking. In 2021, we analyzed 510 organics, 34 inorganics, and 3 microbial groups in 11 residential and community locations to assess (1) TW risks beyond recognized PFAS issues, (2) day-to-day and year-to-year risk variability, and (3) suitability of the underlying sandstone aquifer as an alternative source to mitigate TW-PFAS exposures. Seventy-six organics and 25 inorganics were detected. Potential human-health risks of detected TW exposures were explored based on cumulative benchmark-based toxicity quotients ($\sum_{TQ}$). Elevated risks ($\sum_{TQ} \geq 1$) from organic and inorganic contaminants were observed in all alluvial-aquifer-sourced synoptic samples but not in sandstone-aquifer-sourced samples. Repeated sampling at 3 sites over 52–55 h indicated limited variability in risk over the short-term. Comparable PFAS-specific $\sum_{TQ}$ for spatial-synoptic, short-term (3 days) temporal, and long-term (3 years quarterly) temporal samples indicated that synoptic results provided useful insight into the risks of TW-PFAS exposures at French Island over the long-term. No PFAS detections in sandstone-aquifer-sourced samples over a 3 year period indicated no PFAS-associated risk and supported the sandstone aquifer as an alternative drinking-water source to mitigate community TW-PFAS exposures. This study illustrated the importance of expanded contaminant monitoring of private-well TW, beyond known concerns (in this case, PFAS), to reduce the risks of a range of unrecognized contaminant exposures.

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Environmental significance

Historically-rural, actively-urbanizing communities that rely on surficial-aquifer private wells incur elevated risks of unrecognized tapwater exposures, including per/polyfluoroalkyl substance(s) (PFAS), due to contaminant-source proliferation in urbanizing landscapes and to owner-dependent and, thus, generally limited private-well monitoring. A broad-analytical-scope tapwater assessment was conducted in a hydrologically-vulnerable, Mississippi River alluvial-island community, where PFAS contamination of the shallow-alluvial drinking-water aquifer was previously documented, but more comprehensive contaminant characterization to realistically inform public-health decision-making was lacking. This study illustrated the importance of expanded contaminant monitoring of private-well tapwater, beyond known concerns (in this case, PFAS), to reduce the cumulative risk of a range of unrecognized contaminant exposures.

[a]U.S. Geological Survey, Columbia, South Carolina, USA. E-mail: pbradley@usgs.gov
[b]U.S. Geological Survey, Lawrenceville, New Jersey, USA
[c]Town of Campbell, Campbell, Wisconsin, USA
[d]U.S. Geological Survey, La Crosse, Wisconsin, USA
[e]U.S. Geological Survey, New Cumberland, Pennsylvania, USA
[f]U.S. Geological Survey, Kearneysville, West Virginia, USA
[g]U.S. Geological Survey, Lawrence, Kansas, USA
[h]U.S. Geological Survey, Boulder, Colorado, USA
[i]U.S. Geological Survey, Iowa City, Iowa, USA

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Introduction

Drinking water (DW) safety and sustainability are priorities in the United States (US) and globally due to the biological imperative for water and its resultant role as a critical and increasingly vulnerable route of potential human exposures to a wide range of environmental contaminants.[6–8] DW contamination by per and polyfluoroalkyl substance(s) (PFAS) is a growing public-health concern due to prolific industrial use and commercial product applications,[9,10] numerous potential surface sources[11–16] and routes to ground and surface DW resources,[6–9] widespread human DW exposures,[17–20] and pervasive occurrence in humans.[18,21–23] The growing list of recognized adverse human-health effects[24–27] includes cancer[28–31] and impacts on endocrine,[32–34] thyroid,[29,35] and immune[36–40] functions, and on birth outcomes.[23,41–43] PFAS DW contamination has been documented in private-well tapwater (TW),[44–48] public-supply TW,[19,46] and bottled water (BW).[49–54] A recent U.S. Geological Survey (USGS) national TW PFAS assessment of 716 locations (269 private-wells; 447 public supply) in all 50 US states, Puerto Rico, and the US Virgin Islands estimated exposure to at least one PFAS in about 45% of US DW.[19] Recent modeling indicates that 11–18 million (27–45%) private-well users in the conterminous US potentially rely on groundwater with detectable concentrations of PFAS.[55]

The risk of unrecognized exposures is notably higher for private-TW due to a comparative lack of information on associated contaminant exposures,[44–48] including PFAS.[19] PFAS have been monitored in public-supply by many US states for more than a decade,[56] by the United States Environmental Protection Agency (EPA) in large (>10 000 served) DW facilities since the third Unregulated Contaminant Monitoring Rule (UCMR3, 6 PFAS),[57] and more broadly by EPA (29 PFAS; small [<3300 served] to large [>10 000 served] facilities) under the ongoing fifth UCMR (UCRM5).[58] However, EPA is not authorized to regulate or monitor private-TW,[59] and about 14% of the US population relies on private wells for DW.[60] High analytical costs, lack of technical training and awareness, and conflation of aesthetic quality with safety severely limit homeowner monitoring of private-well TW. The TW-contaminant-exposure data gap in private-well-dependent remote and rural locations undermines individual and community DW risk-management decision making.[46,48,61]

The recent USGS national TW PFAS survey indicated similar overall probability of PFAS occurrence in private-TW and public-TW, with increasing probabilities of PFAS contamination for both in developed landscapes.[19] Thus, historically-rural, actively-urbanizing communities that depend on shallow, surficial aquifer sources incur elevated risks of unrecognized TW-contaminant-mixture exposures, including PFAS, due to combined vulnerabilities of limited private-well monitoring and proliferation of surface contaminant sources in urbanizing landscapes. For example, a recent study to inform community and end-user risk-management/-mitigation decision-making at hydrologically-vulnerable Cape Cod, Massachusetts;[46] which depends on a shallow, surficial sole-source DW aquifer[62–64] with documented PFAS concerns;[65,66] demonstrated broad exposures to a range of additional TW-contaminants of potential human-health concern, including metal, volatile organic chemical(s) (VOC), and wastewater-derived contaminants. Herein, the same broad-analytical-scope TW-assessment approach was applied to a hydrologically-vulnerable, alluvial-island, suburban community, where PFAS-contamination of the shallow DW aquifer has recently been documented but more comprehensive contaminant characterization to inform decision-making is currently lacking.

The Town of Campbell, Wisconsin (2020 population: 4284 (ref. 67)), is located on an alluvial island (French Island) in the Mississippi River, next to the city of La Crosse, Wisconsin (2020 population: 52 680 (ref. 67)), which owns and operates a regional airport and several municipal DW-supply wells on the northeastern corner of the island (Fig. 1). Persistent detection of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in excess of then existing Wisconsin Department of Health Services recommended enforcement standards and preventive action limits[68] in a municipal well during UCMR3 monitoring (2013–2015) prompted a 2020–2021 Wisconsin Department of Natural Resources (Wisconsin DNR) PFAS-

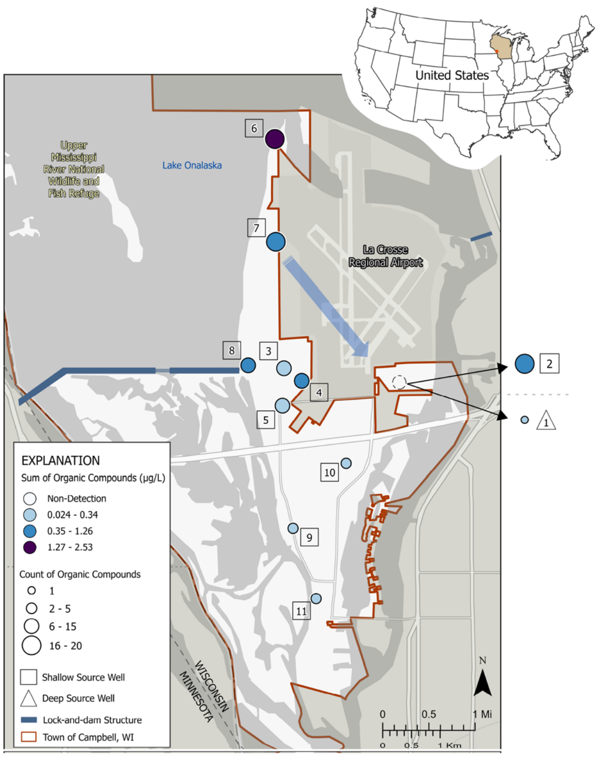

Fig. 1 Cumulative (sum of all detected) concentrations (µg L^{-1}) and numbers of organics detected in spatial-synoptic tapwater samples collected in 2021 at Town of Campbell, Wisconsin. TW samples from Sites 2–11 are sourced from the shallow alluvial-aquifer, which served as the principal drinking-water supply for residences and public facilities. Site 1 tapwater is sourced from the underlying, Mount Simon, sandstone aquifer. Arrow indicates general northwest to southeast groundwater flow direction within the alluvial aquifer. Basemap;[4] Town boundary.[5]

contamination investigation on the island.[69,70] Identification of PFAS-contamination source areas and events at the La Crosse Airport[71] triggered a 2021 island-wide DW advisory due to the then unknown extent of PFAS contamination in the French Island surficial DW aquifer.[69,70] A subsequent 2021 spatial surveillance of 200 private and 20 public-supply wells documented widespread private-well PFAS contamination.[72] Efforts to mitigate DW PFAS exposures include ongoing delivery of bottled water to affected residential locations and assessment of alternative DW sourcing from the underlying, confined, Mount Simon sandstone aquifer,[73] as a long-term solution.

The USGS Drinking Water and Wastewater Infrastructure Research Team[74,75] collaborates with federal and state agencies, Tribal nations, universities, utilities, and communities to inform contaminant-mixture exposures at the DW point-of-use (POU) and associated distal (*e.g.*, ambient source water) and proximal (*e.g.*, premise plumbing) drivers in a range of socioeconomic and source-water vulnerability settings across the US.[44–47,76–78] In 2021, we assessed exposures to a broad suite of potential inorganic/organic/microbial TW contaminants in 11 locations (residential, public) on French Island within the Town of Campbell to (1) provide insight into cumulative contaminant risk to human health[79–81] of private-well TW, (2) assess day-to-day and year-to-year variability in TW exposures, (3) more broadly assess potential shallow DW-aquifer contaminant-exposure concerns beyond recognized PFAS issues, (4) comprehensively characterize water quality in the underlying, Mount Simon, confined, sandstone aquifer currently under consideration as an alternative DW source (*i.e.*, long-term DW-exposure mitigation option), and (5) continue to expand the national perspective on contaminant-mixture exposures in POU DW by maintaining the same general sampling protocol and analytical toolbox employed in previous studies.[44–47,76–78]

For this study, TW exposures were operationally represented as concentrations of 510 organics, 34 inorganics, and 3 microbial groups in residential and community TW samples. Potential human-health risks of individual and cumulative TW exposures were explored based on effects-weighted quotients, including cumulative benchmark-based toxicity quotients ($\sum_{TQ}$)[46,82] for detected inorganics and organics and on cumulative molecular-scale, *in vitro* exposure-activity ratio(s) ($\sum_{EAR}$)[46,83] for detected organics.

Methodology

Site selection and sample collection

Individual private wells tapping the unconfined, shallow, alluvial aquifer comprise the principal DW source for public facilities and private residences on French Island. Because this study was conducted under SARS-CoV-2 pandemic and associated social-distancing constraints, TW samples for spatial and temporal variability assessments were collected primarily from Town of Campbell public buildings/facilities and from the USGS Upper Midwest Environmental Sciences Center (UMESC), with samples from 3 residential locations collected at externals taps to avoid entering homes.

TW samples for broad-scope target analysis of spatial variability were collected from Town of Campbell public building (Sites 3, 5, and 10), public park (Sites 4 and 6), and fire-department pump-station (Site 9) locations, UMESC (Sites 1 and 2), and three (Sites 7, 8, and 11) residences (Fig. 1). Locations were chosen to provide broad spatial coverage of the Town of Campbell, with emphasis on sites bordering the La Crosse Regional Airport, a documented source area for PFAS contamination in the shallow alluvial aquifer.[69,71,72] All taps (cold water) were sampled at least once during October 2021 (Table S1†). Except as noted below for the 3 days short-term variability samples, taps/faucets were sampled as is (*i.e.*, without pre-cleaning, screen removal, *etc.*) throughout the day without Lead and Copper Rule stagnant-sample protocols,[84,85] with one exception. A non-potable-brass hose adapter was removed from the potable fixture at Site 2 immediately prior to TW-sample collection, potentially resulting in metal-particulate surface contamination as discussed further below.

All TW samples were sourced from individual wells drawing from the surficial, alluvial, sand and gravel aquifer, except for Site 1 TW samples, which were sourced from a well (well 972; Fig. S1†) drawing from the underlying, Mount Simon, confined, sandstone aquifer[73] that is currently under consideration as a potential alternative DW supply for the Town of Campbell. For Site 1, the source-well construction was steel casing to a depth of 52 m below land surface (bls), with a 24 m open interval (*i.e.*, withdrawal depth) approximately 52–76 m bls.[86] For Site 2, TW was sourced from three UMESC source-water wells (wells 122–124), each constructed of steel with a total depth of approximately 23 m bls and a bottom-positioned 6 m stainless-steel screened interval approximately 17–23 m bls.[86] For all other spatial sampling locations, source-well construction was black steel, with total depths ranging approximately 14–25 m bls and bottom-positioned, 1 m stainless-steel screened intervals.[86] See Table S1† for all estimated withdrawal depths.

The lock-and-dam structure (Lock and Dam 7), which separates Lake Onalaska (Mississippi River Pool 7) from downstream Mississippi River and Black River sections (Pool 8), extends from the northeast corner of the La Crosse Regional Airport to the Wisconsin eastern bank and from near Site 8 to the Minnesota western bank (Fig. 1 and S1†). This configuration creates a general northwest to southeast hydrologic gradient and associated groundwater-flow direction in the highly transmissive, unconfined, surficial aquifer, with locally curving downstream flow lines around the dam structures.[71,73] TW Site 2 and corresponding surficial source wells (122–124) are located along the presumptive groundwater flowpath, downgradient from confirmed and suspected PFAS source areas (*e.g.*, burn pits, terminal apron, aqueous film-forming foam [AFFF] nozzle test area, fire station) at the airport.[71]

To assess short-term variability in TW contaminant-mixture exposures, Sites 1–3 were sampled for broad-scope target-analysis 6 more times each (total of 7 samples per site) over a 3 days period (Table S1†). For 3 consecutive days, a first-flush, 6 h over-night stagnant sample (consistent with Lead and Copper Rule stagnant-sample protocols[84,85]) was collected at each location in the morning, followed by a second afternoon sample collection approximately 6 h later. To assess potential premise-plumbing-derived contaminants, a one-time, immediate post-flush sample also was collected at each site on day 1, approximately 30 min after the first-flush sample.

Multi-year variabilities in TW PFAS exposures were assessed by quarterly sampling at UMESC (1st quarter 2021–1st quarter 2024), including the underlying Mount Simon sandstone aquifer source well for Site 1 TW (well 972, Fig. S1†) and the three, shallow, alluvial-aquifer, source wells (wells 122–124) for Site 2 TW. Complete sampling details are provided elsewhere.[87–89]

Analytical methods and quality assurance

Briefly, TW samples were analyzed by USGS for 510 unique organic analytes, 34 inorganic (ions/trace elements) analytes, 3 microbial indicators, and 3 field parameters (Table S2†), as discussed[44,46,76,87] and described in detail previously.[90–109] Organic analytes included cyanotoxin, disinfection byproduct(s) (DBP), pesticide, PFAS, pharmaceutical, and semi-volatile/volatile organic chemical (VOC collectively, herein) classes. Additional method details and all analytical results are in Tables S3, S4a and S5† and in Romanok *et al.*[1–3]

Quantitative (≥limit of quantitation, ≥LOQ) and semi-quantitative (between LOQ and long-term method detection limit, MDL[110,111]) results were treated as detections.[110,112,113] Quality-assurance/quality-control included analyses of 3 field blanks (Table S6†), as well as laboratory blanks, spikes, and stable-isotope surrogates (Table S4b†). Only nitrate–nitrogen (NO_3–N) was detected in inorganic blanks at concentrations in the range observed in TW samples; corresponding results were censored at the maximum blank concentration (0.01 mg L^{-1}), as footnoted (Tables S3 and S6†). Among the detected organics, only butyl benzyl phthalate (0.8 μg L^{-1}), diethyl phthalate (0.1 μg L^{-1}), and di-*n*-butyl phthalate (0.17 μg L^{-1}) were detected in any blank (once each) in the concentration range observed in TW samples; corresponding results were censored at 2 times the maximum blank concentration, as footnoted (Tables S4 and S6†). The median surrogate recovery (Table S4b†) was 102% (interquartile range [IQR]: 93.5–116%).

Risk and molecular-effects screening

A human-health DW-benchmark-based screening assessment of cumulative inorganic and organic contaminant risk ($\sum_{TQ}$) was conducted, consistent with World Health Organization/International Programme on Chemical Safety [WHO/IPCS] framework Tier 1 Hazard Index risk screening,[114] European Food Safety Authority Tier 1 Reference Point Index (RPI) risk screening,[115] and EPA Tier 1–2 cumulative risk screening[116–119] guidance, as described previously (*e.g.*,[45,78]). Potential molecular-level effects of mixed-organic contaminant exposures also were explored, using an exposure-activity ratio (EAR) approach based on Toxicity ForeCaster (ToxCast™)[120] high-throughput data,[121] as described previously (*e.g.*,[45,78]). ToxEval version 1.3.0 (ref. 122) of R[123] was used to sum (non-interactive concentration addition model[124–126]) individual benchmark-based TQ or ToxCast-based[127,128] EAR, respectively. For the former, the lowest benchmark concentration (*i.e.*, most protective human-health benchmark) among National Primary Drinking Water Regulation (NPDWR) maximum contaminant limit goal(s) (MCLG),[129,130] EPA Drinking-Water Health Advisories (DWHA),[131] WHO guidelines,[132] state MCL or DWHA,[133] or USGS Health-Based Screening Level(s) (HBSL) or Human Health Benchmark(s) for Pesticides (HHBP)[134] was used. MCLG values of zero (*i.e.*, set when there is evidence that chemical may cause cancer and there is no dose below which the chemical is considered safe, emphasizing vulnerable sub-populations, including infants, children, the elderly, and those with compromised immune systems and chronic diseases[130,135]) were set to 0.1 μg L^{-1} for metals (arsenic [As], lead [Pb], uranium [U]) and VOC and to 0.0001 μg L^{-1} for PFOS and PFOA, as described in detail.[136]

Human-health risks of individual and cumulative contaminant exposures are screened herein based on MCLG and other human-health advisories, for the following reasons. (1) EPA MCL/AL are applicable to public supplies only.[59,129,130] (2) Although set as close as feasible, MCL/AL take into account technical and financial constraints of DW monitoring and treatment and, consequently, are often higher than corresponding human-health-only MCLG targets.[135] (3) MCLG and health-advisory values generally include a margin of exposure to provide a safety threshold, in the case of MCLG defined as "the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, allowing an adequate margin of safety," and are determined in consideration of risks to presumptive "most vulnerable" (*e.g.*, infants, children, the elderly, those with compromised immune systems and chronic diseases) sub-populations.[135] MCLG is set at "zero" if "there is evidence that a chemical may cause cancer" and "there is no dose below which the chemical is considered safe".[135] Health-based benchmarks, $\sum_{TQ}$, ToxCast exclusions, and $\sum_{EAR}$ are summarized in Tables S7a and S8c.†

Results and discussion

Seventy-six (15% of analytes) organics (Fig. 1–3, S2–S3; Table S4a†) and 25 (76%) inorganics (Fig. 4 and Table S3†) were detected in French Island TW samples. The following sections address spatial and short-term (3 days) temporal variability in broad-scope TW-contaminant (*i.e.*, mixtures) exposures and respective potential human-health risks as well as longer-term (multi-year quarterly) variability in PFAS-specific exposures and potential human-health risks.

TW mixtures spatial synoptic

Regulated and unregulated organic/inorganic contaminants, beyond previously-documented PFAS, were detected in TW samples across French Island (Fig. 1–4, S2–S3, Tables S3, S4a and S5†), including at concentrations of potential human-health concern (Tables S7a and b†). In the following subsections, only the results for the first collection (day 1, morning) were included in the spatial-synoptic assessment, for locations (Sites 1–3) with multiple TW-sample collections (Table S1†).

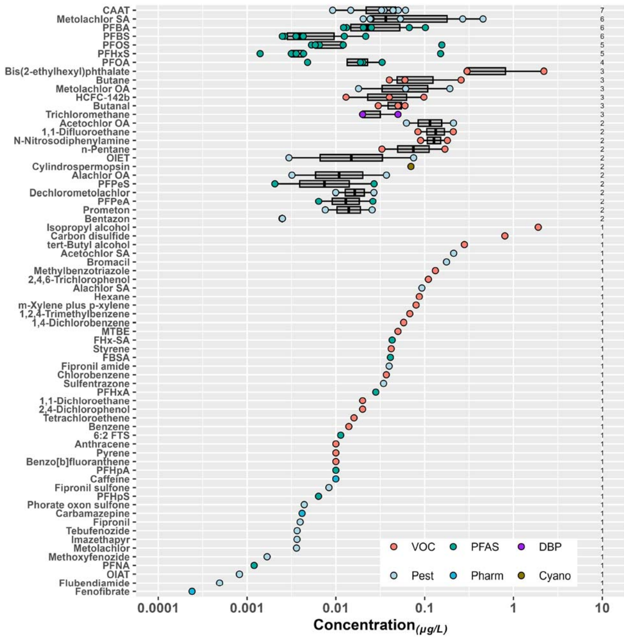

Fig. 2 Detected concentrations (μg L^{-1}) and number of sites (right axes) for 76 organic analytes (left axis, in order of decreasing total detections) detected in tapwater samples collected in 2021 at Town of Campbell, Wisconsin. Circles are data for individual samples. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively.

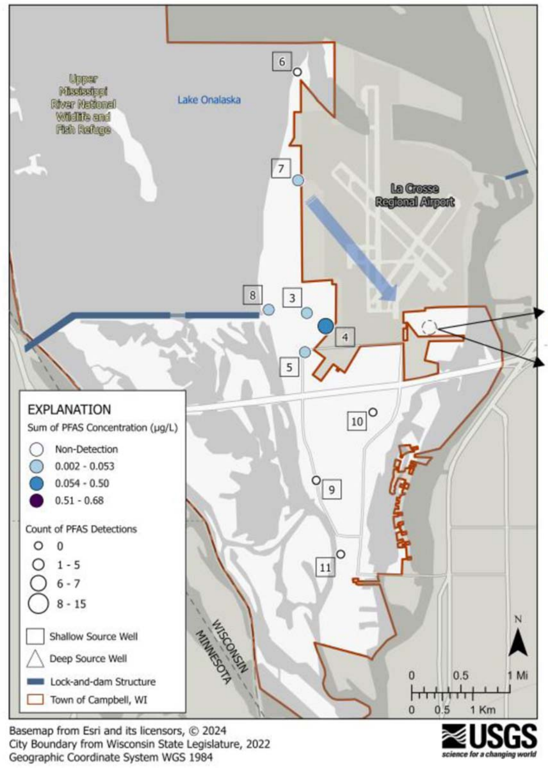

Fig. 3 Cumulative (sum of all detected) concentrations (μg L^{-1}) and numbers of per/polyfluoroalkyl substance(s) detected in spatial-synoptic tapwater samples collected in 2021 at Town of Campbell, Wisconsin. Tapwater samples from Sites 2–11 are sourced from the shallow alluvial-aquifer, which serves as the principal drinking-water supply for residences and public facilities. Site 1 tapwater is sourced from the underlying, Mount Simon, sandstone aquifer. Arrow indicates general northwest to southeast groundwater flow direction within the alluvial aquifer. Basemap;[4] Town boundary.[5]

Organic exposures and individual benchmark comparisons

French Island TW samples were screened for 4 cyanotoxins, 22 DBP, 213 pesticide, 32 PFAS, 112 pharmaceutical, and 141 VOC analytes, of which 16 were included in 2 methods resulting in 510 unique organic analytes (Table S2†). Seventy-six unique organic analytes were detected at least once across all sites (Fig. 1, 2 and Table S4a†). Multiple organic analytes (median: 12; IQR: 6–19; range: 2–20) were detected in all spatial-synoptic samples at cumulative concentrations ranging 0.06–2.53 μg L^{-1} (median: 0.696 μg L^{-1}; IQR: 0.342–2.00 μg L^{-1}).

As expected based on (1) previous PFAS assessment results at French Island,[70–72] (2) growing concerns for adverse effects of TW PFAS exposures,[24–27] and (3) corresponding promulgation of increasingly strict, federal-/state-level, drinking-water PFAS regulations and health-advisories,[56,137,138] multiple co-occurring PFAS were the primary TW organic exposures of recognized human-health concern, with common-place co-occurring detections of a range of additional organics including pesticides and VOC (Fig. 2, 3, S2 and Table S4a†). Consistent with previous findings,[70–72] PFAS detections and individual/cumulative concentrations (Fig. 3) observed in alluvial-aquifer-sourced (Sites 2–11) TW samples were greatest near and south of the airport (Sites 2–5, 7), with no PFAS detections in this study north of the airport (Site 6) or south of Interstate 90 (Sites 9–11). Cumulative PFAS detections and concentrations in spatial-synoptic TW samples ranged 0–14 (median: 2) and not detected (nd) up to 0.609 μg L^{-1} (median: 0.023 μg L^{-1}), respectively (Fig. 3). Likewise expected based on previous results,[71,72] the highest PFAS cumulative (14) and percent (70% of all organic) detections and cumulative (0.609 μg L^{-1}) and percent (56% of all organic) concentrations were observed in TW from Site 2, sourced from 3 shallow alluvial wells located along the presumptive flowpath downgradient of documented PFAS-use areas at the airport. In contrast, perfluorobutanoic acid (PFBA) was the only PFAS detected (0.025 μg L^{-1}) in TW from Site 1, sourced from the deeper sandstone aquifer.

Notably, the TW location with co-maximum cumulative detections (20; same as Site 2) and maximum cumulative concentrations (2.526 μg L^{-1}) was Site 6, a public water fountain (locked down during SARS-CoV-2 pandemic, except for sample collection) at the northern tip of French Island, up-gradient of the airport (Fig. 1). In contrast to Site 2, organic detections and cumulative concentrations at Site 6 were predominantly VOC (80% of organic detections; 99.5% of organic cumulative concentrations), consistent with proximal surface-water infiltration[73] and respective contamination of the shallow-alluvial-aquifer and with the location of Site 6 adjacent to and immediately down-gradient of a marina and public boat launch. Other notable contaminant profiles observed in alluvial-aquifer-sourced sample locations were the pesticide compositions of

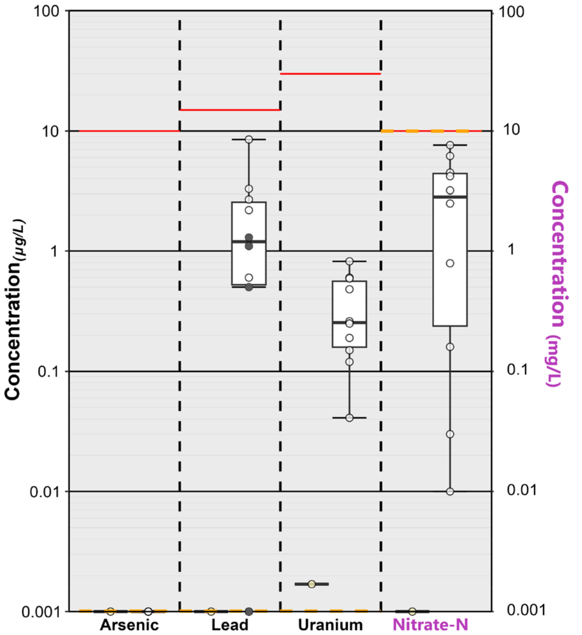

Fig. 4 Concentrations (circles, ●) of select inorganics (left Y-axis [µg L^{-1}]: arsenic [As], lead [Pb], uranium [U]; right Y-axis [mg L^{-1}]: nitrate–nitrogen [NO_3–N]) detected in spatial-synoptic tapwater samples collected in 2021 at Town of Campbell, Wisconsin. Solid red lines indicate public-supply enforceable maximum contaminant level(s) (MCL) or technology treatment action level (Pb only). MCL goals (MCLG; dashed orange lines) are 'zero' for As, U, and Pb and 10 mg L^{-1} (same as MCL) for NO_3–N. For each analyte, single result on the left is for Site 1 and boxes, centerlines, and whiskers on the right indicate interquartile range, median, and 5th and 95th percentiles, respectively, for Sites 2–11. For Pb, shaded circles indicate non-potable samples not included in the tapwater exposure and risk assessment.

samples at the western side of French Island, comprising 53% of detections and 64% of cumulative concentrations of organics detected at Site 7, increasing to 92% of detections and >99% of cumulative concentrations at Site 8, immediately adjacent to and upstream of the western lock-and-dam structure (Fig. 1 and S1†). The high percentage detections and concentrations of pesticides (predominantly herbicides and herbicide degradates) at Sites 7 and 8 are consistent with proximal infiltration of Mississippi River water into the shallow-alluvial aquifer upstream of the western lock-and-dam structure;[73] agricultural pesticide use and corresponding surface-water contamination are well-documented in Corn Belt drainage basins,[139] including the Mississippi River.[140–143] In contrast to the alluvial-aquifer-sourced synoptic samples, only 3 organics were detected in the TW sample from the sandstone-aquifer-sourced Site 1 location, with more than 95% of the detected concentration attributable to a one-time (*i.e.*, not detected in any subsequent Site 1 samples, as discussed below) detection of isopropyl alcohol, a commonplace household and commercial solvent.

Among the 76 organics detected in this study, 14 (18%) have EPA MCL/MCLG promulgated for public supply. Three (PFOS, PFOA, perfluorohexanesulfonic acid [PFHxS]) exceeded concentrations equivalent to respective, newly-established MCL and corresponding MCLG[137,138] in samples from 5, 4, and 1 spatial-synoptic locations, respectively, all alluvial-aquifer sourced. In addition to the above, bis(2-ethylhexyl)phthalate [DEHP], benzene, and tetrachloroethene [PCE] have MCLG of "zero", with DEHP detected in 3 spatial-synoptic locations and benzene and PCE detected once each (all *de facto* MCLG exceedances). Multiple MCLG exceedances per sample were common (7/10 or 70% of sites) in spatial-synoptic samples sourced from the shallow alluvial aquifer (Sites 2–10; median: 1.5; range: 0–3 per site); no MCLG exceedances were observed in the sandstone-aquifer-sourced Site 1 synoptic sample.

Inorganic exposures and individual benchmark comparisons

TW inorganic results of potential human-health concern included detections of uranium (U), lead (Pb), nitrate–nitrogen (NO_3–N), manganese (Mn), and fluoride (F), all at less than MCL-equivalent (90th percentile AL-equivalent[84,85,130] or WHO guideline[132] value of 10 µg L^{-1} for Pb) concentrations (Fig. 4 and Table S3†). Although detected U and Pb concentrations were well-below MCL-equivalent 30 µg L^{-1} and AL-equivalent 10 µg L^{-1} concentrations, respectively, both have MCLG of 'zero' ("chemical may cause cancer" and "there is no dose below which the chemical is considered safe"[135]) and, thus, corresponding detections (*de facto* MCLG exceedances) warrant discussion.

The redox-reactive geogenic radionuclide U was detected at low concentrations (median: 0.26 µg L^{-1}; IQR: 0.14–0.59 µg L^{-1}; range: 0.04–0.82 µg L^{-1}) in every shallow alluvial-aquifer-sourced sample (Sites 2–11) in this study (Fig. 4). The concentration of U detected in TW sourced from the deeper sandstone aquifer (Site 1) was 1–2 orders of magnitude less (0.002 µg L^{-1}). Drinking-water U exposure is associated with human nephrotoxicity[144–148] and osteotoxicity,[146,147,149] thyroid cancer,[150] inhibition of DNA-repair mechanisms in human embryonic kidney 293 (HEK293) cells,[151] estrogen-receptor effects in mice,[152] a range of reproductive endpoints in humans,[146,147,153] and elevated odds of type 2 diabetes.[154]

Including only samples from the 6 alluvial-aquifer-sourced sites with potable-tap collection points (Sites 2–6, 10), Pb was detected in 5 (83%) at concentrations ranging nd–8.5 µg L^{-1} (median: 2.7 µg L^{-1}; IQR: 1.4–5.9 µg L^{-1}) but was not detected in the Site 1 sandstone-aquifer-sourced TW sample (Fig. 4). Drinking-water Pb is attributed primarily to premise-plumbing and distribution-infrastructure materials[155] that predate 1986 SDWA amendments.[156] Accordingly, Pb detections in samples collected from non-potable (*i.e.*, outdoor spigots, fire-department pump station) tap locations (Sites 7–9, 11) were not included, due to unknown residential-exposure relevance. Based on associations with neurocognitive impairment in infants and children,[155,157,158] the American Academy of Pediatrics[157] recommends that drinking-water Pb not exceed 1 µg L^{-1}, a routine method detection limit for US public-supply compliance monitoring;[84,85] 66% (4/6) of potable-tap, shallow-aquifer-sourced samples exceeded 1 µg L^{-1}.

NO_3–N concentrations in alluvial-aquifer-sourced TW samples (median: 2.8 mg L^{-1}; IQR: 0.14–4.9 mg L^{-1}; range: nd–7.6 mg L^{-1}) also were below the respective MCL-equivalent (also

MCLG) 10 mg L^{-1} level (Fig. 4). The NO_3–N MCL was established to protect against bottle-fed infant (<6 months) methemoglobinemia.[130] However, growing evidence, which links <MCL NO_3–N concentrations with other adverse health outcomes,[159,160] including cancer,[161–166] thyroid disease,[167,168] and neural tube defects,[169] raises concerns for the human-health effects of long-term consumption of alluvial-aquifer-sourced TW at French Island. NO_3–N was not detected (MDL = 0.01 mg L^{-1}) in the Site 1 sandstone-aquifer-sourced sample.

No EPA MCL or MCLG[131] (or WHO guideline value[132]) presently exist for Mn. Instead, EPA maintains a federally non-enforceable, aesthetic-based National Secondary Drinking Water Standard secondary maximum contaminant level (SMCL) of 50 μg L^{-1} Mn,[170] a concentration determined, during the Contaminant Candidate List 1 (CCL1) process, to be below expected health-concern levels for the general population.[171] EPA established a 300 μg L^{-1} Mn life-time DW health advisory (assumes 100% exposure from drinking water),[131] and Wisconsin has set 300 μg L^{-1} as its public-welfare groundwater quality Enforcement Standard.[172] However, growing concerns for cognitive, neurodevelopmental, and behavioral effects of long-term Mn exposures in children have prompted calls for regulatory reevaluation,[173,174] and DW Mn is again undergoing regulatory determination under Contaminant Candidate List 5 (CCL5).[175] To protect against neurological effects in bottle-fed infants, WHO[176] has established a provisional guideline value of 80 μg L^{-1} Mn, a value exceeded in TW samples from 30% (3/10) of alluvial-aquifer-sourced locations (median: 22 μg L^{-1}; IQR: 1.75–88.2 μg L^{-1}; range: nd–203 μg L^{-1}), in the current study (Table S3†).

In addition to the above TW inorganic exposures of potential concern, all TW F concentrations observed in the spatial-synoptic assessment (median: 0.1 mg L^{-1}; range: nd–0.1 mg L^{-1}), including for the sandstone-aquifer-sourced sample (Site 1), were below the US Public Health Service[177] optimum of 0.7 mg L^{-1} to prevent dental caries (Table S3†), consistent with national groundwater results[178,179] and dental-health concerns for children on private-wells across the US.[180] The American Academy of Pediatrics[181] and Centers for Disease Control [CDC][182] recommend F supplementation for children with drinking-water concentrations <0.6 mg L^{-1} F.

Microbial exposures and benchmark comparisons

French Island TW samples also were screened in triplicate using heterotrophic plate (HPC), total coliform, and *Escherichia coli* (*E. coli*) counts as indicators of microbial exposures (Table S5†). General heterotrophs (HPC) were detected in all synoptic TW samples (median: 13.4 colony forming units per mL [CFU mL^{-1}]; IQR: 6–52 CFU mL^{-1}; range: 1.8–>200 CFU mL^{-1}), exceeding the quantitation limit ("too numerous to count" >200 CFU mL^{-1}) in one sample. HPC bacteria are ubiquitous, common in DW, and not intrinsic health concerns but are useful indicators of system maintenance,[130,131] which would include routine disinfection in private wells.[59] Total coliform bacteria were detected only in 2 shallow-alluvial-aquifer locations (Site 4: park water fountain; Site 9 fire department water-filling station), both outdoor fixtures for which some level of fixture-surface contamination (and corresponding initial sample contamination) is expected. Although the MCLG for total coliforms in TW is zero,[130,131] the lack of total coliform detections in any other alluvial-aquifer TW samples contradicts systematic microbial contamination of the shallow-groundwater system. No spatial-synoptic TW samples were positive for *E. coli* (fecal indicator bacteria).

Cumulative organic and inorganic chemical risk screening

Widespread co-occurring exposures to organic and inorganic contaminants of human-health concern in alluvial-aquifer-sourced samples suggest potential cumulative risk, at a minimum to the health of the island's most vulnerable populations. Accordingly, we screened for TW risk employing a $\sum_{TQ}$ approach that provides insight into potential effects of simultaneous inorganic and organic exposures, is targeted at apical human-health effects, but is notably limited to available human-health benchmarks. Of the 101 total chemical analytes (25 inorganic; 76 organic) detected in the study, 56% (13 inorganic; 44 organic) have available human-health benchmarks focused on risks to presumptive most-vulnerable populations (Fig. S4 and Table S7a†). Every alluvial-aquifer-sourced (Sites 2–11) synoptic sample exceeded $\sum_{TQ} = 1$ (Fig. 5, S5 and Table S7b†), indicating high probabilities of aggregated risks in French Island private-supply TW samples when considering exposures to both organic and inorganic chemicals. All but 2 alluvial-aquifer-sourced sites (Sites 9 and 11: U only) had

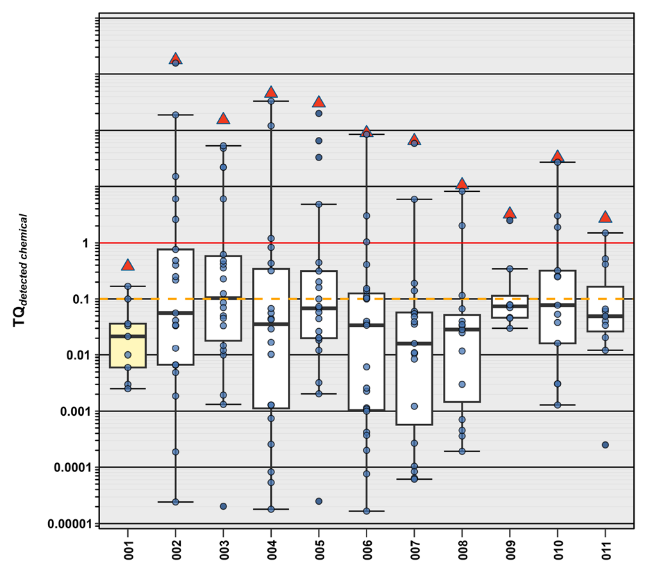

Fig. 5 Human-health benchmark-based individual toxicity quotient (TQ) values (circles, ●) and cumulative TQ (Σ_{TQ}, sum of all detected; red triangles, ▲) for inorganic and organic analytes with benchmarks in Table S7a† and detected in spatial-synoptic tapwater samples collected in 2021 at Town of Campbell, Wisconsin. Solid-red and orange-dashed lines indicate benchmark-equivalent level (TQ = 1) 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.

multiple individual TQ ≥ 1 (median: 3; IQR: 1.75–4.25; range: 1–5), comprising, in decreasing detection frequency, U (9/10 sites), Pb (5/6 potable-tap sites only), PFOS (5/10), PFOA (4/10), DEHP (3/10), and Mn (2/10). Frequent exceedances of $\sum_{TQ} = 1$ in unregulated and generally unmonitored private-supply TW in this and previous studies[44–48] emphasize the intrinsic human-health challenge of unrecognized contaminant exposures in unmonitored TW.[61,179,183–185] Growing documentation of co-occurring inorganic and organic exposures and corresponding cumulative human-health-effects potentials support previous recommendations for systematic private-supply monitoring,[61] incorporating a broad analytical scope that more realistically reflects the range of inorganic and organic environmental contamination.[186,187]

In contrast, the $\sum_{TQ}$ for the sandstone-aquifer-sourced Site 1 synoptic sample was 0.38 and primarily attributable to one-time detections of the cyanotoxin cylindrospermopsin and elevated (4 times higher than all other detections) boron (B) concentrations (Fig. 5, S5 and Table S7b†). Compared to alluvial-aquifer-sourced TW, the Site 1 results indicate substantially lower cumulative risk and support consideration of the sandstone aquifer as an alternative DW source to mitigate human exposures to a wide range of TW-contaminant exposures of human-health concern, including PFAS.

Cumulative organic EAR screening

To explore possible additional (beyond those with available benchmarks) TW-organic exposures of potential human-health interest at French Island, an EAR approach based on ToxCast[120] high-throughput data[121] was employed to screen for potential molecular-level effects of mixed-organic-contaminant exposures. The $\sum_{EAR}$ approach[46,83] leverages high-throughput exposure-effects data for 10 000+ organics and approximately 1000 vertebrate-cell-line molecular endpoints[120,188] in the invitroDBv3.2 release[189] of the ToxCast database to estimate potential cumulative activity at sensitive and perhaps more protective sublethal molecular endpoints but has limited to no coverage of inorganic contaminants and unknown transferability to organ/organism scales.[190] Notably, herein we aggregated contaminant bioactivity ratios across all endpoints without restriction to recognized modes of action as a precautionary screening for further investigation, but not as a direct indicator of health risk, due to uncertainties extrapolating from *in vitro* to *in vivo* (apical) effects[83,190–192] and the fact that not all bioactivities captured in ToxCast are necessarily adverse and may, in some instances (*e.g.*, xenobiotic-metabolism activation[193]), reflect adaptive responses.

Forty-seven of the 76 organics detected in TW in this study had exact Chemical Abstract Services (CAS) number matches in the ToxCast invitroDBv3.2 database; among these, 38 had at least one individual EAR $\geq$0.00001 and were included in the $\sum_{EAR}$ assessment (Fig. S6 and Table S8b†). The EAR ($\sum_{EAR}$) results aligned with the cumulative-risk ($\sum_{TQ}$) assessment discussed above, with exceedances of $\sum_{EAR} = 0.001$ (precautionary screening-level threshold of interest) observed in all synoptic TW samples. The results indicate further investigation of the cumulative biological activity from TW exposures is warranted, even when considering only the organic contaminants detected in this study. No exceedance of an *in vitro* effects level (*i.e.*, solid red $\sum_{EAR} = 1$ line) was observed. Individual EAR (and $\sum_{EAR}$) above 0.1 in TW samples collected from DW fountains in 2 parks (Sites 4 and 6) indicated elevated probability of molecular-effects and were attributable to *N*-nitrosodiphenylamine.

TW-mixtures exposure: 3 days temporal assessment

To inform the short-term (few days) representativeness of the one-time synoptic TW samples and potentially provide insight into contaminant sourcing (*e.g.*, groundwater system, premise-plumbing, TW-fixture surface), short-term variability in TW contaminant-mixture exposures was assessed in a total of 7 samples each collected from Sites 1–3 over a 3 days period using the same broad-scope target-analysis approach employed in the spatial synoptic. This discussion focuses on those detections of potential human-health concern discussed above and on summary metrics for inorganic and organic TW detections; however, all results are provided in Tables S3, S4 and S7b.† Short-term (53 h–55 h total) temporal variability in individual and cumulative TW-mixture exposures and associated risks (TQ, $\sum_{TQ}$) was limited in this study (Fig. S7 and Table S7b†), with two exceptions comprising (1) elevated individual concentrations detected in an initial sample but not sustained in subsequent site-specific samples and (2) substantially lower concentrations in immediate post-flush (2nd sample day 1) TW samples than observed in any other site-specific TW samples.

Elevated initial-sample exposures and risks included organics (Site 1: isopropyl alcohol, cylindrospermopsins; Site 3: DEHP) and inorganics (Site 2: Pb), detected in the first sample but not thereafter, and boron (B), detected in the first sample collected at Site 1 at a concentration (84 μg L^{-1}) greater than 4 times that observed in any other sample (range: 13–20 μg L^{-1}) from this location (Table S7b†). These one-time anomalous detections were ascribed to probable contamination at the collection point (TW fixture) and not to source-water contaminants. Because the focus of this and previous studies is better understanding of TW-contaminant exposures to humans regardless of where/when the contaminant is introduced, taps are sampled as is (*i.e.*, without any alteration/cleaning of the fixtures) and some potential for fixture-surface-derived contamination (*e.g.*, isopropyl alcohol from SARS-CoV-2 disinfection activities; B from borate-containing cleaning products) exists during sample collection, as it also does during residential TW use. Metal-particulate contamination resulting from the removal of a non-potable-brass hose adapter immediately prior to TW-sample collection is a plausible explanation for the one-time detection of Pb (0.6 μg L^{-1}) in the initial Site 2 TW-sample.

Contaminants which exhibited lower concentrations in immediate post-flush (*i.e.*, 2nd sample) TW samples (Table S7b†), notably at Site 3 and to lesser extents at Sites 1 and 2, than in other site-specific TW samples, were attributed as premise-plumbing derived. The order of magnitude lower copper (Cu) concentration (30 μg L^{-1}) observed post-flush, compared with other TW samples (median: 460 μg L^{-1}; range:

332–617 μg L^{-1}) at Site 3, is consistent with plumbing-derived contamination, as, to a lesser extent, are post-flush non-detect and 10 μg L^{-1} Cu results compared to median concentrations of 9 μg L^{-1} (range: 5–17 μg L^{-1}) and 45 μg L^{-1} (range: 29–74 μg L^{-1}) at Sites 2 and 1, respectively. As noted above, detections of Pb in TW (*i.e.*, concentrations greater than 1 μg L^{-1} MDL common to public-supply regulatory monitoring) are generally attributed to legacy use in distribution-system and premise-plumbing infrastructure.[155] In light of the Cu results, the 50% lower Pb concentration (1.4 μg L^{-1}) in the Site 3 post-flush sample, compared with the other TW samples (median: 3.2 μg L^{-1}; range: 2.2–4.3 μg L^{-1}) collected at the site, combined with sporadic detection of Pb in alluvial-aquifer synoptic TW samples collected from potable taps, are consistent with premise-plumbing as the probable source of TW Pb detection, rather than an alluvial-aquifer source.

Source attribution of the elevated TW zinc (Zn) exposures observed in the French Island alluvial-aquifer TW samples, however, is less clear (Table S7b†). TW Zn exposures (median: 177 μg L^{-1}; IQR: 63–726 μg L^{-1}; range: 21–968 μg L^{-1}) and associated risk (TQ) estimates (median: 0.088; IQR: 0.031–0.363; range: 0.010–0.484) varied substantially in alluvial-aquifer spatial-synoptic samples. The 48% lower Zn concentration in the Site 2 post-flush sample (557 μg L^{-1}), compared with the other TW samples (median: 1080 μg L^{-1}; range: 968–1280 μg L^{-1}) collected at the site, indicate that premise-plumbing may contribute in part to TW Zn exposures at Site 2. However, continued detection of substantial Zn concentrations post-flush at Site 2, the lack of a post-flush depression in Zn concentrations at Site 3, and the notable spatial variability in TW Zn exposures in spatial-synoptic samples raise the possibility of elevated groundwater Zn concentrations of potential human-health interest in the shallow-alluvial aquifer at French Island.

Remarkably, little variability was observed for individual or cumulative PFAS concentrations and associated risks in TW samples from Site 2 (Fig. S7; Tables S4 and S7b†), where concentrations were well above method detection limit(s) (MDL). In contrast, detected (*de facto* MCLG 'zero' exceedances) concentrations of the high-risk contaminants, PFOA and PFOS, in Site 3 TW samples were near the MDL; thus, while little variability in detected concentrations of PFOA and PFOS was observed at Site 3, intermittent non-detection of these compounds resulted in substantial variability in cumulative risk ($\sum_{TQ}$). Notably, concentrations of PFBA, the only PFAS detected at Site 1, decreased over time in the sandstone-aquifer-sourced samples, and PFBA was not detected in the last three samples. This finding raised the possibility that early-sample detections at Site 1 may have originated from fixture-surface or proximal premise-plumbing contamination and not from source-water contamination. As discussed in the following section, PFBA was not detected in 2021–2024 quarterly PFAS samples collected from the Site 1 source well (well 972), supporting the hypothesized fixture/premise-plumbing origin for PFBA contamination detected in the early short-term-variability samples at Site 1.

Consistent with the limited short-term variability in individual and cumulative TW exposures, little variability in cumulative risk ($\sum_{TQ}$) was observed in TW samples from Sites 1–3 (Fig. S7 and Table S7b†). A median-absolute-difference-based, nonparametric, robust coefficient of variation (RCV_{MAD}[194]) was calculated to evaluate short-term $\sum_{TQ}$ variability. The $\sum_{TQ}$ short-term variability (RCV_{MAD}) was approximately 42% for TW samples collected at Site 1 ($\sum_{TQ}$ median: 0.133; IQR: 0.119–0.276; range: 0.096–0.380), due primarily to the unrepeated, initial-sample detection of cylindrospermopsin (Table S4a†) and elevated B (Table S3†), as discussed. RCV_{MAD} at Site 3 was approximately 28% ($\sum_{TQ}$ median: 112; IQR: 73–131; range: 36–153) and largely attributed to circa-MDL detections and corresponding intermittent non-detections of PFOA and PFOS at the Site, as discussed. At Site 2, where PFAS concentrations were well-above MDL, RCV_{MAD} was substantially lower at approximately 12% ($\sum_{TQ}$ median: 1775; IQR: 1629–1935; range: 1607–1976).

The results indicate that the spatial-synoptic assessment provided reasonable insight into the risk of TW-mixture exposures at French Island over the short-term, and that corresponding cumulative TW-contaminant risks ($\sum_{TQ}$) were relatively stable. Further, the results illustrated the additional interpretive insight into TW-contaminant sourcing afforded by temporal sampling. Importantly, consistently lower $\sum_{TQ}$ for Site 1 short-term variability samples corroborated substantially lower cumulative risk in sandstone-aquifer-sourced TW samples compared to alluvial-aquifer-sourced samples and supported the use of the sandstone aquifer as an alternative DW source to mitigate human exposures to a wide range of TW-contaminant exposures of human-health concern, including PFAS.

TW-PFAS exposure: multi-year temporal assessment

Multi-year variabilities and trends in TW PFAS exposures were assessed by quarterly sampling at UMESC during February 2021 to March 2024, including from the underlying Mount Simon sandstone aquifer source well for Site 1 TW (well 972) and the three, shallow-alluvial-aquifer, source wells (wells 122–124) for Site 2 TW (Fig. 1; Tables S9a and b†). During this 3 year period, PFAS were continuously detected in samples from wells 122–124 (Fig. 6), documenting persistent PFAS contamination of the shallow-alluvial-aquifer DW source and corresponding persistent TW-exposure risks (*i.e.*, $\sum_{TQ} \gg 1$; Fig. S8†) to human-health. Kendall Tau rank correlation indicated no statistical ($a = 0.05$) trend in total PFAS (p-value range: 0.153–0.590) or PFOA (p-value range: 0.178–0.945) concentrations in any samples from wells 122–124 or in PFOS (p-value range: 0.459–0.841) concentrations in samples from wells 122–123. A statistical (Kendall's Tau p-value = 0.021) decrease in PFOS concentrations of approximately 22% was observed in samples from well 124 during the 3 year period. In contrast to the shallow alluvial well results, no PFAS were detected in well 972 samples over the 3 year period (Fig. 6 and Table S9a†), apart from a single, unrepeated detection of perfluorobutanesulfonic acid (PFBS) below the method detection limit (MDL), indicating no PFAS-associated human-health risk (*i.e.*, $\sum_{TQ} < 0.01$; Fig. S8†) from corresponding TW consumption and supporting managed utilization of the sandstone aquifer as an alternative DW source

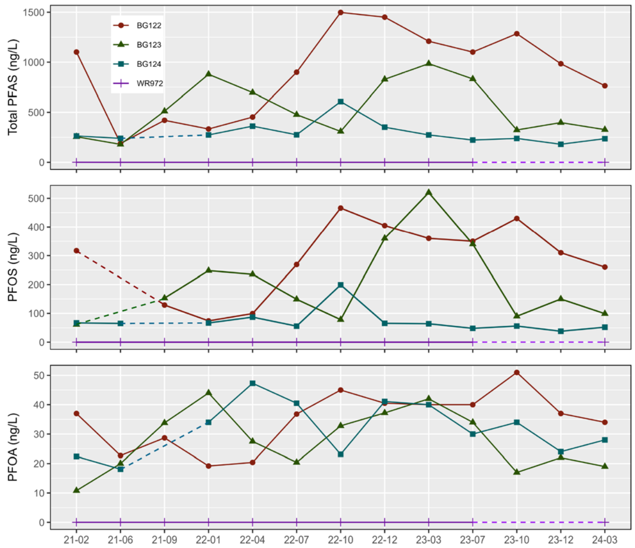

Fig. 6 Concentrations (μg L^{-1}) of total per/polyfluoroalkyl substances (total PFAS, top), perfluorooctane sulfonate (PFOS, middle), and perfluorooctanoic acid (PFOA, bottom) detected during quarterly monitoring of Site 1 (972) and Site 2 (122–124) source wells, during 2021–2022. Dashed lines indicate samples not collected or missing.

to mitigate TW-PFAS exposures to French Island residents. Comparable PFAS-specific cumulative risk ($\sum_{TQ}$) estimates for synoptic (*i.e.*, 1st sample), short-term (3 days) temporal, and long-term (3 years) assessment samples (Fig. S8†) indicated that the spatial-synoptic assessment also provided reasonable insight into the risks of TW-PFAS exposures at French Island over the long-term, and that corresponding cumulative TW-contaminant risks ($\sum_{TQ}$) were relatively stable.

Study limitations

Several limitations deserve consideration when interpreting the results of this study. First, the extensive and environmentally-informative target-analytical scope employed in this and previous studies by the research group is only a fractional indicator of the estimated 350 000 commercially produced chemicals (not including environmental transformation products and degradates) potentially present in the environment;[195] thus, the cumulative TW exposure and associated risk assessments presented herein are potential orders-of-magnitude underestimates. Second, the $\sum_{TQ}$ and $\sum_{EAR}$ approaches employed herein are constrained by available weighting-factors; human-health benchmarks and ToxCast ACC were available for 55% of detected inorganic/organic TW constituents and 50% of detected organics, respectively. Third, for both approaches, approximate concentration addition was assumed (*e.g.*, (ref. 124, 126, 196 and 197), potentially underestimating or overestimating cumulative effects in the event of synergism/potentiation or antagonism, respectively;[198] while documented,[199–202] departures from approximate concentration addition are considered comparatively rare, increasingly unlikely with increasing number of mixture components, and typically within one order of magnitude.[197,203,204] Fourth, EAR estimates were aggregated across all ToxCast endpoints without restriction to recognized modes of action to provide a precautionary lower-bound estimate of *in vivo* adverse-effect level,[205] a useful approach for bioactivity screening but not necessarily indicative of adverse apical effects.[83,190] Fifth, the PFAS results reflect then-available methods, with reporting limits generally above current PFAS human-health concern levels (*e.g.*, 2024 PFAS MCLG and associated benchmarks[137,138]), and, thus, should be considered underestimates of TW PFAS exposures and risks; methods with reporting limits ≤1 ng L^{-1} are available now (*e.g.*,[206]). Sixth, MCLG values of 'zero' were set to 0.1 μg L^{-1} for metals and VOC and to 0.0001 μg L^{-1} for PFOS and PFOA to avoid overinflating TQ estimates, but this approach may not be sufficiently precautionary for toxicities like endocrine disruption and carcinogenicity. Lastly, the extensive analytical scope employed in this study provided critical and actionable insight into potential residential and public-facility TW-contaminant exposures to inform exposure-mitigation decision-making at individual-household and community levels, but the limited number of samples and sample locations may not represent the full range of source-water- and premise-plumbing-derived TW-exposures on French Island.

Conclusions

The broad-analytical-scope spatial synoptic results indicated that simultaneous exposures to contaminants of human-health interest are common in alluvial-aquifer-sourced TW locations across the study area. The human-health-benchmark-based $\sum_{TQ}$ results indicated that exposures to PFAS, including above MCL concentrations, are the primary drivers of human-health risks from shallow alluvial-aquifer-sourced TW exposures for locations adjacent to and downgradient of the municipal airport. However, comparable $\sum_{TQ}$ results attributable to inorganic and VOC exposures in several TW samples without detectable PFAS (collected upgradient of the airport and south of Interstate 90), illustrated that human-health risks from shallow alluvial-aquifer-sourced TW-contaminant exposures are widespread and not solely attributable to PFAS (Fig. S5†).

Common co-occurrences of multiple analytes with human-health implications in private-well TW samples, including co-occurring exceedances of MCLG and $\sum_{TQ} > 1$, have raised community concerns[6,7] and corresponding interest in exposure-mitigation, including POE-/POU-treatment options[207–211] and DW-source alternatives. The median health-benchmark exceedances per sample in TW sourced from the shallow alluvial aquifer (current primary DW source for Town of Campbell residences, businesses, and public facilities) was 2 (range: 1–5), illustrating the importance of identifying stand-alone POE/POU treatment options for unregulated private-well TW, which are effective against multiple contaminants[207,212] or identifying a more suitable DW aquifer for new private wells or a public-supply system. Regarding the former, broadly effective single-stage treatment technologies (*e.g.*, reverse osmosis [RO]) or multi-stage/multi-filtration (sediment filter, redox media, activated carbon, ion exchange, RO, UV disinfection) systems are generally considered more appropriate for organic-/inorganic-contaminant-mixtures,[207] like those observed in alluvial-aquifer-sourced TW at Town of Campbell. Regarding the latter, notably lower organic-/inorganic-contaminant exposures and associated cumulative risks, including PFAS exposures and risks, in sandstone-aquifer-sourced TW samples over a 3 year period support consideration of the sandstone aquifer as an alternative DW source to mitigate alluvial-aquifer TW-PFAS exposures to French Island residents.

Assessment and communication of TW contaminant exposures is essential to DW-risk management and public-health decision-making at household and community scales. Analytically extensive datasets like this study, which are intended to inform scientific and public-health understanding of DW as a vector for human contaminant exposures and associated human-health outcomes, remain limited because broad assessments of regulated and unregulated contaminants are not generally conducted at the TW point-of-use in the US or worldwide. These results emphasize the importance of continued broad characterization of POU-DW exposures, especially in unregulated and unmonitored private-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[186,187] to improve models of TW contaminant exposures and related risks. Increased availability of such health-based monitoring data, including results below current, technically- or economically-constrained public-supply enforceable standards (*e.g.*, MCL), is important to support engagement in source-water protection and DW treatment and to inform community- and consumer-level DW decision-making throughout the US.

Data availability

Data discussed in this paper are summarized in ESI† (Tables S1–S9b†) and in the USGS data releases.[1–3]

Author contributions

Conceptualization: PMB, KMR, KLS, LD, MPG. Data curation: PMB, KMR, SMM. Formal analysis: PMB, KMR, KLS. Investigation: PMB, KMR, KLS, KAL, RBM, SMM. Methodology: PMB. Project administration: PMB, KLS. Resources: MPG, RKH. Visualization: PMB, KMR, SEG. Writing – original draft: PMB. Writing – review & editing: PMB, KMR, KLS, LD, MPG, RKH, SEB, SEG, KAL, RBM, SMM, MLS.

Conflicts of interest

There are no conflicts to declare.

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References

1 K. M. Romanok, S. M. Meppelink, P. M. Bradley, S. E. Breitmeyer, L. Donahue, M. Gaikowski, R. K. Hines and K. L. Smalling, Occurrence of Mixed Organic and Inorganic Chemicals in in Groundwater and Tapwater, Town of Campbell, Wisconsin, 2021–22, *Report U.S. Geological Survey Open-File Report 2023-1088*, Reston, VA, 2023, DOI: 10.3133/ofr20231088.

2 K. M. Romanok, P. M. Bradley, K. Smalling, S. M. Meppelink, R. B. McCleskey, M. L. Hladik, J. L. Gray and L. K. Kanagy, Target-Chemical Concentrations and Bioassay Results for Assessment of Mixed-Organic/Inorganic Chemical and Biological Exposures in Private-Well Tapwater at French Island, Wisconsin, 2021, *Report U.S. Geological Survey Data Release*, 2023, DOI: 10.5066/P9EUBGUF.

3 K. M. Romanok, R. K. Hines, M. P. Gaikowski, P. M. Bradley and K. Smalling, Quarterly Sample Results for Per- and Polyfluoroalkyl Substances (PFAS) for Locations in Campbell, Wisconsin, 2021-22, *Report U.S. Geological Survey Data Release*, 2023, DOI: 10.5066/P9J6XKVS.

4 Esri, *Human Geography Base*, 2017, https://www.arcgis.com/home/item.html?id=3582b744bba84668b52a16b0b6942544.

5 Wisconsin State Legislature, WI Cities, Towns and Villages, 2022, https://gis-ltsb.hub.arcgis.com/datasets/LTSB::wi-cities-towns-and-villages-january-2024/about.

6 G. Pierce and S. Gonzalez, Mistrust at the tap? Factors contributing to public drinking water (mis) perception across US households, *Water Policy*, 2017, **19**, 1–12, DOI: 10.2166/wp.2016.143.

7 d. F. M. Doria, Factors influencing public perception of drinking water quality, *Water Policy*, 2010, **12**, 1–19, DOI: 10.2166/wp.2009.051.

8 C. M. Villanueva, M. Kogevinas, S. Cordier, M. R. Templeton, R. Vermeulen, J. R. Nuckols, M. J. Nieuwenhuijsen and P. Levallois, Assessing exposure and health consequences of chemicals in drinking water: current state of knowledge and research needs, *Environ. Health Perspect.*, 2014, **122**, 213, DOI: 10.1289/ehp.1206229.

9 M. G. Evich, M. J. B. Davis, J. P. McCord, B. Acrey, J. A. Awkerman, D. R. U. Knappe, A. B. Lindstrom, T. F. Speth, C. Tebes-Stevens, M. J. Strynar, Z. Wang, E. J. Weber, W. M. Henderson and J. W. Washington, Per- and polyfluoroalkyl substances in the environment, *Science*, 2022, **375**, eabg9065, DOI: 10.1126/science.abg9065.

10 J. Glüge, M. Scheringer, I. T. Cousins, J. C. DeWitt, G. Goldenman, D. Herzke, R. Lohmann, C. A. Ng, X. Trier and Z. Wang, An overview of the uses of per- and polyfluoroalkyl substances (PFAS), *Environ. Sci.: Processes Impacts*, 2020, **22**, 2345–2373, DOI: 10.1039/d0em00291g.

11 E. F. Houtz, C. P. Higgins, J. A. Field and D. L. Sedlak, Persistence of Perfluoroalkyl Acid Precursors in AFFF-Impacted Groundwater and Soil, *Environ. Sci. Technol.*, 2013, **47**, 8187–8195, DOI: 10.1021/es4018877.

12 J. R. Masoner, D. W. Kolpin, I. M. Cozzarelli, L. B. Barber, D. S. Burden, W. T. Foreman, K. J. Forshay, E. T. Furlong, J. F. Groves, M. L. Hladik, M. E. Hopton, J. B. Jaeschke, S. H. Keefe, D. P. Krabbenhoft, R. Lowrance, K. M. Romanok, D. L. Rus, W. R. Selbig, B. H. Williams and P. M. Bradley, Urban stormwater: an overlooked pathway of extensive mixed contaminants to surface and groundwaters in the United States, *Environ. Sci. Technol.*, 2019, **53**, 10070–10081, DOI: 10.1021/acs.est.9b02867.

13 S. Kurwadkar, J. Dane, S. R. Kanel, M. N. Nadagouda, R. W. Cawdrey, B. Ambade, G. C. Struckhoff and R. Wilkin, Per- and polyfluoroalkyl substances in water and wastewater: a critical review of their global occurrence and distribution, *Sci. Total Environ.*, 2022, **809**, 151003, DOI: 10.1016/j.scitotenv.2021.151003.

14 J. Masoner, D. Kolpin, I. Cozzarelli, K. Smalling, S. Bolyard, J. A. Field, E. T. Furlong, J. Gray, D. Lozinski, D. Reinhart, A. Rodowa and P. M. Bradley, Landfill Leachate Contributes Per-/Poly-Fluoroalkyl Substances (PFAS) and Pharmaceuticals to Municipal Wastewater, *Environ. Sci.:Water Res. Technol.*, 2020, **6**, 1300–1311, DOI: 10.1039/D0EW00045K.

15 J. L. Sims, K. M. Stroski, S. Kim, G. Killeen, R. Ehalt, M. F. Simcik and B. W. Brooks, Global occurrence and probabilistic environmental health hazard assessment of per- and polyfluoroalkyl substances (PFASs) in groundwater and surface waters, *Sci. Total Environ.*, 2022, **816**, 151535, DOI: 10.1016/j.scitotenv.2021.151535.

16 D. Salvatore, K. Mok, K. K. Garrett, G. Poudrier, P. Brown, L. S. Birnbaum, G. Goldenman, M. F. Miller, S. Patton, M. Poehlein, J. Varshavsky and A. Cordner, Presumptive Contamination: A New Approach to PFAS Contamination Based on Likely Sources, *Environ. Sci. Technol. Lett.*, 2022, **9**, 983–990, DOI: 10.1021/acs.estlett.2c00502.

17 D. Q. Andrews and O. V. Naidenko, Population-Wide Exposure to Per- and Polyfluoroalkyl Substances from Drinking Water in the United States, *Environ. Sci. Technol. Lett.*, 2020, **7**, 931–936, DOI: 10.1021/acs.estlett.0c00713.

18 X. C. Hu, A. K. Tokranov, J. Liddie, X. Zhang, P. Grandjean, J. E. Hart, F. Laden, Q. Sun, L. W. Y. Yeung and E. M. Sunderland, Tap Water Contributions to Plasma Concentrations of Poly- and Perfluoroalkyl Substances (PFAS) in a Nationwide Prospective Cohort of U.S. Women, *Environ. Health Perspect.*, 2019, **127**, 067006, DOI: 10.1289/EHP4093.

19 K. L. Smalling, K. M. Romanok, P. M. Bradley, M. C. Morriss, J. L. Gray, L. K. Kanagy, S. E. Gordon, B. M. Williams, S. E. Breitmeyer, D. K. Jones, L. A. DeCicco, C. A. Eagles-Smith and T. Wagner, Per- and Polyfluoroalkyl Substances (PFAS) in United States Tapwater: Comparison of Underserved Private-Well and Public-Supply Exposures and Associated Health Implications, *Environ. Int.*, 2023, **178**, 108033, DOI: 10.1016/j.envint.2023.108033.

20 P. B. McMahon, A. K. Tokranov, L. M. Bexfield, B. D. Lindsey, T. D. Johnson, M. A. Lombard and E. Watson, Perfluoroalkyl and Polyfluoroalkyl Substances in Groundwater Used as a Source of Drinking Water in the Eastern United States, *Environ. Sci. Technol.*, 2022, DOI: 10.1021/acs.est.1c04795.

21 E. M. Sunderland, X. C. Hu, C. Dassuncao, A. K. Tokranov, C. C. Wagner and J. G. Allen, A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects, *J. Exposure Sci. Environ. Epidemiol.*, 2019, **29**, 131–147, DOI: 10.1038/s41370-018-0094-1.

22 C. C. Bach, A. Vested, K. T. Jørgensen, J. P. E. Bonde, T. B. Henriksen and G. Toft, Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review, *Crit. Rev. Toxicol.*, 2016, **46**, 735–755, DOI: 10.1080/10408444.2016.1182117.

23 B. E. Blake and S. E. Fenton, Early life exposure to per- and polyfluoroalkyl substances (PFAS) and latent health outcomes: a review including the placenta as a target tissue and possible driver of peri- and postnatal effects, *Toxicology*, 2020, **443**, 152565, DOI: 10.1016/j.tox.2020.152565.

24 P. Grandjean and E. Budtz-Jørgensen, Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children, *Environ. Health*, 2013, **12**, 35, DOI: 10.1186/1476-069X-12-35.

25 G. Liu, K. Dhana, J. D. Furtado, J. Rood, G. Zong, L. Liang, L. Qi, G. A. Bray, L. DeJonge, B. Coull, P. Grandjean and Q. Sun, Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: a prospective study, *PLoS Med.*, 2018, **15**, e1002502, DOI: 10.1371/journal.pmed.1002502.

26 V. Barry, A. Winquist and K. Steenland, Perfluorooctanoic Acid (PFOA) Exposures and Incident Cancers among Adults Living Near a Chemical Plant, *Environ. Health Perspect.*, 2013, **121**, 1313–1318, DOI: 10.1289/ehp.1306615.

27 G. B. Post, Recent US State and Federal Drinking Water Guidelines for Per- And Polyfluoroalkyl Substances (PFAS), *Environ. Toxicol. Chem.*, 2020, **40**, 550–563, DOI: 10.1002/etc.4863.

28 J. J. Shearer, C. L. Callahan, A. M. Calafat, W.-Y. Huang, R. R. Jones, V. S. Sabbisetti, N. D. Freedman, J. N. Sampson, D. T. Silverman, M. P. Purdue and J. N. Hofmann, Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma, *JNCI, J. Natl. Cancer Inst.*, 2020, **113**, 580–587, DOI: 10.1093/jnci/djaa143.

29 M. van Gerwen, E. Colicino, H. Guan, G. Dolios, G. N. Nadkarni, R. C. H. Vermeulen, M. S. Wolff, M. Arora, E. M. Genden and L. M. Petrick, Per- and polyfluoroalkyl substances (PFAS) exposure and thyroid cancer risk, *EBioMedicine*, 2023, **97**, 104831, DOI: 10.1016/j.ebiom.2023.104831.

30 S. E. Fenton, A. Ducatman, A. Boobis, J. C. DeWitt, C. Lau, C. Ng, J. S. Smith and S. M. Roberts, Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research, *Environ. Toxicol. Chem.*, 2021, **40**, 606–630, DOI: 10.1002/etc.4890.
31 M. Liu, G. Zhang, L. Meng, X. Han, Y. Li, Y. Shi, A. Li, M. E. Turyk, Q. Zhang and G. Jiang, Associations between Novel and Legacy Per- and Polyfluoroalkyl Substances in Human Serum and Thyroid Cancer: A Case and Healthy Population in Shandong Province, East China, *Environ. Sci. Technol.*, 2022, **56**, 6144–6151, DOI: 10.1021/acs.est.1c02850.
32 L. Dunder, P. M. Lind, S. Salihovic, J. Stubleski, A. Kärrman and L. Lind, Changes in plasma levels of per- and polyfluoroalkyl substances (PFAS) are associated with changes in plasma lipids – a longitudinal study over 10 years, *Environ. Res.*, 2022, **211**, 112903, DOI: 10.1016/j.envres.2022.112903.
33 Y. Li, L. Barregard, Y. Xu, K. Scott, D. Pineda, C. H. Lindh, K. Jakobsson and T. Fletcher, Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water, *Environ. Health*, 2020, **19**, 33, DOI: 10.1186/s12940-020-00588-9.
34 P. Sen, S. Qadri, P. K. Luukkonen, O. Ragnarsdottir, A. McGlinchey, S. Jäntti, A. Juuti, J. Arola, J. J. Schlezinger, T. F. Webster, M. Orešič, H. Yki-Järvinen and T. Hyötyläinen, Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic fatty liver disease, *J. Hepatol.*, 2022, **76**, 283–293, DOI: 10.1016/j.jhep.2021.09.039.
35 D. Melzer, N. Rice, M. H. Depledge, W. E. Henley and T. S. Galloway, Association between Serum Perfluorooctanoic Acid (PFOA) and Thyroid Disease in the U.S. National Health and Nutrition Examination Survey, *Environ. Health Perspect.*, 2010, **118**, 686–692, DOI: 10.1289/ehp.0901584.
36 X. Zhang, L. Xue, Z. Deji, X. Wang, P. Liu, J. Lu, R. Zhou and Z. Huang, Effects of exposure to per- and polyfluoroalkyl substances on vaccine antibodies: a systematic review and meta-analysis based on epidemiological studies, *Environ. Pollut.*, 2022, **306**, 119442, DOI: 10.1016/j.envpol.2022.119442.
37 P. Grandjean, C. A. G. Timmermann, M. Kruse, F. Nielsen, P. J. Vinholt, L. Boding, C. Heilmann and K. Mølbak, Severity of COVID-19 at elevated exposure to perfluorinated alkylates, *PLoS One*, 2021, **15**, e0244815, DOI: 10.1371/journal.pone.0244815.
38 L. Crawford, S. A. Halperin, M. W. Dzierlenga, B. Skidmore, M. W. Linakis, S. Nakagawa and M. P. Longnecker, Systematic review and meta-analysis of epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances, *Environ. Int.*, 2023, **172**, 107734, DOI: 10.1016/j.envint.2023.107734.
39 P. Grandjean, E. W. Andersen, E. Budtz-Jørgensen, F. Nielsen, K. Mølbak, P. Weihe and C. Heilmann, Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds, *JAMA*, 2012, **307**, 391–397, DOI: 10.1001/jama.2011.2034.
40 V. Ehrlich, W. Bil, R. Vandebriel, B. Granum, M. Luijten, B. Lindeman, P. Grandjean, A.-M. Kaiser, I. Hauzenberger, C. Hartmann, C. Gundacker and M. Uhl, Consideration of pathways for immunotoxicity of per- and polyfluoroalkyl substances (PFAS), *Environ. Health*, 2023, **22**, 19, DOI: 10.1186/s12940-022-00958-5.
41 S. M. Hall, S. Zhang, K. Hoffman, M. L. Miranda and H. M. Stapleton, Concentrations of per- and polyfluoroalkyl substances (PFAS) in human placental tissues and associations with birth outcomes, *Chemosphere*, 2022, **295**, 133873, DOI: 10.1016/j.chemosphere.2022.133873.
42 Y. Zhang, V. Mustieles, Q. Sun, B. Coull, T. McElrath, S. L. Rifas-Shiman, L. Martin, Y. Sun, Y.-X. Wang, E. Oken, A. Cardenas and C. Messerlian, Association of Early Pregnancy Perfluoroalkyl and Polyfluoroalkyl Substance Exposure With Birth Outcomes, *JAMA Network Open*, 2023, **6**, e2314934, DOI: 10.1001/jamanetworkopen.2023.14934.
43 H. Gardener, Q. Sun and P. Grandjean, PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes, *Environ. Res.*, 2021, **192**, 110287, DOI: 10.1016/j.envres.2020.110287.
44 P. M. Bradley, D. W. Kolpin, K. M. Romanok, K. L. Smalling, M. J. Focazio, J. B. Brown, M. C. Cardon, K. D. Carpenter, S. R. Corsi, L. A. DeCicco, J. E. Dietze, N. Evans, E. T. Furlong, C. E. Givens, J. L. Gray, D. W. Griffin, C. P. Higgins, M. L. Hladik, L. R. Iwanowicz, C. A. Journey, K. M. Kuivila, J. R. Masoner, C. A. McDonough, M. T. Meyer, J. L. Orlando, M. J. Strynar, C. P. Weis and V. S. Wilson, Reconnaissance of mixed organic and inorganic chemicals in private and public supply tapwaters at selected residential and workplace sites in the United States, *Environ. Sci. Technol.*, 2018, **52**, 13972–13985, DOI: 10.1021/acs.est.8b04622.
45 P. M. Bradley, D. W. Kolpin, D. A. Thompson, K. M. Romanok, K. L. Smalling, S. E. Breitmeyer, M. C. Cardon, D. M. Cwiertny, N. Evans, R. W. Field, M. J. Focazio, L. E. Beane Freeman, C. E. Givens, J. L. Gray, G. L. Hager, M. L. Hladik, J. N. Hofmann, R. R. Jones, L. K. Kanagy, R. F. Lane, R. B. McCleskey, D. Medgyesi, E. K. Medlock-Kakaley, S. M. Meppelink, M. T. Meyer, D. A. Stavreva and M. H. Ward, Juxtaposition of intensive agriculture, vulnerable aquifers, and mixed chemical/microbial exposures in private-well tapwater in northeast Iowa, *Sci. Total Environ.*, 2023, **868**, 161672, DOI: 10.1016/j.scitotenv.2023.161672.
46 P. M. Bradley, D. R. LeBlanc, K. M. Romanok, K. L. Smalling, M. J. Focazio, M. C. Cardon, J. M. Clark, J. M. Conley, N. Evans, C. E. Givens, J. L. Gray, L. Earl Gray, P. C. Hartig, C. P. Higgins, M. L. Hladik, L. R. Iwanowicz, K. A. Loftin, R. Blaine McCleskey, C. A. McDonough, E. K. Medlock-Kakaley, C. P. Weis and V. S. Wilson, Public and private tapwater: comparative

analysis of contaminant exposure and potential risk, Cape Cod, Massachusetts, USA, *Environ. Int.*, 2021, **152**, 106487, DOI: 10.1016/j.envint.2021.106487.

47 P. M. Bradley, I. Y. Padilla, K. M. Romanok, K. L. Smalling, M. J. Focazio, S. E. Breitmeyer, M. C. Cardon, J. M. Conley, N. Evans, C. E. Givens, J. L. Gray, L. Earl Gray, P. C. Hartig, C. P. Higgins, M. L. Hladik, L. R. Iwanowicz, R. F. Lane, K. A. Loftin, R. Blaine McCleskey, C. A. McDonough, E. Medlock-Kakaley, S. Meppelink, C. P. Weis and V. S. Wilson, Pilot-scale expanded assessment of inorganic and organic tapwater exposures and predicted effects in Puerto Rico, USA, *Sci. Total Environ.*, 2021, **788**, 147721, DOI: 10.1016/j.scitotenv.2021.147721.

48 P. M. Bradley, K. M. Romanok, K. L. Smalling, M. J. Focazio, R. Charboneau, C. M. George, A. Navas-Acien, M. O''Leary, R. Red Cloud, T. Zacher, M. C. Cardon, C. Cuny, G. Ducheneaux, K. Enright, N. Evans, J. L. Gray, D. E. Harvey, M. L. Hladik, K. A. Loftin, R. B. McCleskey, E. K. Medlock Kakaley, S. M. Meppelink, J. F. Valder and C. P. Weis, Tapwater exposures, effects potential, and residential risk management in northern plains nations, *Environmental Science and Technology Water*, 2022, **2**, 1772–1788, DOI: 10.1021/acsestwater.2c00293.

49 R. Akhbarizadeh, S. Dobaradaran, T. C. Schmidt, I. Nabipour and J. Spitz, Worldwide bottled water occurrence of emerging contaminants: a review of the recent scientific literature, *J. Hazard. Mater.*, 2020, **392**, 122271, DOI: 10.1016/j.jhazmat.2020.122271.

50 V. Gellrich, H. Brunn and T. Stahl, Perfluoroalkyl and polyfluoroalkyl substances (PFASs) in mineral water and tap water, *J. Environ. Sci. Health, Part A: Toxic/Hazard. Subst. Environ. Eng.*, 2013, **48**, 129–135, DOI: 10.1080/10934529.2013.719431.

51 T. G. Schwanz, M. Llorca, M. Farré and D. Barceló, Perfluoroalkyl substances assessment in drinking waters from Brazil, France and Spain, *Sci. Total Environ.*, 2016, **539**, 143–152, DOI: 10.1016/j.scitotenv.2015.08.034.

52 C. Kunacheva, S. Fujii, S. Tanaka, S. K. Boontanon, S. Poothong, T. Wongwatthana and B. R. Shivakoti, Perfluorinated compounds contamination in tap water and bottled water in Bangkok, Thailand, *J. Water Supply: Res. Technol. – Aqua*, 2010, **59**, 345–354, DOI: 10.2166/aqua.2010.063.

53 S. J. Chow, N. Ojeda, J. G. Jacangelo and K. J. Schwab, Detection of ultrashort-chain and other per- and polyfluoroalkyl substances (PFAS) in U.S. bottled water, *Water Res.*, 2021, **201**, 117292, DOI: 10.1016/j.watres.2021.117292.

54 T. Teymoorian, G. Munoz, S. Vo Duy, J. Liu and S. Sauvé, Tracking PFAS in Drinking Water: A Review of Analytical Methods and Worldwide Occurrence Trends in Tap Water and Bottled Water, *ACS ES&T Water*, 2023, **3**, 246–261, DOI: 10.1021/acsestwater.2c00387.

55 A. K. Tokranov, K. M. Ransom, L. M. Bexfield, B. D. Lindsey, E. Watson, D. I. Dupuy, P. E. Stackelberg, M. S. Fram, S. A. Voss, J. A. Kingsbury, B. C. Jurgens, K. L. Smalling and P. M. Bradley, Predictions of groundwater PFAS occurrence at drinking water supply depths in the United States, *Science*, 2024, eado6638, DOI: 10.1126/science.ado6638.

56 Interstate Technology Regulatory Council, *PFAS — Per- and Polyfluoroalkyl Substances*, https://pfas-1.itrcweb.org/, accessed October 3, 2024.

57 U.S. Environmental Protection Agency, *Third Unregulated Contaminant Monitoring Rule*, https://www.epa.gov/dwucmr/third-unregulated-contaminant-monitoring-rule, accessed January 5, 2024.

58 U.S. Environmental Protection Agency, *Fifth Unregulated Contaminant Monitoring Rule*, https://www.epa.gov/dwucmr/fifth-unregulated-contaminant-monitoring-rule, accessed January 5, 2024.

59 U.S. Environmental Protection Agency, *Private drinking water wells*, https://www.epa.gov/privatewells, accessed January 23, 2025.

60 C. A. Dieter, M. A. Maupin, R. R. Caldwell, M. A. Harris, T. I. Ivahnenko, J. K. Lovelace, N. L. Barber and K. S. Linsey, Estimated Use of Water in the United States in 2015, *Report U.S. Geological Survey Circular 1441*, Reston, VA, 2018, DOI: 10.3133/cir1441.

61 Y. Zheng and S. V. Flanagan, The case for universal screening of private well water quality in the U.S. and testing requirements to achieve it: evidence from arsenic, *Environ. Health Perspect.*, 2017, **125**, 085002, DOI: 10.1289/EHP629.

62 Cape Cod Commission, *Water Resources*, https://capecodcommission.org/our-work/topic/water-resources/, accessed June 24, 2020.

63 Cape Cod Groundwater Guardians, *Drinking Water on Cape Cod*, accessed March 14, 2020.

64 D. LeBlanc, J. Guswa, F. MH and C. Londquist, Groundwater resources of Cape Cod, Massachusetts, *Report U.S. Geological Survey Hydrologic Investigations Atlas HA-692*, 1986, http://pubs.usgs.gov/ha/692/.

65 L. Schaider, J. Ackerman, R. Rudel, S. Dunagan and J. Brody, *Emerging Contaminants in Cape Cod Private Drinking Water Wells, Researching the environment and women's health*, Silent Spring Institute, 2011, https://www.silentspring.org/sites/default/files/publication/2019-04/Emerging-contaminants-private-wells.pdf.

66 L. Schaider, R. Rudel, S. Dunagan, J. Ackerman, L. Perovich and J. Brody, *Emerging Contaminants in Cape Cod Drinking Water*, Silent Spring Institute, Boston, MA, 2010, http://www.commwater.com/wp-content/uploads/2014/03/silentspringreport2010.pdf.

67 United States Census Bureau, Data, https://data.census.gov/, accessed January 23, 2025.

68 Wisconsin Department of Health Services, *Recommended Public Health Groundwater Quality Standards: Scientific support documents for Cycle 10 substances*, https://dnr.wisconsin.gov/sites/default/files/topic/Groundwater/NR140/DHSLetter20220201.pdf, accessed January 17, 2024.

69 Wisconsin Department of Natural Resources, *PFAS Contamination in the Town Of Campbell and French Island*,

https://dnr.wisconsin.gov/topic/PFAS/Campbell.html, accessed January 2, 2024.

70 Wisconsin Department of Natural Resources, *Environmental Cleanup & Brownfields Redevelopment BRRTS on the Web: 02-32-587347 La Crosse Airport PFAS Investigation*, https://apps.dnr.wi.gov/botw/GetActivityDetail.do?detailSeqNo=587347, accessed January 15, 2024.

71 The OS Group LLC, *Interim Site Investigation Report: La Crosse Airport PFAS Investigation, WDNR BRRTS # 02-32-587347*, 2021, https://apps.dnr.wi.gov/botw/DownloadBlobFile.do?`docSeqNo=227704&docName=20220119_43_SI_Status_Update.pdf&docDsn=587347.

72 Wood Environment & Infrastructure Solutions Inc, *Potable Well Sampling Report: Potable Well Sampling for Analysis of Per- and Polyfluorinated Alkyl Substances (PFAS) in the Town of Campbell, La Crosse County, Wisconsin Wisconsin Department of Natural Resources*, 2021, https://townofcampbellwi.gov/potable-well-sampling-report-by-the-dnr/.

73 R. J. Hunt, D. A. Saad and D. M. Chapel, *Numerical Simulation of Ground-Water Flow in La Crosse County, Wisconsin, and into Nearby Pools of the Mississippi River, Report 2003-4154*, 2003, DOI: 10.3133/wri034154.

74 U.S. Geological Survey, Environmental Health Program, *Drinking Water and Wastewater Infrastructure Science Team*, https://www.usgs.gov/programs/environmental-health-program/science/drinking-water-and-wastewater-infrastructure-science, accessed January 16, 2024.

75 S. E. Gordon, P. M. Bradley, K. L. Smalling, S. E. Breitmeyer and K. M. Romanok, *Drop by Drop*, https://geonarrative.usgs.gov/drinkingwaterinvestigations/, accessed January 16, 2024.

76 P. M. Bradley, M. Argos, D. W. Kolpin, S. M. Meppelink, K. M. Romanok, K. L. Smalling, M. J. Focazio, J. M. Allen, J. E. Dietze, M. J. Devito, A. R. Donovan, N. Evans, C. E. Givens, J. L. Gray, C. P. Higgins, M. L. Hladik, L. R. Iwanowicz, C. A. Journey, R. F. Lane, Z. R. Laughrey, K. A. Loftin, R. B. McCleskey, C. A. McDonough, E. Medlock-Kakaley, M. T. Meyer, A. R. Putz, S. D. Richardson, A. E. Stark, C. P. Weis, V. S. Wilson and A. Zehraoui, Mixed organic and inorganic tapwater exposures and potential effects in greater Chicago area, USA, *Sci. Total Environ.*, 2020, **719**, 137236, DOI: 10.1016/j.scitotenv.2020.137236.

77 K. L. Smalling, P. M. Bradley, K. M. Romanok, S. M. Elliot, J. de Lambert, M. Focazio, S. E. Gordon, J. Gray, L. K. Kanagy, M. L. Hladik, K. Loftin, R. B. McCleskey, E. Medlock Kakaley, M. C. Cardon, N. Evans and C. P. Weis, Exposures and potential health implications of contaminant mixtures in linked source water, finished drinking water, and tapwater from public-supply drinking water systems in Minneapolis/St. Paul area, USA, *Environ. Sci.:Water Res. Technol.*, 2023, **9**, 1813–1828, DOI: 10.1039/d3ew00066d.

78 P. M. Bradley, K. M. Romanok, K. L. Smalling, M. J. Focazio, N. Evans, S. C. Fitzpatrick, C. E. Givens, S. E. Gordon, J. L. Gray, E. M. Green, D. W. Griffin, M. L. Hladik, L. K. Kanagy, J. T. Lisle, K. A. Loftin, R. Blaine McCleskey, E. K. Medlock-Kakaley, A. Navas-Acien, D. A. Roth, P. South and C. P. Weis, Bottled water contaminant exposures and potential human effects, *Environ. Int.*, 2023, **171**, 107701, DOI: 10.1016/j.envint.2022.107701.

79 A. Moretto, A. Bachman, A. Boobis, K. R. Solomon, T. P. Pastoor, M. F. Wilks and M. R. Embry, A framework for cumulative risk assessment in the 21st century, *Crit. Rev. Toxicol.*, 2017, **47**, 85–97, DOI: 10.1080/10408444.2016.1211618.

80 S. B. Norton, D. J. Rodier, W. H. van der Schalie, W. P. Wood, M. W. Slimak and J. H. Gentile, A framework for ecological risk assessment at the EPA, *Environ. Toxicol. Chem.*, 1992, **11**, 1663–1672, DOI: 10.1002/etc.5620111202.

81 National Research Council, *Risk Assessment in the Federal Government: Managing the Process*, The National Academies Press, Washington, DC, 1983, DOI: 10.17226/366.

82 S. R. Corsi, L. A. De Cicco, D. L. Villeneuve, B. R. Blackwell, K. A. Fay, G. T. Ankley and A. K. Baldwin, Prioritizing chemicals of ecological concern in Great Lakes tributaries using high-throughput screening data and adverse outcome pathways, *Sci. Total Environ.*, 2019, **686**, 995–1009, DOI: 10.1016/j.scitotenv.2019.05.457.

83 B. R. Blackwell, G. T. Ankley, S. R. Corsi, L. A. De Cicco, K. A. Houck, R. S. Judson, S. Li, M. T. Martin, E. Murphy and A. Schroeder, 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, DOI: 10.1021/acs.est.7b01613.

84 U.S. Environmental Protection Agency, *40 C. F. R. § 141 and § 142: National Primary Drinking Water Regulations for Lead and Copper: Improvements (LCRI)*, 2024, vol. 115, https://www.federalregister.gov/documents/2024/10/30/2024-23549/national-primary-drinking-water-regulations-for-lead-and-copper-improvements-lcri.

85 U.S. Environmental Protection Agency, *Fact Sheet: Lead and Copper Rule Improvements*, 2024, https://www.epa.gov/system/files/documents/2024-10/final_lcri_fact-sheet_general_public.pdf.

86 Wisconsin Department of Natural Resources, *Well Construction Information System*, https://apps.dnr.wi.gov/wellconstructionpub/#!/PublicSearch/Index, accessed January 11, 2024.

87 K. M. Romanok, D. W. Kolpin, S. M. Meppelink, M. Argos, J. Brown, M. DeVito, J. E. Dietz, C. E. Givens, J. Gray, C. P. Higgins, M. L. Hladik, L. R. Iwanowicz, B. R. McCleskey, C. McDonough, M. T. Meyers, M. Strynar, C. P. Weis, V. Wilson and P. M. Bradley, Methods Used for the Collection and Analysis of Chemical and Biological Data for the Tapwater Exposure Study, United States, 2016–17, *Report U.S. Geological*

Survey Open-File Report 2018-1098, Reston, VA, 2018, DOI: 10.3133/ofr20181098.

88 K. M. Romanok and P. M. Bradley, Target-Chemical Concentration Results for Assessment of Mixed-Organic/Inorganic Chemical and Biological Exposures in North Dakota and South Dakota Tapwater, 2019, *Report U.S. Geological Survey Data Release*, 2021, DOI: 10.5066/P9KP2NP4.

89 K. M. Romanok, P. M. Bradley and R. B. McCleskey, Inorganic Concentration Results for Assessment of Mixed-Organic/Inorganic Chemical and Biological Exposures in North Dakota and South Dakota Tapwater, 2019, *Report U.S. Geological Survey Data Release*, 2021, DOI: 10.5066/P9DBCKT4.

90 D. Rose, M. Sandstrom and L. Murtagh, 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, *Report U.S. Geological Survey Techniques and Methods. Book 5. Laboratory Analysis*, 2016, DOI: 10.3133/tm5B12.

91 M. W. Sandstrom, L. K. Kanagy, C. A. Anderson and C. J. Kanagy, Methods of the National Water Quality Laboratory. Chapter B11. Determination of Pesticides and Pesticide Degradates in Filtered Water by Direct Aqueous-Injection Liquid Chromatography-Tandem Mass Spectrometry, *Report U.S. Geological Survey Techniques and Methods. Book 5. Laboratory Analysis*, 2015, DOI: 10.3133/tm5B11.

92 M. L. Hladik, M. J. Focazio and M. Engle, 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**, 1085–1093, DOI: 10.1016/j.scitotenv.2013.08.008.

93 E. Furlong, M. Noriega, C. Kanagy, L. Kanagy, L. Coffey and M. Burkhardt, 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, *Report U.S. Geological Survey Techniques and Methods. Book 5. Laboratory Analysis. Chap. B10*, 2014, doi: DOI: 10.3133/tm5B10.

94 M. J. Fishman and L. C. Friedman, Methods for Determination of Inorganic Substances in Water and Fluvial sediments, *Report U.S. Geological Survey Techniques of Water-Resources Investigations 05-A1*, 1989, doi: DOI: 10.3133/twri05A1.

95 G. L. Hoffman, M. J. Fishman and J. R. Garbarino, Methods of Analysis by the US Geological Survey National Water Quality Laboratory: In-Bottle Acid Digestion of Whole-Water Samples, *Report U.S. Geological Survey Open-File Report 96-225*, US Department of the Interior, US Geological Survey, 1996, DOI: 10.3133/ofr96225.

96 J. L. Graham, K. A. Loftin, M. T. Meyer and A. C. Ziegler, Cyanotoxin mixtures and taste-and-odor compounds in cyanobacterial blooms from the Midwestern United States, *Environ. Sci. Technol.*, 2010, **44**, 7361–7368, DOI: 10.1021/es1008938.

97 K. A. Loftin, J. L. Graham, E. D. Hilborn, S. C. Lehmann, M. T. Meyer, J. E. Dietze and C. B. Griffith, Cyanotoxins in inland lakes of the United States: Occurrence and potential recreational health risks in the EPA National Lakes Assessment 2007, *Harmful Algae*, 2016, **56**, 77–90, DOI: 10.1016/j.hal.2016.04.001.

98 J. D. Pfaff, Method 300.0, Determination of inorganic anions by ion chromatography. Revision 2.1, *Report EPA/600/R-93/100*, U.S. Environmental Protection Agency, 1993, https://www.epa.gov/sites/production/files/2015-08/documents/method_300-0_rev_2-1_1993.pdf.

99 J. W. Ball and R. B. McCleskey, A new cation-exchange method for accurate field speciation of hexavalent chromium, *Talanta*, 2003, **61**, 305–313, DOI: 10.1016/S0039-9140(03)00282-0.

100 R. L. Hergenreder, Trace Metals in Waters by GFAAS, in *Accordance with U.S. EPA and Health Canada Requirements*, Perkin Elmer, Inc., Waltham, MA, 2011, https://www.perkinelmer.com/lab-solutions/resources/docs/PinAAcleTraceMetalsinWaterbyGFAAAppNote.pdf.

101 U.S. Environmental Protection Agency, Inductively coupled plasma-optical emission spectrometry, Method 6010D, *Report EPA SW-846 Update V*, 2014, accessed November 2, 2017, https://www.epa.gov/sites/production/files/2015-12/documents/6010d.pdf.

102 D. W. Kolpin, L. E. Hubbard, D. M. Cwiertny, S. M. Meppelink, D. A. Thompson and J. L. Gray, A comprehensive statewide spatiotemporal stream assessment of per- and polyfluoroalkyl substances (PFAS) in an agricultural region of the United States, *Environ. Sci. Technol. Lett.*, 2021, **8**, 981–988, DOI: 10.1021/acs.estlett.1c00750.

103 U.S. Environmental Protection Agency, Method 300.1: Determination of inorganic anions in drinking Water by ion chromatography, Revision 1.0, *Report EPA/815-R-00-014*, U.S. Environmental Protection Agency, 1997, https://www.epa.gov/sites/default/files/2015-06/documents/epa-300.1.pdf.

104 R. B. McCleskey, D. A. Roth, D. Mahony, D. K. Nordstrom and S. Kinsey, Sources, fate, and flux of geothermal solutes in the Yellowstone and Gardner Rivers, Yellowstone National Park, WY, *Appl. Geochem.*, 2019, **111**, 104458, DOI: 10.1016/j.apgeochem.2019.104458.

105 R. B. McCleskey, D. K. Nordstrom and J. W. Ball, Metal interferences and their removal prior to the determination of As(T) and As(III) in acid mine waters by hydride generation atomic absorption spectrometry, *Report U.S. Geological Survey Water-Resources Investigations Report 2003-4117*, 2003, DOI: 10.3133/wri034117.

106 American Public Health Association, in *Standard Methods For the Examination of Water and Wastewater*, 2018, p. , p. 4, https://www.standardmethods.org/doi/abs/10.2105/smww.2882.194.

107 American Public Health Association, in *Standard Methods For the Examination of Water and Wastewater*, 2018,

https://www.standardmethods.org/doi/abs/10.2105/SMWW.2882.188.

108 M. J. Fishman, Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory-Determination of inorganic and organic constituents in water and fluvial sediments, *Report U.S. Geological Survey Open-File Report 93-125*, 1993, https://pubs.usgs.gov/of/1993/0125/report.pdf.

109 U. S. Geological Survey, USGS National Field Manual for the Collection of Water-Quality Data: Use of Multiparameter Instruments for Routine Field Measurements, *Report U.S. Geological Survey Techniques and Methods 9-A6.8*, Reston, VA, 2023, DOI: 10.3133/tm9A6.8.

110 C. Childress, W. Foreman, B. Conner and T. Maloney, 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, *Report U.S. Geological Survey Open-File Report 99-193*, 1999, DOI: 10.3133/ofr99193.

111 U.S. Environmental Protection Agency, *40 C. F. R. § 136: Guidelines Establishing Test Procedures for the Analysis of Pollutants*, 2020, pp. , pp. 319–322, http://www.ecfr.gov/cgi-bin/text-idx?SID=3c78b6c8952e5e79268e429ed98bad84&mc=true&node=pt40.23.136&rgn=div5.

112 D. K. Mueller, T. L. Schertz, J. D. Martin and M. W. Sandstrom, Design, Analysis, and Interpretation of Field Quality-Control Data for Water-Sampling Projects, *Report U.S. Geological Survey Techniques and Methods Book 4 Chapter C4*, 2015, DOI: 10.3133/tm4C4.

113 W. T. Foreman, T. L. Williams, E. T. Furlong, D. M. Hemmerle, S. J. Stetson, V. K. Jha, M. C. Noriega, J. A. Decess, C. Reed-Parker and M. W. Sandstrom, Comparison of detection limits estimated using single- and multi-concentration spike-based and blank-based procedures, *Talanta*, 2021, **228**, 122139, DOI: 10.1016/j.talanta.2021.122139.

114 M. E. B. Meek, A. R. Boobis, K. M. Crofton, G. Heinemeyer, M. Van Raaij and C. Vickers, Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework, *Regul. Toxicol. Pharmacol.*, 2011, **60**, S1–S14, DOI: 10.1016/j.yrtph.2011.03.010.

115 EFSA Scientific Committee, S. J. More, V. Bampidis, D. Benford, S. H. Bennekou, C. Bragard, T. I. Halldorsson, A. F. Hernández-Jerez, K. Koutsoumanis, H. Naegeli, J. R. Schlatter, V. Silano, S. S. Nielsen, D. Schrenk, D. Turck, M. Younes, E. Benfenati, L. Castle, N. Cedergreen, A. Hardy, R. Laskowski, J. C. Leblanc, A. Kortenkamp, A. Ragas, L. Posthuma, C. Svendsen, R. Solecki, E. Testai, B. Dujardin, G. E. Kass, P. Manini, M. Z. Jeddi, J.-L. C. Dorne and C. Hogstrand, Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals, *EFSA J.*, 2019, **17**, e05634, DOI: 10.2903/j.efsa.2019.5634.

116 U.S. Environmental Protection Agency, Advances in dose addition for chemical mixtures: a white paper, *Report EPA/100/R23/001*, 2023, https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=548169.

117 U.S. Environmental Protection Agency, *Exposure Assessment Tools by Tiers and Types – Screening-Level and Refined*, https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-screening-level-and-refined, accessed August 6, 2024.

118 U.S. Environmental Protection Agency, Air Toxics Risk Assessment Reference Library: Volume 3 – Community-Scale Assessment, *Report EPA-452/K-06-001C*, U.S. Environmental Protection Agency, Washington DC, 2006, https://www.epa.gov/sites/default/files/2013-08/documents/volume_3_communityassess.pdf.

119 U.S. Environmental Protection Agency, Air Toxics Risk Assessment Reference Library: Volume 1 – Technical Resource Manual, *Report EPA-453-K-04-001A*, U.S. Environmental Protection Agency, Washington DC, 2004, https://www.epa.gov/sites/default/files/2013-08/documents/volume_1_reflibrary.pdf.

120 D. L. Filer, P. Kothiya, R. W. Setzer, R. S. Judson and M. T. Martin, tcpl: the ToxCast pipeline for high-throughput screening data, *Bioinformatics*, 2017, **33**, 618–620, DOI: 10.1093/bioinformatics/btw680.

121 U.S. Environmental Protection Agency, *CompTox Chemicals Dashboard*, 2024.

122 L. De Cicco, S. R. Corsi, D. Villeneuve, B. R. Blackwell and G. T. Ankley, *toxEval: Exploring Biological Relevance of Environmental Chemistry Observations. R package version 1.4.0*, https://github.com/DOI-USGS/toxEval, accessed February 10, 2025.

123 R Development Core Team, *The R Project for Statistical Computing: R version 4.4.2*, R Foundation for Statistical Computing, Vienna Austria, 2024, https://www.R-project.org.

124 N. Cedergreen, A. M. Christensen, A. Kamper, P. Kudsk, S. K. Mathiassen, J. C. Streibig and H. Sørensen, 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, DOI: 10.1897/07-474.1.

125 R. Altenburger, M. Scholze, W. Busch, B. I. Escher, G. Jakobs, M. Krauss, J. Krüger, P. A. Neale, S. Ait-Aissa and A. C. Almeida, Mixture effects in samples of multiple contaminants–An inter-laboratory study with manifold bioassays, *Environ. Int.*, 2018, **114**, 95–106, DOI: 10.1016/j.envint.2018.02.013.

126 D. Stalter, E. O'Malley, U. von Gunten and B. I. Escher, Mixture effects of drinking water disinfection by-products: implications for risk assessment, *Environ. Sci.:Water Res. Technol.*, 2020, **6**, 2341–2351, DOI: 10.1039/C9EW00988D.

127 U.S. Environmental Protection Agency National Center for Computational Toxicology, *ToxCast Database invitroDBv3.3*, 2020, DOI: 10.23645/epacomptox.6062623.v5.

128 U.S. Environmental Protection Agency National Center for Computational Toxicology, *ToxCast Database InvitroDBv3.1*, 2019, DOI: 10.23645/epacomptox.6062623.v3.

129 U.S. Environmental Protection Agency, *40 C. F. R. § 141: National Primary Drinking Water Regulations*, 2024, https://www.ecfr.gov/current/title-40/chapter-I/subchapter-D/part-141#_top.

130 U.S. Environmental Protection Agency, *National Primary Drinking Water Regulations*, https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations, accessed February 10, 2025.

131 U.S. Environmental Protection Agency, 2018 Edition of the Drinking Water Standards and Health Advisories, *Report EPA 822-F-18-001*, 2018, https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf.

132 World Health Organization (WHO), *Guidelines for drinking-water quality, Fourth edition incorporating the first addendum*, 2011, https://apps.who.int/iris/rest/bitstreams/1080656/retrieve.

133 Minnesota Department of Health, *Human Health-Based Water Guidance Table*, https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html#NaN, accessed February 10, 2025.

134 J. E. Norman, P. L. Toccalino and S. A. Morman, *Health-Based Screening Levels for Evaluating Water-Quality Data, 2nd edn*, DOI: 10.5066/F71C1TWP, accessed February 10, 2020.

135 U.S. Environmental Protection Agency, *How EPA Regulates Drinking Water Contaminants*, https://www.epa.gov/dwregdev/how-epa-regulates-drinking-water-contaminants, accessed February 10, 2025.

136 P. M. Bradley, K. M. Romanok, K. L. Smalling, S. E. Gordon, B. J. Huffman, K. Paul Friedman, D. L. Villeneuve, B. R. Blackwell, S. C. Fitzpatrick, M. J. Focazio, E. Medlock-Kakaley, S. M. Meppelink, A. Navas-Acien, A. E. Nigra and M. L. Schreiner, Private, public, and bottled drinking water: shared contaminant-mixture exposures and effects challenge, *Environ. Int.*, 2024, **195**, 109220, DOI: 10.1016/j.envint.2024.109220.

137 U.S. Environmental Protection Agency, *40 C. F. R. § 141: PFAS National Primary Drinking Water Regulation; Correction*, 2024, https://www.federalregister.gov/documents/2024/06/11/2024-12645/pfas-national-primary-drinking-water-regulation-correction#print.

138 U.S. Environmental Protection Agency, Fact Sheet: PFAS National Primary Drinking Water Regulation, *Report EPA Fact Sheet*, 2024, https://www.epa.gov/system/files/documents/2024-04/pfas-npdwr_fact-sheet_general_4.9.24v1.pdf.

139 A. V. Vecchia, R. J. Gilliom, D. J. Sullivan, D. L. Lorenz and J. D. Martin, Trends in concentrations and use of agricultural herbicides for corn belt rivers, 1996–2006, *Environ. Sci. Technol.*, 2009, **43**, 9096–9102, DOI: 10.1021/es902122j.

140 R. J. Gilliom, Pesticides in US streams and groundwater, *Environ. Sci. Technol.*, 2007, **41**, 3408–3414, DOI: 10.1021/es072531u.

141 W. W. Stone, R. J. Gilliom and K. R. Ryberg, Pesticides in US streams and rivers: occurrence and trends during 1992–2011, *Environ. Sci. Technol.*, 2014, **48**, 11025–11030, DOI: 10.1021/es5025367.

142 S. M. Stackpoole, M. E. Shoda, L. Medalie and W. W. Stone, Pesticides in US Rivers: Regional differences in use, occurrence, and environmental toxicity, 2013 to 2017, *Sci. Total Environ.*, 2021, 147147, DOI: 10.1016/j.scitotenv.2021.147147.

143 K. R. Ryberg and R. J. Gilliom, Trends in pesticide concentrations and use for major rivers of the United States, *Sci. Total Environ.*, 2015, **538**, 431–444.

144 H. S. Magdo, J. Forman, N. Graber, B. Newman, K. Klein, L. Satlin, R. W. Amler, J. A. Winston and P. J. Landrigan, Grand rounds: nephrotoxicity in a young child exposed to uranium from contaminated well water, *Environ. Health Perspect.*, 2007, **115**, 1237, DOI: 10.1289/ehp.9707.

145 A. I. Seldén, C. Lundholm, B. Edlund, C. Högdahl, B.-M. Ek, B. E. Bergström and C.-G. Ohlson, Nephrotoxicity of uranium in drinking water from private drilled wells, *Environ. Res.*, 2009, **109**, 486–494, DOI: 10.1016/j.envres.2009.02.002.

146 G. Bjørklund, Y. Semenova, L. Pivina, M. Dadar, M. M. Rahman, J. Aaseth and S. Chirumbolo, Uranium in drinking water: a public health threat, *Arch. Toxicol.*, 2020, **94**, 1551–1560, DOI: 10.1007/s00204-020-02676-8.

147 M. Ma, R. Wang, L. Xu, M. Xu and S. Liu, Emerging health risks and underlying toxicological mechanisms of uranium contamination: lessons from the past two decades, *Environ. Int.*, 2020, **145**, 106107, DOI: 10.1016/j.envint.2020.106107.

148 P. Kurttio, A. Harmoinen, H. Saha, L. Salonen, Z. Karpas, H. Komulainen and A. Auvinen, Kidney Toxicity of Ingested Uranium From Drinking Water, *Am. J. Kidney Dis.*, 2006, **47**, 972–982, DOI: 10.1053/j.ajkd.2006.03.002.

149 P. Kurttio, H. Komulainen, A. Leino, L. Salonen, A. Auvinen and H. Saha, Bone as a possible target of chemical toxicity of natural uranium in drinking water, *Environ. Health Perspect.*, 2005, **113**, 68, DOI: 10.1289/ehp.7475.

150 M. van Gerwen, N. Alpert, W. Lieberman-Cribbin, P. Cooke, K. Ziadkhanpour, B. Liu and E. Genden, Association between Uranium Exposure and Thyroid Health: A National Health and Nutrition Examination Survey Analysis and Ecological Study, *Int. J. Environ. Res. Public Health*, 2020, **17**, 712, DOI: 10.3390/ijerph17030712.

151 K. L. Cooper, E. J. Dashner, R. Tsosie, Y. M. Cho, J. Lewis and L. G. Hudson, Inhibition of poly(ADP-ribose) polymerase-1 and DNA repair by uranium, *Toxicol. Appl. Pharmacol.*, 2016, **291**, 13–20, DOI: 10.1016/j.taap.2015.11.017.

152 S. Raymond-Whish, L. P. Mayer, T. O'Neal, A. Martinez, M. A. Sellers, P. J. Christian, S. L. Marion, C. Begay, C. R. Propper and P. B. Hoyer, Drinking water with uranium below the US EPA water standard causes estrogen receptor–dependent responses in female mice,

Environ. Health Perspect., 2007, **115**, 1711, DOI: 10.1289/ehp.9910.
153 S. Wang, Y. Ran, B. Lu, J. Li, H. Kuang, L. Gong and Y. Hao, A Review of Uranium-Induced Reproductive Toxicity, *Biol. Trace Elem. Res.*, 2020, **196**, 204–213, DOI: 10.1007/s12011-019-01920-2.
154 S. Swayze, M. Rotondi and J. L. Kuk, The Associations between Blood and Urinary Concentrations of Metal Metabolites, Obesity, Hypertension, Type 2 Diabetes, and Dyslipidemia among US Adults: NHANES 1999–2016, *J. Environ. Public Health*, 2021, **2021**, 2358060, DOI: 10.1155/2021/2358060.
155 S. Triantafyllidou and M. Edwards, Lead (Pb) in tap water and in blood: implications for lead exposure in the United States, *Crit. Rev. Environ. Sci. Technol.*, 2012, **42**, 1297–1352, DOI: 10.1080/10643389.2011.556556.
156 U.S. Environmental Protection Agency, *42 U. S. C. § 300g-6: Prohibition on the Use of Lead Pipes, Solder, and Flux*, 2021, pp. , pp. 990–991, https://www.govinfo.gov/content/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapXII-partB-sec300g-6.pdf.
157 B. Lanphear, J. Lowry, S. Ahdoot, C. Baum, A. Bernstein, A. Bole, H. Brumberg, C. Campbell, S. Pacheco, A. Spanier, L. Trasande, K. Osterhoudt, J. Paulson, M. Sandel and P. Rogers, Prevention of childhood lead toxicity: Policy statement of the American Academy of Pediatrics Council on Environmental Health, *Pediatrics*, 2016, **138**, e20161493, DOI: 10.1542/peds.2016-1493.
158 M. S. Collin, S. K. Venkatraman, N. Vijayakumar, V. Kanimozhi, S. M. Arbaaz, R. G. S. Stacey, J. Anusha, R. Choudhary, V. Lvov, G. I. Tovar, F. Senatov, S. Koppala and S. Swamiappan, Bioaccumulation of lead (Pb) and its effects on human: a review, *J. Hazard. Mater. Adv.*, 2022, **7**, 100094, DOI: 10.1016/j.hazadv.2022.100094.
159 M. H. Ward, R. R. Jones, J. D. Brender, T. M. De Kok, P. J. Weyer, B. T. Nolan, C. M. Villanueva and S. G. Van Breda, Drinking water nitrate and human health: an updated review, *Int. J. Environ. Res. Public Health*, 2018, **15**, 1557, DOI: 10.3390/ijerph15071557.
160 E. E. Essien, K. Said Abasse, A. Côté, K. S. Mohamed, M. M. F. A. Baig, M. Habib, M. Naveed, X. Yu, W. Xie, S. Jinfang and M. Abbas, Drinking-water nitrate and cancer risk: a systematic review and meta-analysis, *Arch. Environ. Occup. Health*, 2022, **77**, 51–67, DOI: 10.1080/19338244.2020.1842313.
161 R. R. Jones, P. J. Weyer, C. T. DellaValle, M. Inoue-Choi, K. E. Anderson, K. P. Cantor, S. Krasner, K. Robien, L. E. Freeman, D. T. Silverman and M. H. Ward, Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa, *Environ. Health Perspect.*, 2016, **124**, 1751–1758, DOI: 10.1289/EHP191.
162 R. Picetti, M. Deeney, S. Pastorino, M. R. Miller, A. Shah, D. A. Leon, A. D. Dangour and R. Green, Nitrate and nitrite contamination in drinking water and cancer risk: a systematic review with meta-analysis, *Environ. Res.*, 2022, **210**, 112988, DOI: 10.1016/j.envres.2022.112988.
163 J. M. Elwood and B. v. d. Werf, Nitrates in drinking water and cancers of the colon and rectum: a meta-analysis of epidemiological studies, *Cancer Epidemiol.*, 2022, **78**, 102148, DOI: 10.1016/j.canep.2022.102148.
164 R. Noori, F. Farahani, C. Jun, S. Aradpour, S. M. Bateni, F. Ghazban, M. Hosseinzadeh, M. Maghrebi, M. R. Vesali Naseh and S. Abolfathi, A non-threshold model to estimate carcinogenic risk of nitrate–nitrite in drinking water, *J. Cleaner Prod.*, 2022, **363**, 132432, DOI: 10.1016/j.jclepro.2022.132432.
165 J. Richards, T. Chambers, S. Hales, M. Joy, T. Radu, A. Woodward, A. Humphrey, E. Randal and M. G. Baker, Nitrate contamination in drinking water and colorectal cancer: exposure assessment and estimated health burden in New Zealand, *Environ. Res.*, 2022, **204**, 112322, DOI: 10.1016/j.envres.2021.112322.
166 J. Schullehner, B. Hansen, M. Thygesen, C. B. Pedersen and T. Sigsgaard, Nitrate in drinking water and colorectal cancer risk: a nationwide population-based cohort study, *Int. J. Cancer*, 2018, **143**, 73–79, DOI: 10.1002/ijc.31306.
167 B. Aschebrook-Kilfoy, S. L. Heltshe, J. R. Nuckols, M. M. Sabra, A. R. Shuldiner, B. D. Mitchell, M. Airola, T. R. Holford, Y. Zhang and M. H. Ward, 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, DOI: 10.1186/1476-069X-11-6.
168 E. García Torres, R. Pérez Morales, A. González Zamora, E. Ríos Sánchez, E. H. Olivas Calderón, J. d. J. Alba Romero and E. Y. Calleros Rincón, Consumption of water contaminated by nitrate and its deleterious effects on the human thyroid gland: a review and update, *Int. J. Environ. Health Res.*, 2022, **32**, 984–1001, DOI: 10.1080/09603123.2020.1815664.
169 J. D. Brender, P. J. Weyer, P. A. Romitti, B. P. Mohanty, M. U. Shinde, A. M. Vuong, J. R. Sharkey, D. Dwivedi, S. A. Horel, J. Kantamneni, J. C. Huber, Q. Zheng, M. M. Werler, K. E. Kelley, J. S. Griesenbeck, F. B. Zhan, P. H. Langlois, L. Suarez and M. A. Canfield, 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, DOI: 10.1289/ehp.1206249.
170 U.S. Environmental Protection Agency, *Secondary Drinking Water Standards: Guidance for nuisance chemicals*, https://www.epa.gov/sdwa/secondary-drinking-water-standards-guidance-nuisance-chemicals, accessed June 21, 2024.
171 U.S. Environmental Protection Agency, Health Effects Support Document for Manganese, *Report EPA 822-R-03-003*, United States Environmental Protection Agency, 2003, https://www.epa.gov/sites/default/files/2014-09/documents/support_cc1_magnese_healtheffects_0.pdf.
172 Wisconsin Department of Natural Resources, *WI DNR – Drinking Water and Groundwater Quality Standards/Advisory Levels*, https://dnr.wisconsin.gov/sites/default/files/topic/DrinkingWater/HALtable.pdf, accessed June 21, 2024.

173 P. U. Iyare, The effects of manganese exposure from drinking water on school-age children: a systematic review, *Neurotoxicology*, 2019, **73**, 1–7, DOI: 10.1016/j.neuro.2019.02.013.
174 M. Ramachandran, K. A. Schwabe and S. C. Ying, Shallow groundwater manganese merits deeper consideration, *Environ. Sci. Technol.*, 2021, **55**, 3465–3466, DOI: 10.1021/acs.est.0c08065.
175 U.S. Environmental Protection Agency, Fact Sheet: Fifth Contaminant Candidate List (CCL5), *Report EPA 815-F-22-005*, United States Environmental Protection Agency, 2022, https://www.epa.gov/system/files/documents/2022-10/Fact%20Sheet%20Final%20Fifth%20Contaminant%20Candidate%20List%20%28CCL%205%29.pdf.
176 World Health Organization, *Manganese in Drinking-Water: Background Document for Development of WHO Guidelines for Drinking-water Quality – Version for Public Review*, 2020, https://www.who.int/docs/default-source/wash-documents/wash-chemicals/gdwq-manganese-background-document-for-public-review.pdf?sfvrsn=9296741f_5.
177 U.S. Public Health Service, U.S. Public Health Service recommendation for fluoride concentration in drinking water for the prevention of dental caries, *Public Health Rep.*, 2015, **130**, 318–331, DOI: 10.1177/003335491513000408.
178 P. B. McMahon, C. J. Brown, T. D. Johnson, K. Belitz and B. D. Lindsey, Fluoride occurrence in United States groundwater, *Sci. Total Environ.*, 2020, **732**, 139217, DOI: 10.1016/j.scitotenv.2020.139217.
179 L. A. DeSimone, P. B. McMahon and M. R. Rosen, The Quality of Our Nation's Waters: Water Quality in Principal Aquifers of the United States, 1991–2010, *Report U. S. Geological Survey Circular 1360*, Reston, VA, 2015, DOI: 10.3133/cir1360.
180 American Academy of Pediatrics, Policy statement: drinking water from private wells and risks to children, *Pediatrics*, 2009, **123**, 1599–1605, DOI: 10.1542/peds.2009-0751.
181 American Academy of Pediatrics: Committee on Nutrition, Fluoride supplementation for children: interim policy recommendations, *Pediatrics*, 1995, **95**, 777, DOI: 10.1542/peds.95.5.777.
182 W. G. Kohn, W. R. Maas, D. M. Malvitz, S. M. Presson and K. K. Shaddix, *Recommendations For Using Fluoride To Prevent And Control Dental Caries In The United States*, 2001, https://stacks.cdc.gov/view/cdc/5160.
183 W. J. Rogan and M. T. Brady, Drinking water from private wells and risks to children, *Pediatrics*, 2009, **123**, e1123–e1137, DOI: 10.1542/peds.2009-0752.
184 M. J. Focazio, D. Tipton, S. S. Dunkle and L. H. Geiger, The chemical quality of self-supplied domestic well water in the United States, *Groundwater Monit. Rem.*, 2006, **26**, 92–104, DOI: 10.1111/j.1745-6592.2006.00089.x.
185 J. MacDonald Gibson and K. Pieper, Strategies to improve private-well water quality: a North Carolina perspective, *Environ. Health Perspect.*, 2017, **125**, 076001, DOI: 10.1289/EHP890.
186 P. M. Bradley, C. Journey, K. Romanok, L. Barber, H. T. Buxton, W. T. Foreman, E. T. Furlong, S. Glassmeyer, M. Hladik, L. R. Iwanowicz, D. Jones, D. Kolpin, K. Kuivila, K. Loftin, M. Mills, M. Meyer, J. Orlando, T. Reilly, K. Smalling and D. Villeneuve, Expanded target-chemical analysis reveals extensive mixed-organic-contaminant exposure in USA streams, *Environ. Sci. Technol.*, 2017, **51**, 4792–4802, DOI: 10.1021/acs.est.7b00012.
187 S. T. Glassmeyer, E. T. Furlong, D. W. Kolpin, A. L. Batt, R. Benson, J. S. Boone, O. Conerly, M. J. Donohue, D. N. King, M. S. Kostich, H. E. Mash, S. L. Pfaller, K. M. Schenck, J. E. Simmons, E. A. Varughese, S. J. Vesper, E. N. Villegas and V. S. Wilson, Nationwide reconnaissance of contaminants of emerging concern in source and treated drinking waters of the United States, *Sci. Total Environ.*, 2017, **581–582**, 909–922, DOI: 10.1016/j.scitotenv.2016.12.004.
188 A. M. Richard, R. S. Judson, K. A. Houck, C. M. Grulke, P. Volarath, I. Thillainadarajah, C. Yang, J. Rathman, M. T. Martin and J. F. Wambaugh, ToxCast chemical landscape: paving the road to 21st century toxicology, *Chem. Res. Toxicol.*, 2016, **29**, 1225–1251, DOI: 10.1021/acs.chemrestox.6b00135.
189 U.S. Environmental Protection Agency National Center for Computational Toxicology, *ToxCast Database InvitroDB3.2*, 2020, DOI: 10.23645/epacomptox.6062623.v4.
190 A. L. Schroeder, G. T. Ankley, K. A. Houck and D. L. Villeneuve, Environmental surveillance and monitoring—The next frontiers for high-throughput toxicology, *Environ. Toxicol. Chem.*, 2016, **35**, 513–525, DOI: 10.1002/etc.3309.
191 H. El-Masri, K. Paul Friedman, K. Isaacs and B. A. Wetmore, Advances in computational methods along the exposure to toxicological response paradigm, *Toxicol. Appl. Pharmacol.*, 2022, **450**, 116141, DOI: 10.1016/j.taap.2022.116141.
192 D. L. Villeneuve, K. Coady, B. I. Escher, E. Mihaich, C. A. Murphy, T. Schlekat and N. Garcia-Reyero, High-throughput screening and environmental risk assessment: state of the science and emerging applications, *Environ. Toxicol. Chem.*, 2019, **38**, 12–26, DOI: 10.1002/etc.4315.
193 J. Hakkola, C. Bernasconi, S. Coecke, L. Richert, T. B. Andersson and O. Pelkonen, Cytochrome P450 Induction and Xeno-Sensing Receptors Pregnane X Receptor, Constitutive Androstane Receptor, Aryl Hydrocarbon Receptor and Peroxisome Proliferator-Activated Receptor α at the Crossroads of Toxicokinetics and Toxicodynamics, *Basic Clin. Pharmacol. Toxicol.*, 2018, **123**, 42–50, DOI: 10.1111/bcpt.13004.
194 C. N. P. G. Arachchige, L. A. Prendergast and R. G. Staudte, Robust analogs to the coefficient of variation, *J. Appl. Stat.*, 2022, **49**, 268–290, DOI: 10.1080/02664763.2020.1808599.
195 Z. Wang, G. W. Walker, D. C. G. Muir and K. Nagatani-Yoshida, Toward a global understanding of chemical pollution: a first comprehensive analysis of national and

regional chemical inventories, *Environ. Sci. Technol.*, 2020, **54**, 2575–2584, DOI: 10.1021/acs.est.9b06379.

196 S. Ermler, M. Scholze and A. Kortenkamp, The suitability of concentration addition for predicting the effects of multi-component mixtures of up to 17 anti-androgens with varied structural features in an *in vitro* AR antagonist assay, *Toxicol. Appl. Pharmacol.*, 2011, **257**, 189–197, DOI: 10.1016/j.taap.2011.09.005.

197 A. Kortenkamp, Distinctions between similarly and dissimilarly acting mixture components unnecessarily complicate mixture risk assessments: implications for assessing low dose mixture exposures, *Curr. Opin. Toxicol.*, 2023, **35**, 100418, DOI: 10.1016/j.cotox.2023.100418.

198 P. S. Price, The Hazard index at thirty-seven: new science new insights, *Curr. Opin. Toxicol.*, 2023, **34**, 100388, DOI: 10.1016/j.cotox.2023.100388.

199 M. Faust, R. Altenburger, T. Backhaus, H. Blanck, W. Boedeker, P. Gramatica, V. Hamer, M. Scholze, M. Vighi and L. Grimme, Joint algal toxicity of 16 dissimilarly acting chemicals is predictable by the concept of independent action, *Aquat. Toxicol.*, 2003, **63**, 43–63, DOI: 10.1016/S0166-445X(02)00133-9.

200 T. Backhaus, R. Altenburger, W. Boedeker, M. Faust, M. Scholze and L. H. Grimme, Predictability of the toxicity of a multiple mixture of dissimilarly acting chemicals to *Vibrio fischeri*, *Environ. Toxicol. Chem.*, 2000, **19**, 2348–2356, DOI: 10.1002/etc.5620190927.

201 H. Walter, F. Consolaro, P. Gramatica, M. Scholze and R. Altenburger, Mixture Toxicity of Priority Pollutants at No Observed Effect Concentrations (NOECs), *Ecotoxicology*, 2002, **11**, 299–310, DOI: 10.1023/A:1020592802989.

202 T. J. Thrupp, T. J. Runnalls, M. Scholze, S. Kugathas, A. Kortenkamp and J. P. Sumpter, The consequences of exposure to mixtures of chemicals: something from 'nothing' and 'a lot from a little' when fish are exposed to steroid hormones, *Sci. Total Environ.*, 2018, **619–620**, 1482–1492, DOI: 10.1016/j.scitotenv.2017.11.081.

203 A. Kortenkamp, Invited Perspective: How Relevant Are Mode-of-Action Considerations for the Assessment and Prediction of Mixture Effects?, *Environ. Health Perspect.*, 2022, **130**, 041302, DOI: 10.1289/EHP11051.

204 O. Martin, M. Scholze, S. Ermler, J. McPhie, S. K. Bopp, A. Kienzler, N. Parissis and A. Kortenkamp, Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies, *Environ. Int.*, 2021, **146**, 106206, DOI: 10.1016/j.envint.2020.106206.

205 K. Paul Friedman, M. Gagne, L.-H. Loo, P. Karamertzanis, T. Netzeva, T. Sobanski, J. A. Franzosa, A. M. Richard, R. R. Lougee, A. Gissi, J.-Y. J. Lee, M. Angrish, J. L. Dorne, S. Foster, K. Raffaele, T. Bahadori, M. R. Gwinn, J. Lambert, M. Whelan, M. Rasenberg, T. Barton-Maclaren and R. S. Thomas, Utility of *in vitro* bioactivity as a lower bound estimate of *in vivo* adverse effect levels and in risk-based prioritization, *Toxicol. Sci.*, 2020, **173**, 202–225, DOI: 10.1093/toxsci/kfz201.

206 U.S. Environmental Protection Agency, Method 1633: Analysis of Per- and Polyfluoroalkyl Substances (PFAS) in Aqueous, Solid, Biosolids, and Tissue Samples by LC-MS/MS, *Report EPA 821-R-24-001*, U.S. Environmental Protection Agency, Washington, D.C., 2024, https://www.epa.gov/system/files/documents/2024-01/method-1633-final-for-web-posting.pdf.

207 J. Wu, M. Cao, D. Tong, Z. Finkelstein and E. M. V. Hoek, A critical review of point-of-use drinking water treatment in the United States, *npj Clean Water*, 2021, **4**, 40, DOI: 10.1038/s41545-021-00128-z.

208 R. Mulhern, N. Bynum, C. Liyanapatirana, N. J. DeStefano, D. R. U. Knappe and J. MacDonald Gibson, Longitudinal assessment of point-of-use carbon filters for removal of per- and polyfluoroalkyl substances from private well water, *AWWA Water Sci.*, 2021, **3**, e1262, DOI: 10.1002/aws2.1262.

209 C. Patterson, J. Burkhardt, D. Schupp, E. R. Krishnan, S. Dyment, S. Merritt, L. Zintek and D. Kleinmaier, Effectiveness of point-of-use/point-of-entry systems to remove per- and polyfluoroalkyl substances from drinking water, *AWWA Water Sci.*, 2019, **1**, e1131, DOI: 10.1002/aws2.1131.

210 H. MacKeown, E. Magi, M. Di Carro and B. Benedetti, Removal of perfluoroalkyl and polyfluoroalkyl substances from tap water by means of point-of-use treatment: a review, *Sci. Total Environ.*, 2024, **954**, 176764, DOI: 10.1016/j.scitotenv.2024.176764.

211 N. J. Herkert, J. Merrill, C. Peters, D. Bollinger, S. Zhang, K. Hoffman, P. L. Ferguson, D. R. U. Knappe and H. M. Stapleton, Assessing the Effectiveness of Point-of-Use Residential Drinking Water Filters for Perfluoroalkyl Substances (PFASs), *Environ. Sci. Technol. Lett.*, 2020, **7**, 178–184, DOI: 10.1021/acs.estlett.0c00004.

212 A. S. C. Chen, L. Wang, T. J. Sorg and D. A. Lytle, Removing arsenic and co-occurring contaminants from drinking water by full-scale ion exchange and point-of-use/point-of-entry reverse osmosis systems, *Water Res.*, 2020, **172**, 115455, DOI: 10.1016/j.watres.2019.115455.

