



Cite this: *Environ. Sci.: Water Res. Technol.*, 2025, **11**, 2572

## Tapwater-contaminant mixtures and risk in a biofuel-facility impacted private-well community

Paul M. Bradley,<sup>a</sup> Shannon M. Meppelink,<sup>b</sup> Kristin M. Romanok,<sup>c</sup> Molly L. Schreiner,<sup>c</sup> Kelly L. Smalling,<sup>c</sup> Shannon L. Bartelt-Hunt,<sup>d</sup> Brenda K. Densmore,<sup>e</sup> Stephanie E. Gordon,<sup>f</sup> Keith A. Loftin,<sup>g</sup> Richard Blaine McCleskey,<sup>h</sup> Eleanor G. Rogan,<sup>i</sup> David L. Rus<sup>e</sup> and Daniel D. Snow<sup>d</sup>

We assessed private-well drinking water (DW) at the point of use (*i.e.*, tapwater, TW) within a rural Nebraska community around a state-closed biofuel facility, which used pesticide-treated corn seed as feedstock for ethanol production. Organic (485), inorganic (34), and microbial (13) analytes were assessed at 15 locations in June 2022, to evaluate the relative contribution of facility-consistent pesticides (seed-treatment fungicides and insecticides) to overall TW-contaminant exposures and predicted human-health risks. Thirty-three organics (12 pesticides) and 28 inorganics were detected, the former including the fungicide sedaxane, insecticide chlorantraniliprole, and multiple neonicotinoid insecticides/degradates, all consistent with seed treatment and respective biofuel-facility waste. Assessment of pesticides only at extant point-of-use (POU) treatment taps at three sites demonstrated complete elimination of all TW-pesticide detections. Based on detection of maximum pesticide concentrations in a home located downstream along a creek capturing facility runoff, pesticides only were assessed in January 2023 again at this home and at three adjacent locations, confirming results at the former and documenting decreasing TW-pesticide concentrations, including neonicotinoids, with increasing distance from the creek. Human-health DW benchmarks are not available for many detected pesticides, including the detected fungicide and insecticides, but precautionary screening levels were exceeded frequently due to multiple inorganics. The results indicate that exposures to multiple (median: 4.5; range: 1–7) co-occurring TW contaminants of potential human-health concern are common, warranting consideration of point-of-entry or POU treatment(s) throughout the community to reduce or eliminate unrecognized exposures to TW contaminants, including facility-associated pesticides in down-gradient locations. More broadly, results emphasize the importance of continued characterization of private-TW exposures, employing an environmentally informative analytical scope, to identify and mitigate risks of unrecognized exposures in private-well-dependent rural communities.

Received 29th May 2025,  
Accepted 10th September 2025

DOI: 10.1039/d5ew00490j

rsc.li/es-water

### Water impact

Private-well-dependent rural agricultural communities incur elevated risks of unrecognized tapwater exposures and human-health effects of agrochemical and naturally occurring contaminants, due to owner-dependent and generally limited private-well monitoring. A broad-analytical-scope assessment around a state-closed biofuel facility illustrates the importance of private-well monitoring and precautionary tapwater treatment to reduce cumulative risks of a range of unrecognized contaminant exposures.

## 1 Introduction

Drinking water (DW) safety and sustainability are priorities in the United States (US) and globally,<sup>1–5</sup> given the biological prerequisite for water<sup>6–8</sup> and consequent role as an increasingly vulnerable route of potential human exposures to numerous environmental contaminants, including a wide range of inorganic (*e.g.*, nutrients) and organic (*e.g.*, pesticides) chemicals associated with contemporary agricultural practice,<sup>3–5,9</sup> such as pesticide seed-treatments to

<sup>a</sup> United States Geological Survey, Columbia, South Carolina 29210, USA.

E-mail: pbradley@usgs.gov

<sup>b</sup> United States Geological Survey, Iowa City, Iowa 52240, USA

<sup>c</sup> United States Geological Survey, Lawrenceville, New Jersey 08648, USA

<sup>d</sup> University of Nebraska-Lincoln, Lincoln, Nebraska 68588, USA

<sup>e</sup> U.S. Geological Survey, Lincoln, Nebraska 68512, USA

<sup>f</sup> United States Geological Survey, Kearneysville, West Virginia 25430, USA

<sup>g</sup> U.S. Geological Survey, Lawrence, Kansas 66049, USA

<sup>h</sup> U.S. Geological Survey, Boulder, Colorado 80303, USA

<sup>i</sup> University of Nebraska Medical Center, Omaha, Nebraska 68198, USA



improve corn and soybean crop production.<sup>10</sup> DW-agrochemical contamination has long been a public-health concern,<sup>11–13</sup> notably in agriculturally-intensive areas like US midwestern states and China,<sup>14–19</sup> due to prolific use,<sup>20–22</sup> landscape-scale sources and routes to ground and surface DW resources,<sup>15,17,19,23–27</sup> and well-documented DW exposures.<sup>11,14,15,28–32</sup> Associated DW-organic exposure concerns<sup>14,33</sup> include pesticide links to cancers,<sup>34–39</sup> Parkinson's disease,<sup>40</sup> endocrine disruption,<sup>41</sup> reproductive<sup>42</sup> and cardiovascular toxicities,<sup>43</sup> and developmental neurotoxicity,<sup>44</sup> while example DW-inorganic concerns<sup>14,33</sup> include nitrate-nitrogen (NO<sub>3</sub>-N) links to infant (<6 months) methemoglobinemia<sup>45</sup> and, more recently,<sup>46,47</sup> cancers,<sup>48–53</sup> thyroid disease,<sup>54,55</sup> and neural tube defects.<sup>56</sup>

Pesticides and NO<sub>3</sub>-N have been documented in all three primary point-of-use (POU) DW supplies (private-well tapwater [TW], public-supply TW, and bottled water).<sup>5,11,15,57</sup> The risk of unrecognized exposures, however, is notably higher for private-well TW (private-TW) due to a comparative lack of information on associated contaminant exposures.<sup>5,58</sup> The US Environmental Protection Agency (EPA) is not authorized to regulate or monitor private-TW,<sup>59</sup> and about 14% of the US population relies on private wells,<sup>60–62</sup> with concomitant homeowner-monitoring/-maintenance burdens.<sup>59</sup> High analytical costs, limited technical training/awareness, and conflation of safety and aesthetic quality severely undermine homeowner private-well monitoring;<sup>5</sup> accordingly, TW data, where available, typically comprise only a few analytes (*e.g.*, microbial).<sup>63–65</sup> The resultant TW-contaminant-exposure data gap in private-well-dependent remote/rural locations, including in agriculturally-intensive regions, undermines individual and community DW-risk-management decision making<sup>5,65</sup> and contributes to water insecurity<sup>66,67</sup> and attendant physical- and mental-health burdens.<sup>68,69</sup>

An ongoing, unusual agrochemical-contamination “hotspot/hot event”<sup>70</sup> at and around a bioenergy plant in Mead, Nebraska has raised water insecurity concerns for the largely private-well-dependent community.<sup>71–77</sup> In operation from 2015 until closed under state order in February 2021,<sup>78,79</sup> the facility utilized unused, expired pesticide-treated corn seeds as feedstock for ethanol production, resulting in onsite accumulation of wastewater and “wet cake” (estimated at 67 000 m<sup>3</sup> and 77 000 metric tons, respectively, at site closure) highly contaminated with fungicides and insecticides, including neonicotinoids. Field applications in the surrounding area during 2017–2019,<sup>73</sup> combined with aerial (*e.g.*, windblown dust) and hydrologic (*e.g.*, digester tank and storage-lagoon breaches to surface-water and groundwater systems, respectively<sup>75,78,79</sup>) transport offsite, have raised notable environmental<sup>73,75,76,80</sup> and human<sup>73,74,77,81</sup> exposure concerns, including through private-TW.

Addressing TW insecurity requires extensive inorganic/organic/microbial characterization of respective exposures and cumulative-risks, to disentangle perceived *versus* actual risks and support community and individual-consumer risk-

mitigation actions. The U.S. Geological Survey (USGS) partners with communities, universities, Tribal Nations and colleges, state and federal agencies, utilities, and others to inform DW-exposure data gaps by assessing TW inorganic/organic/microbial contaminant mixtures and associated distal (*e.g.*, ambient source water) and proximal (*e.g.*, premise plumbing, point-of-entry [POE]/POU treatment) drivers in a range of US socioeconomic and source-water-vulnerability settings.<sup>5,18,82–90</sup>

In 2022, USGS partnered with University of Nebraska Lincoln, University of Nebraska Medical Center, and the community of Mead to assess exposures to a broad suite of potential inorganic/organic/microbial TW contaminants in 15 locations surrounding and downgradient of the facility. Research goals included 1) assessing contaminant-mixture exposures and cumulative risks to human health<sup>91–93</sup> in private-TW, 2) quantifying TW exposures and relative risks attributable to biofuel-facility, seed-coat pesticides, and 3) continued expansion of the national perspective on contaminant mixture exposures at the TW point of use by maintaining the same general sampling protocol and analytical toolbox employed in previous studies across the US.<sup>5,18,82–89</sup>

TW exposures were operationally represented as concentrations of 485 organics, 34 inorganics, and 13 microbial indicators in private-TW samples, for this study. Potential human-health risks of individual and aggregate TW exposures were screened<sup>5,94–96</sup> based on individual and cumulative benchmark-based toxicity quotients (TQ and  $\sum_{TQ}$ , respectively)<sup>84,97</sup> and supported by cumulative exposure-activity ratio(s) ( $\sum_{EAR}$ ),<sup>84,98</sup> as described previously.<sup>5</sup> Due to the limited availability of organic benchmarks (*e.g.*, *circa* 100 in Safe Drinking Water Amendments [SDWA] National Primary Drinking Water Regulations [NPDWR]<sup>45,99</sup>) relative to organic chemicals in global commercial use,<sup>100</sup> potential human-health risks of individual TW exposures also were explored based on detections/concentrations of designed-bioactive chemicals (*e.g.*, pesticides, pharmaceuticals).<sup>101</sup> In line with published results by this research group,<sup>5,18,82–89</sup> and by others,<sup>9,64,102–106</sup> simultaneous exposures to multiple organic, inorganic, and microbial constituents of potential human-health interest were hypothesized to occur in private-TW. Specific hypotheses addressed herein included:

I. Human exposures to insecticide(s) and fungicide(s) consistent with pesticide-treated-seed feedstock occurred *via* private-TW in the vicinity and downgradient of the biofuel facility.

II. Systematic TW-organic-contaminant exposures of potential human-health concern comprised primarily co-occurring agricultural pesticides, including fungicides and neonicotinoid insecticides, with detections of other organic classes generally limited and sporadic.

III. Extant POU treatments effectively removed pesticide contaminants from private-TW samples.

IV. Co-occurring inorganic exposures of potential human-health concern were common in private-TW samples.



V. Due to limited human-health DW-pesticide benchmarks, private-TW cumulative risk was driven primarily by co-occurring inorganic exposures.

## 2 Methods

### 2.1 Site selection and sample collection

Mead, Nebraska, and the closed biofuel facility (Fig. 1) are located within Saunders County in the Todd Valley, an abandoned channel of the Platte River.<sup>107,108</sup> The facility lies within the drainage basin of Clear Creek, which flows southeast, discharging in turn to Wahoo Creek, Salt Creek, and the Platte River near the southeast corner of Saunders County.<sup>107</sup> The unnamed, intermittent, tributary network, draining the Eastern Nebraska Research, Extension and Education Center (ENREEC) south of the facility, includes a branch (labelled previously<sup>75</sup> and herein as ENREEC creek) that headwaters within the biofuel-facility grounds, combines into a single streamflow, and passes through a run-of-stream pond near site 4, shortly before the confluence with Clear Creek. Groundwater flow through the Todd Valley, including in the unconfined surficial Quaternary alluvial aquifer, likewise, is generally northwest to southeast toward the Platte River.<sup>79,107,108</sup>

Fifteen private-well sample locations in the area surrounding the biofuel facility, including upgradient [northwest] of Mead and downgradient [southeast] of the facility on ENREEC creek, were selected for broad-scope organic/inorganic/microbial analysis (Fig. 1; Table S1).<sup>109</sup> Sites 1 and 2 were facilities with on-site chlorine disinfection of the respective private-well TW. Kitchen taps (cold water) were sampled for broad-analytical-scope assessment once each in June 2022. Because three of these private-TW locations had POU treatment installed in parallel to the kitchen tap (reverse osmosis [RO]: site 1; under-sink carbon filter: sites 4 and 6), pesticide samples also were collected from the POU-treatment fixture, at the request of the study participants, to assess the efficacy of pesticide-contaminant removal. Samples were collected at the participant's convenience throughout the day, without pre-cleaning, screen removal, or lead and copper rule stagnant-sample requirements.<sup>110,111</sup> Based on maximum observed pesticide concentrations, including insecticides and a fungicide consistent with biofuel-facility feedstock, in a private-TW sample location (site 4) downgradient on ENREEC creek, this and three additional nearby homes (sites: 17, 19, 20), located north (sites 19, 20) and south (site



**Fig. 1** Map of study area near Mead, Nebraska, United States, showing private-TW locations sampled for broad-scope organic/inorganic/microbial analysis in June 2022 (color circles; sites: 01–15) and for pesticides only in January 2023 (empty squares; sites: 17, 19, 20). Number next to symbol indicates site number in Table S1. Size and color of circles indicate number of exceedances of human-health benchmarks for detected analytes. Sample locations are anonymized.



17) of Site 4 and orthogonal to the general flow of ENREEC creek (Fig. 1) and presumptive southeast groundwater flow direction from facility,<sup>79</sup> were resampled/sampled for pesticides only in January 2023, to provide insight into potential pesticide-contaminant hydrologic-transport mechanisms. Complete sampling details are provided elsewhere.<sup>109,112</sup>

## 2.2 Methods, quality assurance, and statistics

Briefly, TW samples were analyzed by USGS using 8 organic (7 classes; 499 total/485 unique analytes), 6 inorganic (34 ions/trace elements), 13 microbial (13 indicators), and 2 field (3 parameters) methods (Table S2), as discussed.<sup>5,82–84,86,112,113</sup> Organic analytes included cyanotoxin, disinfection byproduct(s) (DBP), pesticide, per/polyfluoroalkyl substance(s) (PFAS), pharmaceutical, semi-volatile organic compound(s) (SVOC), and volatile organic compound(s) (VOC) classes; additional method details and links to source publications are in the SI (Table S2). All results are in Tables S3a–S6 and in Meppelink *et al.*<sup>109</sup> Quantitative ( $\geq$ limit of quantitation,  $\geq$ LOQ) and semi-quantitative (between LOQ and long-term method detection limit, MDL<sup>114,115</sup>) results were treated as detections.<sup>114,116,117</sup> Quality-assurance and quality-control included analyses of one field blank and laboratory blanks, spikes, and stable-isotope surrogates. No organic or inorganic analytes or microbial indicators were detected in blanks at concentrations in the range observed in TW samples (Table S6). The median surrogate recovery (Table S4c) was 92.6% (interquartile range: 78.5–104%).

## 2.3 Individual and cumulative contaminant risk assessments

Individual-contaminant private-TW exposures were compared to public-supply-applicable NPDWR maximum contaminant level(s) (MCL)<sup>45,99,118</sup> as a frame of reference for exposures of potential concern for the general-consumer population (*i.e.*, not sensitive subpopulation(s)). However, because the EPA MCL rule-making process includes technical and financial considerations,<sup>45,118</sup> the potential for apical human-health effects of individual contaminant exposures was screened based on health-only MCL goal(s) (MCLG), “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”, when considering sensitive (infants, children, elderly, immune- or disease-compromised) subpopulations,<sup>118</sup> and other similar federal, state, and international health-only DW advisories.

A human-health-only, DW-benchmark-based precautionary screening of cumulative organic/inorganic contaminant risk was conducted consistent with World Health Organization/International Programme on Chemical Safety [WHO/IPCS] framework tier 1 hazard index risk screening,<sup>94</sup> European Food Safety Authority tier 1 reference point index (RPI) risk screening,<sup>95</sup> and 2023 EPA<sup>96</sup> guidance, as described

previously.<sup>5</sup> The toxEval version 1.4.0 package<sup>119</sup> of the open source statistical software R<sup>120</sup> was used to sum (broadly applicable non-interactive concentration/dose addition model<sup>121–126</sup>) the TQ (ratio of detected concentration to corresponding health-based DW benchmark) of individual detections to estimate sample-specific cumulative TQ ( $\sum_{TQ}$ ).<sup>5,97</sup> Departures from approximate concentration addition (*e.g.*, ref. 127–130) are uncommon, limited in magnitude, and increasingly improbable with increasing mixture complexity.<sup>125,131,132</sup> The most protective human-health DW benchmark (*i.e.*, lowest benchmark concentration) among the following was employed, for each detected analyte: NPDWR MCLG,<sup>45,133</sup> EPA Drinking-Water Health Advisory(ies) (DWHA),<sup>134</sup> WHO guideline value (GV),<sup>135</sup> state MCL or DWHA (*e.g.*, ref. 136), or USGS Health-Based Screening Level (HBSL) or Human Health Benchmarks for Pesticides (HHBP).<sup>137</sup> EPA sets MCLG at “zero” for DW contaminants (*e.g.*, bromodichloromethane, lead [Pb]), which “may cause cancer” and for which “there is no dose below which the chemical is considered safe”, including for sensitive (infants, children, elderly, immune- or disease-compromised) subpopulations.<sup>45,118,133</sup> For this  $\sum_{TQ}$  assessment, MCLG values of “zero” were set to 0.1  $\mu\text{g L}^{-1}$  for metals (arsenic [As], lead [Pb], uranium [U]), DBP, and VOC, as described.<sup>5</sup>  $\sum_{TQ}$  results and respective health-based benchmarks are summarized in Table S7a and b.

Potential molecular-level effects of mixed-organic contaminant exposures also were explored, using an exposure-activity ratio (EAR) approach based on Toxicity ForeCaster (ToxCast)<sup>138,139</sup> high-throughput data.<sup>140</sup> In contrast to the human-health DW-concentration benchmarks employed in the mathematically-analogous  $\sum_{TQ}$  assessment above, ToxCast metrics are *in vitro* estimates of chemical-specific exposure-response relations at the site of molecular activity. The approach herein and previously<sup>5,18,82–87,141</sup> assumes that the measured TW concentration provides a reasonable first-level estimate of *in vivo* molecular-level exposure. Accordingly, the R package<sup>120</sup> toxEval version 1.4.0 (ref. 119) was employed to sum (approximate concentration addition model<sup>121–126</sup>) individual-contaminant EAR (ratio of the detected contaminant concentration to the contaminant-specific “activity concentration at cutoff” for a positive response (ACC) metric from ToxCast<sup>140</sup>) to estimate sample-specific cumulative EAR ( $\sum_{EAR}$ ).<sup>5,98</sup> ACC data in the toxEval v1.4.0 employed in the present study were from the September 2023 invitroDBv4.1 release of the ToxCast database.<sup>142</sup> Non-specific-endpoint, baseline, and unreliable response-curve assays were excluded.<sup>82,83,98</sup>  $\sum_{EAR}$  results and exclusions are summarized in Table S8a–c. Approximate contaminant-specific equivalency of the widely-employed TQ = 0.1 screening-level threshold of concern and EAR = 0.001 has been reported.<sup>97</sup> Thus, EAR (and  $\sum_{EAR}$ ) = 0.001 was employed to screen for potential concern (*i.e.*, for additional investigation and characterization) but not necessarily apical health risk, the latter due to uncertainties in *in vitro* to



*in vivo* extrapolation<sup>143,144</sup> and the fact that measured bioactivities are not necessarily adverse and may, in some cases, reflect adaptive (*e.g.*, activation of xenobiotic metabolism<sup>145</sup>) responses.

## 3 Results and discussion

### 3.1 Target-analyte TW exposures

Multiple regulated and unregulated chemical (organic, inorganic) and microbial analytes were routinely detected in private-TW samples collected in 2022 (Fig. 1–3; Tables S3, S4a and S5). At least one detection of potential human-health concern was observed in every sample, with 2–7 in 93% (14/15) of samples.

TW samples were screened for 4 cyanotoxins, 22 DBP, 186 pesticide, 34 PFAS, 111 pharmaceutical, 55 SVOC, and 73 VOC analytes (Fig. 2; Table S2). Of these 485 unique organic analytes, 33 (7%) were detected at least once (Fig. 2), including 4 organics observed at concentrations of human-health concern with analyte-specific concern-level exceedance frequencies ranging 7% (tetrachloromethane, trichloroethene) up to 20% (tribromomethane) of all samples (Table S4a). Among the 33 organic analytes detected during the June 2022 broad-analytical-scope assessment, 16 (49%) were detected only once (Fig. 2; Table S4a). Nineteen (51%) were detected only once, when including the January 2023 pesticide-only follow-up sampling (Table S4b). At least one organic contaminant was detected in every TW-sample location (median: 5; IQR: 2.5–6.5; range: 1–15), with more than one detected in 80% (12/15) of locations (83% or 15 of 18 locations, including 2023 pesticide-only sampling). Analyte-specific detection frequencies for organics ranged up to 53% (deethylatrazine [CIAT], desmethylatrazine). No pesticides were detected in any TW samples collected from POU-treatment taps at sites 1, 4, and 6, indicating effective removal.

Fungicide (sedaxane) and insecticide (chlorantraniliprole, clothianidin, thiamethoxam) or degradate (thiamethoxam degradate CGA-355190) analytes consistent with facility seedcoat feedstock were observed only in the private-TW sample location (site 4) downgradient along ENREEC creek. These feedstock-consistent site 4 detections were confirmed at approximately 2–4 times higher concentrations in January 2023, along with additional neonicotinoid-insecticide detections of imidacloprid and its degradate (Table S4b). During the January 2023 sampling, single detections of feedstock-consistent neonicotinoids also were observed at sites 17 (clothianidin) and 19 (imidacloprid), located adjacent to site 4 and orthogonal to the general southeastern orientation of the ENREEC creek drainage and presumptive groundwater flow.

Twenty-eight (82%) of 34 inorganic analytes were detected at least once (Table S3a). Ten inorganics were detected at concentrations of human-health concern with analyte-specific concern-level exceedance frequencies ranging 7% (single detections for boron [B], fluoride [F], manganese [Mn], strontium [Sr]) up to 100% (U) of samples.

Microbial results included commonplace detections of general heterotrophic bacteria (*i.e.*, heterotrophic plate counts [HPC]) but no detections of total coliforms or *Escherichia coli* (Table S5). However, growth on putative-pathogen selective media indicated possible human-health concern in several sample locations.

### 3.2 Individual contaminant screening: MCL comparison

Concentrations equivalent to the respective NPDWR MCL (frame of reference only; not enforceable in federally unregulated private-TW) were exceeded for four inorganics, comprising nitrate-nitrogen (NO<sub>3</sub>-N), arsenic (As), copper (Cu), and uranium (U) (Table S3). The MCL-equivalent concentration for NO<sub>3</sub>-N was exceeded in three samples (sites: 1, 6, 10), with single MCL-equivalent exceedances for As, Cu, and U. MCL-equivalent exceedances in private-TW samples in this study are consistent with prior findings,<sup>5</sup> reemphasize the inherent risks of unrecognized contaminant exposures in federally-unregulated and rarely-monitored private-TW,<sup>5</sup> and illustrate the potential benefits of systematic private-TW monitoring<sup>65</sup> with a broad analytical scope that credibly reflects extant environmental-contaminant complexity,<sup>26,101,105,146,147</sup> to mitigate unrecognized adverse exposures. While MCL-equivalent exceedances indicate exposures of concern for general consumers, the emphasis hereafter is on human-health-only DW advisories like MCLG, which identify a maximum contaminant level below which no adverse health effect is known or anticipated, allowing an adequate margin of safety for sensitive (infants, children, elderly, immune- or disease-compromised) subpopulations.<sup>118</sup>

### 3.3 Individual contaminant health-risk screening: organics

TW-sample DWHA exceedances were observed for four VOC, of which two are typically associated with chlorine-based DW disinfection (*i.e.*, DBP; Table S4a). All four (bromodichloromethane, tribromomethane (bromoform), tetrachloromethane [carbon tetrachloride], trichloroethene) have no known safe level of exposure for vulnerable subpopulations and corresponding MCLG of “zero”.<sup>45</sup> Other notable, organic detections of potential human-health concern owing to designed-bioactivity were multiple pesticides and associated degradates (median: 1 per sample; IQR: 0–3.5; range: 0–12) and pharmaceutical contaminants (Table S4a).

Detected concentrations of regulated pesticides (atrazine, bentazon, metolachlor, prometon) and degradates (deisopropyl atrazine [CEAT], CIAT) were well-below corresponding DWHA, and human-health DW benchmarks are lacking for many of the detected pesticides, including seed-coat-associated fungicides (sedaxane) and insecticides (chlorantraniliprole, clothianidin, imidacloprid, thiamethoxam). However, pesticide links to multiple adverse outcomes,<sup>34–44</sup> multiple pesticide detections per sample, and growing concerns for neonicotinoid-insecticide health effects (*e.g.*, cancers,<sup>148</sup>



diabetes,<sup>149</sup> developmental neurotoxicity<sup>44</sup>) raise concerns for potential adverse effects of long-term TW-pesticide exposures.<sup>31,74,150</sup>

The diltiazem metabolite, *N*-desmethyldiltiazem, was detected in 53% (8/15) of locations at near-detection-limit concentrations (median: 0.006  $\mu\text{g L}^{-1}$ ; range: 0.004–0.007  $\mu\text{g L}^{-1}$ ). Diltiazem is a calcium-channel-blocker cardiovascular pharmaceutical, prescribed to treat high blood pressure and angina.<sup>151</sup> The lipid-regulating cardiovascular drug fenofibrate was detected in 13% (2/15) of private-TW locations (detected concentration range: 0.008–0.012  $\mu\text{g L}^{-1}$ ). Increasing detections of fenofibrate and other cardiovascular drugs and metabolites (*e.g.*, desmethyldiltiazem) in environmental waters<sup>151</sup> and DW,<sup>152</sup> are ascribed to growing global use, concomitant wastewater discharge, environmental stability, and poor removals in DW treatment.<sup>153–155</sup>

The results demonstrate that TW-organic exposures of human-health concern for vulnerable subpopulations occur in the Mead community, notably downgradient of the facility on ENREEC creek. These organic results are consistent with those in northeast Iowa<sup>18</sup> and emphasize the importance of private-TW monitoring in agriculturally-intensive areas with an analytical scope that realistically reflects the respective environmental organic-contaminant complexity.<sup>26,101,105,146,147</sup>

### 3.4 Individual contaminant health-risk screening: inorganics

DWHA exceedances were observed for multiple inorganics (Fig. 3, S1; Table S3), consistent with previous private-TW results in agriculturally-intensive northeastern Iowa<sup>156</sup> and with hypothesis I. Among these, As, lead (Pb), and U have no known safe level of exposure for vulnerable subpopulations (MCLG of “zero”).<sup>45</sup> Additional TW-inorganic exceedances (in order of discussion) of human-health benchmarks include non-zero MCLG ( $\text{NO}_3\text{-N}$ ) and other human-health-only advisories (boron [B], hexavalent chromium [Cr(vi)], fluoride [F], manganese [Mn], strontium [Sr]).

Geologically-derived (geogenic), redox-reactive, As was detected (*de facto* MCLG exceedance) in 5 (33% of sites) private-TW samples (Fig. 3, top right; Table S3). Tasteless and odorless, DW As has been linked with various cancers,<sup>157,158</sup> organ toxicity,<sup>157</sup> cardiovascular disease,<sup>159,160</sup> diabetes,<sup>159,160</sup> adverse pregnancy outcomes,<sup>161</sup> and mortality.<sup>161,162</sup> Concern for adverse effects at concentrations below the 10  $\mu\text{g L}^{-1}$  EPA MCL<sup>157,159,163,164</sup> prompted New Jersey and New Hampshire to establish a 5  $\mu\text{g L}^{-1}$  MCL,<sup>165,166</sup> a level exceeded in three samples (20% of sites) in the current study. Maximum TW-As concentrations observed in the current study were consistent with elevated C horizon As profiles<sup>167</sup> and groundwater As concentrations<sup>168</sup> documented in eastern Nebraska.

Redox-reactive, geogenic U was detected (*de facto* MCLG exceedance) in every TW sample in this study (Fig. 3, middle left; Table S3), including at a concentration more than double the MCL-equivalent 30  $\mu\text{g L}^{-1}$  at one location (site 11: 74  $\mu\text{g L}^{-1}$ ). U concentrations >3  $\mu\text{g L}^{-1}$  (common method detection limit for public-supply compliance monitoring) or >10  $\mu\text{g L}^{-1}$  were



Fig. 2 Detected concentrations ( $\mu\text{g L}^{-1}$ ) and number of sites (right axes) for 33 organic analytes (left axis, in order of decreasing total detections) detected in private-well tapwater samples collected during 2022 in the vicinity of the state-closed biofuel facility near Mead, Nebraska. Circles are data for individual samples. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. DBP, PEST, PFAS, PHARM, and VOC indicate disinfection byproducts, pesticides, per/polyfluoroalkyl substances, pharmaceuticals, and volatile organic chemicals, respectively.

observed in 40% (6/15) and 13% (2/15) of private-TW samples, respectively. Widespread detections of U concentrations, including sporadic detections at elevated concentrations are consistent with elevated C horizon U contents documented in southeastern Nebraska.<sup>167</sup> DW U is linked to a range of adverse human-health impacts, including nephrotoxicity<sup>169–173</sup> and osteotoxicity,<sup>171,172,174</sup> thyroid cancer,<sup>175</sup> inhibition of DNA-repair *in vitro*,<sup>176</sup> estrogen-receptor effects in mice,<sup>177</sup> reproductive endpoints in humans,<sup>171,172,178</sup> and elevated prediabetes<sup>179</sup> and type-2 diabetes risks.<sup>180,181</sup>

Lead was observed (*de facto* MCLG exceedance) sporadically (33%) in private-TW samples (Fig. 3, top left; Table S3). Three sites (11, 13, 14) had concentrations greater than the American Academy of Pediatrics<sup>182</sup> suggested upper DW-exposure limit of 1  $\mu\text{g L}^{-1}$ , also a common method detection limit for public-supply compliance monitoring.<sup>183</sup> Elevated (>1  $\mu\text{g L}^{-1}$ ) DW-Pb concentrations are generally attributed to legacy (pre-1986) use in distribution-system and premise-plumbing infrastructure.<sup>184</sup> In this study, plumbing-derived TW-Pb exposures may be substantially underestimated, because same-day prior use was common and flushing decreases plumbing-derived contaminant





**Fig. 3** Detected concentrations (y-axis) by site (x-axis) for lead (Pb  $\mu\text{g L}^{-1}$ , upper left), arsenic (As  $\mu\text{g L}^{-1}$ , upper right), uranium (U  $\mu\text{g L}^{-1}$ , middle left), copper (Cu  $\mu\text{g L}^{-1}$ , middle right), hexavalent chromium (Cr(VI)  $\mu\text{g L}^{-1}$ , lower left) and nitrate-nitrogen ( $\text{NO}_3\text{-N}$   $\text{mg L}^{-1}$ , lower right) detected in private-well tapwater samples collected during 2022 in the vicinity of the state-closed biofuel facility near Mead, Nebraska. Red lines (Pb, As, U, Cu,  $\text{NO}_3\text{-N}$ ), indicating the public-supply maximum contaminant level (MCL), are frame-of-reference only for federally unregulated private-well tapwater. Health-only MCL goals (MCLG, orange lines) are 'zero' for Pb, As, and U. Purple line indicates EPA risk screening level for Cr(VI).

concentrations.<sup>184,185</sup> DW-Pb exposures primarily are concerns for potential impacts on infant/child neurocognitive development.<sup>182,184</sup>

MCLG/MCL-equivalent exceedances were observed for Cu in two (13%) locations in this study (Fig. 3, middle right). The EPA MCLG/MCL for Cu in public-supply DW ( $1.3 \text{ mg L}^{-1}$ ) and the WHO GV ( $2.0 \text{ mg L}^{-1}$ ), were promulgated to protect against gastrointestinal distress from short-term exposure and potential liver and kidney damage from long-term exposure.<sup>186–189</sup> Excluding rare autosomal regulatory disorders (e.g., Wilson's disease) that may result in serious health consequences even at normal exposure levels, there is little evidence of liver toxicosis at twice the WHO GV, including for bottle-fed infants.<sup>190</sup> Although elevated DW-Cu concentrations are generally attributed to distribution and premise-plumbing infrastructure and often associated with low DW pH,<sup>184</sup> elevated C horizon Cu concentrations have been documented in southeastern Nebraska.<sup>167</sup>

Well-documented throughout Nebraska,<sup>168,191</sup> elevated (i.e.,  $>1 \text{ mg L}^{-1}$ ) private-TW  $\text{NO}_3\text{-N}$  concentrations were common (87% of samples) in the study area (median:  $7.1 \text{ mg L}^{-1}$ ), with the MCL/MCLG-equivalent ( $10 \text{ mg L}^{-1}$ ) concentration exceeded in three (20%) sample locations (Fig. 3, bottom right; Table S3). The  $\text{NO}_3\text{-N}$  MCL/MCLG was promulgated to prevent methemoglobinemia in bottle-fed infants ( $<6$  months).<sup>45</sup> However, associations with other adverse health outcomes,<sup>46,47</sup>

including cancer,<sup>48–53</sup> thyroid disease,<sup>54,55</sup> and neural tube defects,<sup>56</sup> drive recent concerns for long-term consumption of TW- $\text{NO}_3\text{-N}$  at less than MCL concentrations. Regionally intensive crop agriculture, widespread TW detections of agricultural pesticides (Table S4a and b), and lack of multiple, co-occurring human-waste indicators (e.g., human-use pharmaceuticals [Table S4a], fecal bacteria indicators [Table S5]) are consistent with agricultural surface treatment (e.g., inorganic/organic fertilizers) as presumptive source of elevated  $\text{NO}_3\text{-N}$  concentrations in groundwater<sup>168,191</sup> and private-TW samples (Table S3) and indicate that human-waste infrastructures (septic systems) were not primary contributors.

No MCL/MCLG currently exists for B, and no private-TW sample in this study exceeded the EPA  $6000 \mu\text{g L}^{-1}$  life-time DWHA<sup>134</sup> (Fig. S1, middle right; Table S3), based on male reproductive effects (i.e., testicular lesions).<sup>192,193</sup> However, in 2017, the Minnesota Department of Health lowered its respective risk assessment advice value (previously  $2000 \mu\text{g L}^{-1}$  B; pregnant women sensitive population) to  $500 \mu\text{g L}^{-1}$  B due to uncertainties concerning bottle-fed infant exposures and toxicity,<sup>136,194</sup> a value exceeded in a single private-TW sample (7% of locations).

Consistent with elevated C horizon contents reported previously in southeastern Nebraska,<sup>167</sup> TW-Cr was detected in TW samples, primarily as Cr(VI) (Fig. 3, bottom left; Table S3). While TW-Cr(total) concentrations were well below the NPDWR MCL ( $100 \mu\text{g L}^{-1}$ ), which addresses Cr(VI) as a component,<sup>45,99</sup> and TW-Cr(VI) concentrations were below the recent California MCL ( $10 \mu\text{g L}^{-1}$ ),<sup>195</sup> Cr(VI) is classified as "likely to be carcinogenic" via oral exposure.<sup>196</sup> About 60% of private-TW locations in this study exceeded the USGS cancer HBSL ( $0.04 \mu\text{g L}^{-1}$ )<sup>137</sup> and the EPA Regional Screening Level (RSL)<sup>197</sup> for one-in-one million ( $10^{-6}$ ) cancer risk applied previously,<sup>5,198</sup> with one sample (site 6:  $3.9 \mu\text{g L}^{-1}$ ) circa the one-in-ten thousand ( $10^{-4}$ ) cancer risk HBSL ( $4 \mu\text{g L}^{-1}$ ).<sup>137</sup> These observations raise concerns for elevated risk of stomach cancer from long-term TW-exposures in the study area.<sup>158,199</sup>

All TW-F concentrations (Fig. S1, top left; Table S3) were less than the EPA MCL ( $4 \text{ mg L}^{-1}$ ) for protection against bone fragility and skeletal fluorosis.<sup>45,133</sup> However, the F concentration ( $1.55 \text{ mg L}^{-1}$ ) in one TW sample (site 2) exceeded the WHO GV ( $1.5 \text{ mg L}^{-1}$ ) established to prevent dental fluorosis<sup>135</sup> and, critically, adopted in the recent National Toxicology Program review to mitigate the risks of neurodevelopmental and cognitive effects in children.<sup>200</sup> This result raised concern for TW-F exposures to children within the study area. Consistent with groundwater across the US<sup>201,202</sup> and corresponding dental-health concerns in private-well-dependent children,<sup>203</sup> TW-F concentrations in all but two samples were below the US Public Health Service<sup>204</sup> optimum of  $0.7 \text{ mg L}^{-1}$  to prevent dental caries.

In response to increasing concerns for cognitive, neurodevelopmental, and behavioral effects of long-term TW-Mn exposures in children and especially in bottle-fed infants,<sup>205,206</sup> WHO established a Mn provisional GV of  $80 \mu\text{g L}^{-1}$ , to prevent neurological effects in bottle-fed infants.<sup>207</sup>



This value was exceeded in one private-TW sample (site 15: 212  $\mu\text{g L}^{-1}$ ) in the current study (Fig. S1, middle left). Co-occurring elevated iron (258  $\mu\text{g L}^{-1}$ ) and negligible  $\text{NO}_3\text{-N}$  concentrations indicate occurrence of reducing redox conditions in the private-well groundwater at the time of sample collection. No MCL/MCLG has been promulgated for Mn, but EPA issued a 300  $\mu\text{g L}^{-1}$  life-time DWHA (assumes 100% exposure from drinking water).<sup>134</sup>

A TW-Sr concentration (3950  $\mu\text{g L}^{-1}$ ) of potential human-health concern also was observed in only one sample (site 2) in this study (Fig. S1, bottom right; Table S3). Sr is widely detected in US groundwater.<sup>208</sup> TW-Sr human-health concerns, primarily in children, are driven by potential replacement of bone calcium and resultant abnormal bone development with long-term elevated exposure.<sup>209,210</sup> In 2014, EPA published a preliminary determination to regulate DW-Sr,<sup>211</sup> but to date no MCL/MCLG has been promulgated. The site 2 TW-Sr concentration was more than double the 1500  $\mu\text{g L}^{-1}$  Health Advisory Level (HAL) established by the state of Wisconsin for bone effects in children.<sup>212</sup>

The results demonstrate that TW-inorganic exposures of human-health concern for vulnerable subpopulations also occur in the Mead community, notably downgradient of the facility on ENREEC creek. The results, combined with those for organics above, emphasize the importance of private-TW monitoring with an analytical scope that realistically reflects the documented complexity of environmental contamination.<sup>26,101,105,146,147</sup>

### 3.5 Individual contaminant health-risk screening: microbial

Microbial detections (HPC) were common (92% or 12 of 13 sites; not available for sites 14 and 15) in private-TW samples (median: 6100 most probable number per 100 mL [MPN 100  $\text{mL}^{-1}$ ]; IQR: 4000–6400 MPN 100  $\text{mL}^{-1}$ ; range: 0–7000 MPN 100  $\text{mL}^{-1}$ ) (Table S5). No HPC were detected in the site 2 sample, which had detectable VOC indicative of chlorine disinfection (*i.e.*, DBP). HPC bacteria are ubiquitous in the environment, common in DW, and not inherent health concerns but practical indicators of system maintenance,<sup>45,134</sup> which includes routine disinfection in private wells.<sup>59</sup> Total coliform bacteria and *E. coli* were not detected in any sample in this study. However, growth on selective media for microorganisms of potential human-health concern was observed in several samples.

Detections of *Salmonella* (7 or 47% of samples) and *Campylobacter* (2 or 13%) spp., common causes of food-/water-borne enteric diseases,<sup>213–215</sup> and the opportunistic premise-plumbing (biofilm-related) pathogens<sup>215–217</sup> *Pseudomonas aeruginosa* (8 or 53%), *Legionella* spp. (8 or 53%), and *Mycobacterium* spp. (1 or 7%) raise concerns for adverse TW microbial exposures in the study area.<sup>215</sup> Growth on oxacillin-resistant staphylococci selective media for 3 samples, indicates the potential presence of antibiotic-resistant microorganisms, a growing public-health<sup>218</sup> and DW-quality concern.<sup>219</sup>

Among these, detections of biofilm-related<sup>215</sup> *Pseudomonas aeruginosa* and *Legionella* spp. in more than half of samples and often co-occurring are notable concerns (Table S5). *Legionella* was identified as the leading and increasing cause of biofilm-related disease outbreaks in the US during 2015–2020.<sup>215</sup> The maximum detection of *Legionella* spp. observed in this study was 989 MPN 100  $\text{mL}^{-1}$  in the site 15 sample (Table S5). The MCLG for *Legionella* is “zero”.<sup>45</sup> *Salmonella* spp., *Campylobacter* spp., and staphylococci are well-documented in livestock/poultry wastes<sup>220</sup> and acknowledged human-exposure concerns in nearby private wells,<sup>221,222</sup> due to infiltration from waste storage lagoons<sup>223</sup> and agricultural-land applications.<sup>224</sup> These results reiterate the inherent challenge of unmonitored private-TW<sup>63,64,102,202</sup> and support systematic monitoring,<sup>65</sup> including for microbial contamination.

### 3.6 Precautionary human-health-benchmark $\sum_{\text{TQ}}$ screening

Pervasive, co-occurring inorganic/organic exposures of human-health concern suggest potential cumulative TW risk within the private-well-dependent community, at a minimum to the health of the most vulnerable (infants, children, elderly, immune- or disease-compromised) subpopulations.<sup>45,118,133</sup> We screened for cumulative TW risk using a  $\sum_{\text{TQ}}$  approach that informs apical-human-health effects of inorganic/organic co-exposures but is notably constrained to available human-health DW benchmarks. Regarding the latter, 62% (16 inorganic; 22 organic) of the 61 total detected analytes (28 inorganic; 33 organic) in this study, had available human-health benchmarks focused on risks to presumptive most-vulnerable populations (Table S7a). Among these, all but one organic analyte had at least one exposure resulting in an individual TQ  $\geq 0.00001$  and were included in the  $\sum_{\text{TQ}}$  assessment. All broad-scope-analysis TW samples (*i.e.*, not including 2023 pesticide-only samples) exceeded  $\sum_{\text{TQ}} = 1$  (Fig. 4; Table S7b), indicating high probabilities of cumulative risks to sensitive subpopulations, when accounting for inorganic-/organic-contaminant exposures.

Every location had at least one individual TQ  $\geq 1$  (median: 3; IQR: 2–4.5; range: 1–6), comprising, in decreasing detection frequency, U (15/15 sites), Cr(VI) (9/15), As (5/15), Pb (5/15),  $\text{NO}_3\text{-N}$  (4/15), tribromomethane (bromoform, 2/15), bromodichloromethane (2/15), Cu (2/15), Mn (1/15), B (1/15), and Sr (1/15) (Fig. 4; Table S7b). Frequent exceedances of  $\sum_{\text{TQ}} = 1$  and co-occurring exceedances of TQ = 1 in TW samples from unregulated and generally unmonitored private-wells in this and previous studies<sup>18,83–85,141</sup> emphasize the intrinsic human-health vulnerability of unrecognized exposures in private-well-dependent communities<sup>63–65,90,102,202</sup> and reinforce previous recommendations for systematic private-well monitoring,<sup>65,225–228</sup> with a broad analytical scope reflective of the range of environmental-contaminant mixtures.<sup>5,101,105</sup>





Fig. 4 Individual (circles) and cumulative (red triangles) health-only toxicity quotients (TQ) for private-well tapwater samples collected in the vicinity of the state-closed biofuel facility near Mead, Nebraska. Red (upper) and orange (lower dashed) lines indicate benchmark equivalent exposure (TQ or  $\sum TQ = 1$ ) and screening-level of concern (TQ or  $\sum TQ = 0.1$ ), respectively. Boxes, centerlines, and whiskers indicate interquartile range, median, and 5th and 95th percentiles, respectively. X-Axis labels are sample site numbers.

### 3.7 Human-health-benchmark $\sum_{\text{EAR}}$ screening

Bioactivity-weighted EAR and  $\sum_{\text{EAR}}$  were calculated to identify organic-contaminant drivers of molecular-level human-relevant bioactivities and potentially identify additional concerns not addressed by existing human-health benchmarks. The screening approach employed here specifically assumes that measured private-TW exposures are reasonable first-level estimates of *in vivo* molecular-level exposures. ACC data were available for about 48% (16) of the 33 detected organics (Table S8b), of which 13 (39% of detected) had at least one individual EAR  $\geq 0.00001$  and were included in the  $\sum_{\text{EAR}}$  assessment. Within the 485 organic-contaminant analytical space, only two organics (6% of detected) exceeded the EAR = 0.001 screening-level for potential molecular-level effects<sup>97</sup> at least once and only 4 (26% of locations) TW samples had  $\sum_{\text{EAR}}$  greater than the 0.001 screening level (Fig. S3). Based on EAR-screening-level exceedance, the post-emergent herbicide bentazon was the only additional potential TW-exposure concern identified, beyond those identified by benchmark-based  $\sum TQ$  screening above.

### 3.8 TW-pesticide transport lines of evidence

Agricultural-pesticide use and occurrence in groundwater resources are well-documented throughout the US Corn Belt,<sup>11,25,29,229</sup> including Nebraska<sup>168,191,229,230</sup> and specifically the Platte River valley.<sup>231</sup> Consistent with commonplace historical and ongoing use in corn and soybean agriculture,<sup>232</sup> including within the study area,<sup>231</sup> the herbicide/herbicide-related atrazine and degradates (8 sites), metolachlor (4 sites), and, to a lesser extent, bentazon (3 sites) were commonly detected in TW throughout the study area, including upgradient of the facility (Fig. 1; Table S4a and b) and in areas with no known facility wet-cake or wastewater applications.<sup>75,78</sup>

However, the results also document greater detections and concentrations, including facility-feedstock-consistent pesticides, in TW southeast of the facility downstream on ENREEC creek and downgradient along the general southeast groundwater flowpath reported for the shallow alluvial aquifer in the Todd Valley of Saunders County.<sup>78,107,108</sup> Due to high reported pesticide use (crop application and treated seeds); including the detected chlorantraniliprole, chlothianidin, imidacloprid, sedaxane, and thiamethoxam; in the Todd Valley and throughout Nebraska,<sup>20,232</sup> corresponding detections in private-TW samples cannot be attributed unequivocally to a facility source. However, these detections are consistent with previously hypothesized mechanisms for facility-feedstock-pesticide transport offsite to private-well groundwater supplies, including possible surface-water transport *via* ENREEC creek, groundwater transport from the facility along the reported southeast shallow groundwater flowpath, or land application of contaminated “wet cake”.<sup>75,78,79</sup>

Among these hypothetical pathways from the facility, multiple lines of evidence support proximity to ENREEC creek as the primary driver of facility-consistent TW-pesticide exposures observed in this study. Nearby land application of facility “wet cake” was reported by several study participants, including upgradient of the facility,<sup>75,78,79</sup> without corresponding TW detections of feedstock-consistent pesticides, suggesting that these surface applications were not a primary mechanism of the private-TW contamination observed in this study. In contrast, detections of sedaxane fungicide and elevated concentrations of multiple insecticides, including chlorantraniliprole and neonicotinoids/degradates, at the site 4 location were consistent with containment losses of facility waste, with subsequent hydrologic transport from the facility to the corresponding private-well directly *via* groundwater<sup>79</sup> or indirectly *via* ENREEC creek,<sup>75</sup> the latter followed by



infiltration to the private-well groundwater source. Declining volume within the inactive northwest lagoon after facility closure in 2021 combined with comparable pesticide composition and concentrations in lagoon wastewater and underlying shallow groundwater confirmed lagoon leakage to the shallow groundwater system.<sup>79</sup> In February 2022 a burst pipe for a 15 000 m<sup>3</sup> digester released process wastewater to ENREEC creek,<sup>75</sup> resulting in elevated water (water grab, polar organic chemical integrative samplers [POCIS]) fungicide and insecticide concentrations in ENREEC creek,<sup>75,76,233</sup> and acute exposures to fish and wildlife in and around the creek pond at site 4.<sup>71,76,233</sup> Downstream-flow attenuation within the pond would favor preferential infiltration of surface water and corresponding contaminants into the site 4 private-well groundwater source.

To further inform the relative importance of the two hypothesized hydrologic transport mechanisms, three additional sites, located adjacent to site 4 but further from ENREEC creek orthogonal to surface-water and presumptive groundwater flow (Fig. 1), were assessed for pesticides only in 2023 along with repeat sampling at site 4. Consistently high detected concentrations of multiple facility-consistent pesticides (chlorantraniliprole, chlothianidin, sedaxane, thiamethoxam and degradates) at site 4, contrasted with single neonicotinoid detections of notably lower concentrations at adjacent sites 17 and 19, are most readily reconciled with preferential surface-water transport to the site 4 pond, a hydrologic setting which would delay further downstream transport and favor infiltration of surface-water and associated contaminants into the shallow alluvial aquifer supply for the site 4 private-well. Importantly, the distinctive pesticide signature of chlorantraniliprole, chlothianidin, sedaxane, thiamethoxam and degradates observed in site 4 TW aligned well with results for surface-water samples collected within ENREEC creek and the corresponding site 4 pond during a separate March to July 2022 multi-matrix ecological assessment of pesticide concentrations and impacts in area streams.<sup>76,233</sup>

### 3.9 Study limitations

Several interpretive limitations warrant consideration. As noted previously,<sup>5</sup> the extensive target-analyte scope employed herein is only a fractional indicator of the estimated 350 000 anthropogenic chemicals in commercial production<sup>100</sup> (not including environmental transformation products/degradates) and, thus, potentially in ambient DW-supplies; the current exposure and risk results may be orders-of-magnitude underestimates. Individual (TQ) and cumulative risk ( $\sum_{TQ}$ ) estimates are limited by available weighting-factors (human-health benchmarks and ToxCast ACC, respectively), which are notably lacking for many of the pesticides detected in this study. The employed cumulative risk ( $\sum_{TQ}$ ) and molecular-level-bioactivity ( $\sum_{EAR}$ ) approaches estimated mixture effects assuming approximate concentration addition,<sup>121–126</sup> potentially

underestimating or overestimating cumulative effects in the event of synergism/potential or antagonism, respectively;<sup>234</sup> documented<sup>127–130</sup> departures from approximate concentration addition are uncommon<sup>125,131,132</sup> due in part to uncertainties in quotient denominator point-of-departure estimates,<sup>235,236</sup> increasingly unlikely with increasing number of mixture components,<sup>125</sup> and typically within one order of magnitude.<sup>125,131,132</sup> The employed cumulative risk ( $\sum_{TQ}$ ) screening assumed equivalent lifetime consumption (*i.e.*, no differences in individual and daily consumption). To provide a precautionary lower-bound estimate of *in vivo* adverse-effect levels, EAR was estimated across all ToxCast endpoints (*i.e.*, not constrained by recognized modes of action),<sup>237</sup> a useful screening and prioritization approach but not necessarily reflective of apical health effects.<sup>98,238</sup> MCLG values of “zero” were set to 0.1  $\mu\text{g L}^{-1}$  for metals, DBP, and other VOC, but this approach may not sufficiently protect for molecularly-triggered, self-propagating toxicities, such as carcinogenicity and endocrine-/immune-disruption. The June 2022 spatial-synoptic (one-time sample) broad-scope exposure and the January 2023 pesticide-only exposure assessments were not intended to capture temporal variability, including potential seasonal effects on water quality and groundwater/surface-water contaminant transport. Finally, the extensive analytical scope employed in this study provided actionable insight into TW-contaminant exposures to inform exposure-mitigation decision-making at household and community levels and preliminary information on potential contaminant sourcing, but the pilot-scale sample scope ( $n = 15$ ) was not intended to capture the full range of spatial, groundwater-source, and premise-plumbing drivers of TW-exposures in the study area.

### 3.10 TW treatment and exposure mitigation

Contaminant-specific TQ  $\geq 1$  at every location and commonplace co-occurrence (per site median: 3; IQR: 2–3.5; range: 1–5) demonstrate the benefit of effective multi-contaminant POE-/POU-treatment options to mitigate unrecognized private-TW contaminant exposures in the study area.<sup>239,240</sup> Complete elimination of pesticide detections in the three locations with extant POU-treatment (reverse osmosis [RO]: site 1; under-sink carbon filter: sites 4 and 6) confirms this conclusion, at least for pesticides, the most common organics detected in the study. Several POE-/POU-treatment technologies are effective in reducing all inorganic and organic TW-contaminant exposures identified in this study,<sup>239</sup> with treatment efficacy dependent on selection of suitable filtration technologies for exposures of concern, timely maintenance, and routine performance monitoring. In light of common co-occurring inorganic- and organic-contaminant exposures throughout the study area, broadly effective treatment technologies, such as RO, or multi-stage/multi-filtration



systems (sediment filter, redox media, activated carbon, ion exchange, UV disinfection) may be more appropriate.<sup>239</sup>

## 4 Conclusions

The biological essentiality of water<sup>6–8</sup> makes it an especially vulnerable human-exposure pathway (human-health risk vector) for a vast range of environmental chemical/biological hazards.<sup>5,102,198,227</sup> Consequently, in private-well-dependent communities, DW is a critical leverage point for individual and community-level contaminant-risk mitigation through cognizant chemical use/disposal, improved well/premise-plumbing infrastructure installation and maintenance, well-head/source-water protection, and POE/POU treatment. In general, financial resource, water-quality expertise, and contaminant-exposure data limitations at the household-scale are fundamental obstacles to private-TW decision-making and risk-mitigation actions.<sup>65,84,90</sup> Analytically extensive datasets like this study, which are intended to support household and community-level decision-making and, more broadly, enhance scientific understanding of the role of DW in human-health outcomes, remain rare because extensive TW-contaminant assessments are not routinely conducted at the point-of-exposure in the US or worldwide.

The results of this and previous<sup>82–85</sup> studies highlight the human-health vulnerability inherent to unmonitored TW<sup>63–65,102,202</sup> and the potential value of systematic private-well monitoring<sup>65</sup> with an analytical scope that reasonably reflects the breadth of environmental contamination.<sup>26,101,105,146,147</sup> This study demonstrated elevated human-health risk from simultaneous exposures to multiple TW contaminants throughout the study area, emphasizing the need for improved understanding of the adverse human-health implications of long-term exposures to inorganic/organic-contaminant mixtures in private-TW. The results illustrate the importance of well-maintained POE/POU treatment as prudent protection against unrecognized simultaneous exposures to multiple contaminants in private-TW.<sup>84,241</sup> These findings confirm the importance of continued characterization of private-TW exposures and increased availability of resultant health-based data, including at concentrations below technically/economically-constrained public-supply standards (e.g., MCL), to support community engagement in source-water protection and inform household POE/POU treatment decisions in the study area and throughout the US.

## Author contributions

PMB: conceptualization, methodology, sampling, data curation, formal analysis, project management, funding, writing – original draft, writing – review & editing. SMM: sampling, data curation, writing – review & editing. KMR: methodology, data curation, formal analysis, visualization, writing – review & editing. MLS: writing – review & editing. KLS: methodology, formal analysis, project management, funding, writing – review & editing. SLB-H: conceptualization,

methodology, sampling, writing – review & editing. BKD: writing – review & editing. SEG: visualization, writing – review & editing. KAL: formal analysis, funding, writing – review & editing. RBM: formal analysis, writing – review & editing. EGR: conceptualization, writing – review & editing. DLR: writing – review & editing. DDS: conceptualization, writing – review & editing.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

Supplementary information: All data are available in the SI. See DOI: <https://doi.org/10.1039/D5EW00490J>.

Data discussed in this paper are summarized in SI Tables S1–S8c and in the USGS data releases cited.<sup>109</sup>

## Acknowledgements

This research was conducted and funded by the Environmental Health Program of the U.S. Geological Survey Ecosystems Mission Area. Any use of trade, product, or firm names is for descriptive purposes only and does not imply endorsement by the U.S. Government. This report contains CAS Registry Numbers®, which is a registered trademark of the American Chemical Society. CAS recommends the verification of the CASRNs through CAS Client Services<sup>SM</sup>.

## References

- 1 G. Pierce and S. Gonzalez, Mistrust at the tap? Factors contributing to public drinking water (mis) perception across US households, *Water Qual.*, 2017, **19**, 1–12, DOI: [10.2166/wp.2016.143](https://doi.org/10.2166/wp.2016.143).
- 2 d. F. M. Doria, Factors influencing public perception of drinking water quality, *Water Qual.*, 2010, **12**, 1–19, DOI: [10.2166/wp.2009.051](https://doi.org/10.2166/wp.2009.051).
- 3 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](https://doi.org/10.1289/ehp.1206229).
- 4 M. Allaire, H. Wu and U. Lall, National trends in drinking water quality violations, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, 2078–2083, DOI: [10.1073/pnas.1719805115](https://doi.org/10.1073/pnas.1719805115).
- 5 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](https://doi.org/10.1016/j.envint.2024.109220).



- 6 European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies (NDA), EFSA Panel on Dietetic Products and Allergies, Scientific Opinion on Dietary Reference Values for water, *EFSA J.*, 2010, **8**, 1459, DOI: [10.2903/j.efsa.2010.1459](https://doi.org/10.2903/j.efsa.2010.1459).
- 7 Institute of Medicine, in *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*, The National Academies Press, Washington, DC, 2005, ch. 4, pp. 73–185, DOI: [10.17226/10925](https://doi.org/10.17226/10925).
- 8 F. Westall and A. Brack, The Importance of Water for Life, *Space Sci. Rev.*, 2018, **214**, 50, DOI: [10.1007/s11214-018-0476-7](https://doi.org/10.1007/s11214-018-0476-7).
- 9 R. Levin, C. M. Villanueva, D. Beene, A. L. Craddock, C. Donat-Vargas, J. Lewis, I. Martinez-Morata, D. Minovi, A. E. Nigra, E. D. Olson, L. A. Schaidler, M. H. Ward and N. C. Deziel, US drinking water quality: exposure risk profiles for seven legacy and emerging contaminants, *J. Exposure Sci. Environ. Epidemiol.*, 2024, **34**, 3–22, DOI: [10.1038/s41370-023-00597-z](https://doi.org/10.1038/s41370-023-00597-z).
- 10 K. L. Smalling, M. L. Hladik, C. J. Sanders and K. M. Kuivila, Leaching and sorption of neonicotinoid insecticides and fungicides from seed coatings, *J. Environ. Sci. Health, Part B*, 2018, **53**, 176–183, DOI: [10.1080/03601234.2017.1405619](https://doi.org/10.1080/03601234.2017.1405619).
- 11 L. M. Bexfield, K. Belitz, B. D. Lindsey, P. L. Toccalino and L. H. Nowell, Pesticides and Pesticide Degradates in Groundwater Used for Public Supply across the United States: Occurrence and Human-Health Context, *Environ. Sci. Technol.*, 2021, **55**, 362–372, DOI: [10.1021/acs.est.0c05793](https://doi.org/10.1021/acs.est.0c05793).
- 12 J. A. Goodrich, B. W. Lykins, Jr. and R. M. Clark, Drinking water from agriculturally contaminated groundwater, *J. Environ. Qual.*, 1991, **20**, 707–717.
- 13 Z. Li and A. Jennings, Global variations in pesticide regulations and health risk assessment of maximum concentration levels in drinking water, *J. Environ. Manage.*, 2018, **212**, 384–394, DOI: [10.1016/j.jenvman.2017.12.083](https://doi.org/10.1016/j.jenvman.2017.12.083).
- 14 I. El-Nahhal and Y. El-Nahhal, Pesticide residues in drinking water, their potential risk to human health and removal options, *J. Environ. Manage.*, 2021, **299**, 113611, DOI: [10.1016/j.jenvman.2021.113611](https://doi.org/10.1016/j.jenvman.2021.113611).
- 15 G. Mahai, Y. Wan, W. Xia, A. Wang, L. Shi, X. Qian, Z. He and S. Xu, A nationwide study of occurrence and exposure assessment of neonicotinoid insecticides and their metabolites in drinking water of China, *Water Res.*, 2021, **189**, 116630, DOI: [10.1016/j.watres.2020.116630](https://doi.org/10.1016/j.watres.2020.116630).
- 16 M. Syafrudin, R. A. Kristanti, A. Yuniarto, T. Hadibarata, J. Rhee, W. A. Al-onazi, T. S. Algarni, A. H. Almarri and A. M. Al-Mohaimed, Pesticides in Drinking Water—A Review, *Int. J. Environ. Res. Public Health*, 2021, **18**, 468, DOI: [10.3390/ijerph18020468](https://doi.org/10.3390/ijerph18020468).
- 17 D. A. Thompson, D. W. Kolpin, M. L. Hladik, K. K. Barnes, J. D. Vargo and R. W. Field, Prevalence of neonicotinoids and sulfoxaflor in alluvial aquifers in a high corn and soybean producing region of the Midwestern United States, *Sci. Total Environ.*, 2021, **782**, 146762, DOI: [10.1016/j.scitotenv.2021.146762](https://doi.org/10.1016/j.scitotenv.2021.146762).
- 18 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](https://doi.org/10.1016/j.scitotenv.2023.161672).
- 19 K. L. Smalling, O. H. Devereux, S. E. Gordon, P. J. Phillips, V. S. Blazer, M. L. Hladik, D. W. Kolpin, M. T. Meyer, A. J. Sperry and T. Wagner, Environmental and anthropogenic drivers of contaminants in agricultural watersheds with implications for land management, *Sci. Total Environ.*, 2021, **774**, 145687, DOI: [10.1016/j.scitotenv.2021.145687](https://doi.org/10.1016/j.scitotenv.2021.145687).
- 20 U.S. Geological Survey, Pesticide National Synthesis Project: Estimated Annual Agricultural Pesticide Use, <https://water.usgs.gov/nawqa/pnsp/usage/maps/>, (accessed March 31, 2025).
- 21 N. T. Baker and W. W. Stone, Estimated Annual Agricultural Pesticide Use for Counties of the Conterminous United States, 2008–12, Report U.S. Geological Survey Data Series 907, Reston, VA, 2015, DOI: [10.3133/ds907](https://doi.org/10.3133/ds907).
- 22 A. Sharma, A. Shukla, K. Attri, M. Kumar, P. Kumar, A. Suttee, G. Singh, R. P. Barnwal and N. Singla, Global trends in pesticides: A looming threat and viable alternatives, *Ecotoxicol. Environ. Saf.*, 2020, **201**, 110812, DOI: [10.1016/j.ecoenv.2020.110812](https://doi.org/10.1016/j.ecoenv.2020.110812).
- 23 B. Husk, J. S. Sanchez, R. Leduc, L. Takser, O. Savary and H. Cabana, Pharmaceuticals and pesticides in rural community drinking waters of Quebec, Canada – A regional study on the susceptibility to source contamination, *Water Qual. Res. J.*, 2019, **54**, 88–103, DOI: [10.2166/wqrj.2019.038](https://doi.org/10.2166/wqrj.2019.038).
- 24 T. Sultana, C. Murray, S. Kleywegt and C. D. Metcalfe, Neonicotinoid pesticides in drinking water in agricultural regions of southern Ontario, Canada, *Chemosphere*, 2018, **202**, 506–513, DOI: [10.1016/j.chemosphere.2018.02.108](https://doi.org/10.1016/j.chemosphere.2018.02.108).
- 25 R. J. Gilliom, Pesticides in US streams and groundwater, *Environ. Sci. Technol.*, 2007, **41**, 3408–3414, DOI: [10.1021/es072531u](https://doi.org/10.1021/es072531u).
- 26 C. Moschet, I. Wittmer, J. Simovic, M. Junghans, A. Piazzoli, H. Singer, C. Stamm, C. Leu and J. Hollender, How a complete pesticide screening changes the assessment of surface water quality, *Environ. Sci. Technol.*, 2014, **48**, 5423–5432, DOI: [10.1021/es500371t](https://doi.org/10.1021/es500371t).
- 27 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](https://doi.org/10.1016/j.scitotenv.2021.147147).
- 28 D. A. Thompson, D. W. Kolpin, M. L. Hladik, H.-J. Lehmler, S. M. Meppelink, M. C. Poch, J. D. Vargo, V. A. Soupene, N. M. Irfan, M. Robinson, K. Kannan, L. E. Beane Freeman, J. N. Hofmann, D. M. Cwiertny and R. W. Field, Prevalence of neonicotinoid insecticides in paired private-well tap water and human urine samples in a region of intense agriculture overlying vulnerable aquifers in eastern Iowa, *Chemosphere*, 2023, **319**, 137904, DOI: [10.1016/j.chemosphere.2023.137904](https://doi.org/10.1016/j.chemosphere.2023.137904).



- 29 L. A. DeSimone, P. A. Hamilton and R. J. Gilliom, Quality of Water from Domestic Wells in Principal Aquifers of the United States, 1991–2004: Overview of Major Findings, Report 1332, 2009, DOI: [10.3133/cir1332](https://doi.org/10.3133/cir1332).
- 30 G. Mahai, Y. Wan, A. Wang, W. Xia, L. Shi, P. Wang, Z. He and S. Xu, Selected transformation products of neonicotinoid insecticides (other than imidacloprid) in drinking water, *Environ. Pollut.*, 2021, **291**, 118225, DOI: [10.1016/j.envpol.2021.118225](https://doi.org/10.1016/j.envpol.2021.118225).
- 31 C. Lu, Z. Lu, S. Lin, W. Dai and Q. Zhang, Neonicotinoid insecticides in the drinking water system – Fate, transportation, and their contributions to the overall dietary risks, *Environ. Pollut.*, 2020, **258**, 113722, DOI: [10.1016/j.envpol.2019.113722](https://doi.org/10.1016/j.envpol.2019.113722).
- 32 Y. He, B. Zhang, Y. Wu, J. Ouyang, M. Huang, S. Lu, H. Sun and T. Zhang, A pilot nationwide baseline survey on the concentrations of Neonicotinoid insecticides in tap water from China: Implication for human exposure, *Environ. Pollut.*, 2021, **291**, 118117, DOI: [10.1016/j.envpol.2021.118117](https://doi.org/10.1016/j.envpol.2021.118117).
- 33 K.-H. Kim, E. Kabir and S. A. Jahan, Exposure to pesticides and the associated human health effects, *Sci. Total Environ.*, 2017, **575**, 525–535, DOI: [10.1016/j.scitotenv.2016.09.009](https://doi.org/10.1016/j.scitotenv.2016.09.009).
- 34 L. A. Pardo, L. E. Beane Freeman, C. C. Lerro, G. Andreotti, J. N. Hofmann, C. G. Parks, D. P. Sandler, J. H. Lubin, A. Blair and S. Koutros, Pesticide exposure and risk of aggressive prostate cancer among private pesticide applicators, *Environ. Health*, 2020, **19**, 30, DOI: [10.1186/s12940-020-00583-0](https://doi.org/10.1186/s12940-020-00583-0).
- 35 K. J. Yang, J. Lee and H. L. Park, Organophosphate Pesticide Exposure and Breast Cancer Risk: A Rapid Review of Human, Animal, and Cell-Based Studies, *Int. J. Environ. Res. Public Health*, 2020, **17**, 5030, DOI: [10.3390/ijerph17145030](https://doi.org/10.3390/ijerph17145030).
- 36 Z. Liang, X. Wang, B. Xie, Y. Zhu, J. Wu, S. Li, S. Meng, X. Zheng, A. Ji and L. Xie, Pesticide exposure and risk of bladder cancer: A meta-analysis, *Oncotarget*, 2016, **7**, 66959–66969, DOI: [10.18632/oncotarget.11397](https://doi.org/10.18632/oncotarget.11397).
- 37 S. Koutros, C. F. Lynch, X. Ma, W. J. Lee, J. A. Hoppin, C. H. Christensen, G. Andreotti, L. B. Freeman, J. A. Rusiecki, L. Hou, D. P. Sandler and M. C. R. Alavanja, Heterocyclic aromatic amine pesticide use and human cancer risk: Results from the U.S. Agricultural Health Study, *Int. J. Cancer*, 2009, **124**, 1206–1212, DOI: [10.1002/ijc.24020](https://doi.org/10.1002/ijc.24020).
- 38 S. Koutros, D. T. Silverman, M. C. Alavanja, G. Andreotti, C. C. Lerro, S. Heltshe, C. F. Lynch, D. P. Sandler, A. Blair and L. E. Beane Freeman, Occupational exposure to pesticides and bladder cancer risk, *Int. J. Epidemiol.*, 2015, **45**, 792–805, DOI: [10.1093/ije/dyv195](https://doi.org/10.1093/ije/dyv195).
- 39 C. Panis, L. Z. P. Candiotto, S. C. Gaboardi, S. Gurzenda, J. Cruz, M. Castro and B. Lemos, Widespread pesticide contamination of drinking water and impact on cancer risk in Brazil, *Environ. Int.*, 2022, **165**, 107321, DOI: [10.1016/j.envint.2022.107321](https://doi.org/10.1016/j.envint.2022.107321).
- 40 C. Pouchieu, C. Piel, C. Carles, A. Gruber, C. Helmer, S. Tual, E. Marcotullio, P. Lebailly and I. Baldi, Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study, *Int. J. Epidemiol.*, 2017, **47**, 299–310, DOI: [10.1093/ije/dyx225](https://doi.org/10.1093/ije/dyx225).
- 41 J. Zhang, J. Zhang, R. Liu, J. Gan, J. Liu and W. Liu, Endocrine-Disrupting Effects of Pesticides through Interference with Human Glucocorticoid Receptor, *Environ. Sci. Technol.*, 2016, **50**, 435–443, DOI: [10.1021/acs.est.5b03731](https://doi.org/10.1021/acs.est.5b03731).
- 42 Y. El-Nahhal, Pesticide residues in honey and their potential reproductive toxicity, *Sci. Total Environ.*, 2020, **741**, 139953, DOI: [10.1016/j.scitotenv.2020.139953](https://doi.org/10.1016/j.scitotenv.2020.139953).
- 43 Y. El-Nahhal and I. El-Nahhal, Cardiotoxicity of some pesticides and their amelioration, *Environ. Sci. Pollut. Res.*, 2021, **28**, 44726–44754, DOI: [10.1007/s11356-021-14999-9](https://doi.org/10.1007/s11356-021-14999-9).
- 44 J. B. Sass, N. Donley and W. Freese, Neonicotinoid pesticides: evidence of developmental neurotoxicity from regulatory rodent studies, *Front. Toxicol.*, 2024, **6**, 1438890, DOI: [10.3389/ftox.2024.1438890](https://doi.org/10.3389/ftox.2024.1438890).
- 45 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).
- 46 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](https://doi.org/10.3390/ijerph15071557).
- 47 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](https://doi.org/10.1080/19338244.2020.1842313).
- 48 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](https://doi.org/10.1289/EHP191).
- 49 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](https://doi.org/10.1016/j.envres.2022.112988).
- 50 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](https://doi.org/10.1016/j.canep.2022.102148).
- 51 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](https://doi.org/10.1016/j.jclepro.2022.132432).



- 52 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](https://doi.org/10.1016/j.envres.2021.112322).
- 53 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](https://doi.org/10.1002/ijc.31306).
- 54 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](https://doi.org/10.1186/1476-069X-11-6).
- 55 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](https://doi.org/10.1080/09603123.2020.1815664).
- 56 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](https://doi.org/10.1289/ehp.1206249).
- 57 L. Le Coadou, K. Le Ménach, P. Labadie, M.-H. Dévier, P. Pardon, S. Augagneur and H. Budzinski, Quality survey of natural mineral water and spring water sold in France: Monitoring of hormones, pharmaceuticals, pesticides, perfluoroalkyl substances, phthalates, and alkylphenols at the ultra-trace level, *Sci. Total Environ.*, 2017, **603–604**, 651–662, DOI: [10.1016/j.scitotenv.2016.11.174](https://doi.org/10.1016/j.scitotenv.2016.11.174).
- 58 P. M. Bradley, K. M. Romanok, K. L. Smalling, L. Donahue, M. P. Gaikowski, R. K. Hines, S. E. Breitmeyer, S. E. Gordon, K. A. Loftin, R. B. McCleskey, S. M. Meppelink and M. L. Schreiner, Tapwater exposures, residential risk, and mitigation in a PFAS-impacted-groundwater community, *Environ. Sci.: Processes Impacts*, 2025, **27**, 1368–1388, DOI: [10.1039/D5EM00005J](https://doi.org/10.1039/D5EM00005J).
- 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](https://doi.org/10.3133/cir1441).
- 61 T. D. Johnson, K. Belitz and M. A. Lombard, Estimating domestic well locations and populations served in the contiguous U.S. for years 2000 and 2010, *Sci. Total Environ.*, 2019, **687**, 1261–1273, DOI: [10.1016/j.scitotenv.2019.06.036](https://doi.org/10.1016/j.scitotenv.2019.06.036).
- 62 U.S. Geological Survey, Domestic (Private) Supply Wells, <https://www.usgs.gov/mission-areas/water-resources/science/domestic-private-supply-wells>, (accessed March 20, 2025).
- 63 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/EHP690](https://doi.org/10.1289/EHP690).
- 64 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, *Ground Water Monit. Rem.*, 2006, **26**, 92–104, DOI: [10.1111/j.1745-6592.2006.00089.x](https://doi.org/10.1111/j.1745-6592.2006.00089.x).
- 65 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](https://doi.org/10.1289/EHP629).
- 66 K. Meehan, W. Jepson, L. M. Harris, A. Wutich, M. Beresford, A. Fencl, J. London, G. Pierce, L. Radonic, C. Wells, N. J. Wilson, E. A. Adams, R. Arsenault, A. Brewis, V. Harrington, Y. Lambrinidou, D. McGregor, R. Patrick, B. Pauli, A. L. Pearson, S. Shah, D. Splichalova, C. Workman and S. Young, Exposing the myths of household water insecurity in the global north: A critical review, *Wiley Interdiscip. Rev.: Water*, 2020, **7**, e1486, DOI: [10.1002/wat2.1486](https://doi.org/10.1002/wat2.1486).
- 67 L. Radonic and C. E. Jacob, Examining the Cracks in Universal Water Coverage: Women Document the Burdens of Household Water Insecurity, *Water Altern.*, 2021, **14**, 60–78, <https://www.scopus.com/inward/record.uri?eid=2-s2.0-85102138019&partnerID=40&md5=de0e57bd8bd2d8171f11eed586f875a5>.
- 68 A. Y. Rosinger and S. L. Young, The toll of household water insecurity on health and human biology: Current understandings and future directions, *Wiley Interdiscip. Rev.: Water*, 2020, **7**, e1468, DOI: [10.1002/wat2.1468](https://doi.org/10.1002/wat2.1468).
- 69 A. Sultana, J. Wilson, D. Martin-Hill, L. Davis-Hill and J. Homer, Assessing the Impact of Water Insecurity on Maternal Mental Health at Six Nations of the Grand River, *Front. Water*, 2022, **4**, 834080, DOI: [10.3389/frwa.2022.834080](https://doi.org/10.3389/frwa.2022.834080).
- 70 S. L. Bartelt-Hunt and J. E. Bell, Surface and Groundwater Contamination, Community and Ecosystem Exposures Are the Unintentional Consequences from “Recycling” Treated Seed Products, *Environ. Sci. Technol.*, 2021, **55**, 5605–5607, DOI: [10.1021/acs.est.1c01305](https://doi.org/10.1021/acs.est.1c01305).
- 71 C. Gillam, We want it back to what it was: the US village blighted by toxic waste, *The Guardian*, April 26, 2022, <https://www.theguardian.com/environment/2022/apr/26/pollution-mead-nebraska-pesticide-waste>.
- 72 C. Dunker, Scientists from across country lending expertise to AltEn study, *Lincoln Journal Star*, July 20, 2022, [https://journalstar.com/news/state-and-regional/nebraska/scientists-from-across-country-lending-expertise-to-alt-en-study/article\\_2181ab5b-ea58-5a8f-bf88-ac4ccdee3db0.html#tracking-source=home-top-story](https://journalstar.com/news/state-and-regional/nebraska/scientists-from-across-country-lending-expertise-to-alt-en-study/article_2181ab5b-ea58-5a8f-bf88-ac4ccdee3db0.html#tracking-source=home-top-story).



- 73 J. Taiba, E. G. Rogan, D. D. Snow, C. Achutan and M. Zahid, Characterization of Environmental Levels of Pesticide Residues in Household Air and Dust Samples near a Bioenergy Plant Using Treated Seed as Feedstock, *Int. J. Environ. Res. Public Health*, 2023, **20**, 12, DOI: [10.3390/ijerph20216967](https://doi.org/10.3390/ijerph20216967).
- 74 M. Zahid, J. Taiba, K. Cox, A. S. Khan, T. Uhing and E. Rogan, Pesticide residues in adults living near a bioenergy plant with 85,000 tons of contaminated wetcake, *Chemosphere*, 2024, **349**, 140941, DOI: [10.1016/j.chemosphere.2023.140941](https://doi.org/10.1016/j.chemosphere.2023.140941).
- 75 J. A. A. Maclean, S. Bartelt-Hunt, D. D. Snow, J. F. Borsuah, R. W. Becker and M. Hazra, Aquatic occurrence, fate and potential ecotoxicity of insecticide and fungicide residues originating from a biofuels production facility using pesticide-treated seeds, *J. Hazard. Mater.*, 2025, **486**, 136922, DOI: [10.1016/j.jhazmat.2024.136922](https://doi.org/10.1016/j.jhazmat.2024.136922).
- 76 M. L. Hladik, D. W. Kolpin, M. D. De Parsia, D. D. Snow, S. L. Bartelt-Hunt, B. K. Densmore, L. E. Hubbard, D. L. Rus, J. J. Spurgeon, B. G. Perrotta, K. A. Kidd, J. M. Kraus, C. E. Givens, C. J. Kotalik and D. M. Walters, Pesticide concentrations in multiple physical and biological stream matrices are impacted by a bioenergy production facility receiving pesticide coated corn seeds, *Environ. Toxicol. Chem.*, 2025, **44**(8), 2143–2153, DOI: [10.1093/etohl/vgaf139](https://doi.org/10.1093/etohl/vgaf139).
- 77 K. C. Gribben, K. Johnson, P. Greenberg, R. Mencia, J. Taiba, K. W. Kintziger, K. Michaud, E. Rogan, T. Uhing and J. E. Bell, Environmental contamination associated with biofuel production involving pesticide-coated seed corn as feedstock: a survey of community environmental and health impacts, *Environ. Health*, 2025, **24**, 17, DOI: [10.1186/s12940-025-01174-7](https://doi.org/10.1186/s12940-025-01174-7).
- 78 EA Engineering Inc., AltEn Ethanol Plant AltEn Off-Site Assessment Mead, Saunders County, Nebraska Work Plan and QAPP Addendum, 2025, <https://ecmp.nebraska.gov/PublicAccess/api/Document/ASgDkYNG10aOvUwBjigitHJkO1S% C3 % 81UpTWU76gLZlmIhkd76ZQSnU4rEWz6% C3 % 89Kg1UU8kABz9nmSFCyTRPBYZMhzHyM%3D/>.
- 79 I. New Fields, Groundwater Data Gap Work Plan AltEn Site, Mead Nebraska, 2024, <https://ecmp.nebraska.gov/PublicAccess/api/Document/ARpPR7UGXVhCHC% C3 % 89frIBNkvIz8Kiev3d% C3 % 89gEnk0% C3 % 81DDqxu3dcBdjYi8qRojAATZSuvimDMKmlz33gh6rhy6T2i3BQ%3D/>.
- 80 R. Tokach, Adverse health impacts on honey bee (*Apis mellifera* L.) colonies from a contaminated environment and resources, Master of Science, University of Nebraska Lincoln, 2022, <https://digitalcommons.unl.edu/entomologydiss/85>.
- 81 J. Rodriguez-Paar, *Health Effects of Neonicotinoids on an Agricultural Community*, Master of Public Health, University of Nebraska, Lincoln, 2022, [https://digitalcommons.unmc.edu/coph\\_slce/230](https://digitalcommons.unmc.edu/coph_slce/230).
- 82 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](https://doi.org/10.1016/j.scitotenv.2020.137236).
- 83 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](https://doi.org/10.1021/acs.est.8b04622).
- 84 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](https://doi.org/10.1016/j.envint.2021.106487).
- 85 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](https://doi.org/10.1016/j.scitotenv.2021.147721).
- 86 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](https://doi.org/10.1039/D3EW00066D).
- 87 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](https://doi.org/10.1016/j.envint.2022.107701).



- 88 J. Von Behren, P. Reynolds, P. M. Bradley, J. L. Gray, D. W. Kolpin, K. M. Romanok, K. L. Smalling, C. Carpenter, W. Avila, A. Ventura, P. B. English, R. R. Jones and G. M. Solomon, Per- and polyfluoroalkyl substances (PFAS) in drinking water in Southeast Los Angeles: Industrial legacy and environmental justice, *Sci. Total Environ.*, 2024, 176067, DOI: [10.1016/j.scitotenv.2024.176067](https://doi.org/10.1016/j.scitotenv.2024.176067).
- 89 K. L. Smalling, K. M. Romanok, P. M. Bradley, M. L. Hladik, J. L. Gray, L. K. Kanagy, R. B. McCleskey, D. A. Stavreva, A. K. Alexander-Ozinskas, J. Alonso, W. Avila, S. E. Breitmeyer, R. Bustillo, S. E. Gordon, G. L. Hager, R. R. Jones, D. W. Kolpin, S. Newton, P. Reynolds, J. Sloop, A. Ventura, J. Von Behren, M. H. Ward and G. M. Solomon, Mixed Contaminant Exposure in Tapwater and the Potential Implications for Human-Health in Disadvantaged Communities in California, *Water Res.*, 2024, 122485, DOI: [10.1016/j.watres.2024.122485](https://doi.org/10.1016/j.watres.2024.122485).
- 90 P. M. Bradley, K. M. Romanok, K. L. Smalling, L. Donahue, M. P. Gaikowski, R. K. Hines, S. E. Breitmeyer, S. E. Gordon, K. A. Loftin, B. R. McCleskey, S. M. Meppelink and M. L. Schreiner, Tapwater Exposures, Residential Risk, and Mitigation in a PFAS-Impacted-Groundwater Community, *Environ. Sci.: Processes Impacts*, 2025, 27, 1368–1388, DOI: [10.1039/d5em00005j](https://doi.org/10.1039/d5em00005j).
- 91 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](https://doi.org/10.1080/10408444.2016.1211618).
- 92 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](https://doi.org/10.1002/etc.5620111202).
- 93 National Research Council, *Risk Assessment in the Federal Government: Managing the Process*, The National Academies Press, Washington, DC, 1983, DOI: [10.17226/366](https://doi.org/10.17226/366).
- 94 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](https://doi.org/10.1016/j.yrtph.2011.03.010).
- 95 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](https://doi.org/10.2903/j.efsa.2019.5634).
- 96 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](https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=548169).
- 97 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](https://doi.org/10.1016/j.scitotenv.2019.05.457).
- 98 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](https://doi.org/10.1021/acs.est.7b01613).
- 99 U.S. Environmental Protection Agency, 40 C.F.R. § 141: National Primary Drinking Water Regulations, 2025, [https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=339dba02478821f8412c44292656bd34&ty=HTML&h=L&mc=true&n=pt40.25.141&r=PART#\\_top](https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=339dba02478821f8412c44292656bd34&ty=HTML&h=L&mc=true&n=pt40.25.141&r=PART#_top).
- 100 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](https://doi.org/10.1021/acs.est.9b06379).
- 101 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](https://doi.org/10.1021/acs.est.7b00012).
- 102 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](https://doi.org/10.1542/peds.2009-0752).
- 103 K. A. Baken, R. M. A. Sjerps, M. Schriks and A. P. van Wezel, Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern, *Environ. Int.*, 2018, 118, 293–303, DOI: [10.1016/j.envint.2018.05.006](https://doi.org/10.1016/j.envint.2018.05.006).
- 104 K. Belitz, M. S. Fram, B. D. Lindsey, P. E. Stackelberg, L. M. Bexfield, T. D. Johnson, B. C. Jurgens, J. A. Kingsbury, P. B. McMahon and N. M. Dubrovsky, Quality of Groundwater Used for Public Supply in the Continental United States: A Comprehensive Assessment, *ACS ES&T Water*, 2022, 2, 2645–2656, DOI: [10.1021/acsestwater.2c00390](https://doi.org/10.1021/acsestwater.2c00390).
- 105 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](https://doi.org/10.1016/j.scitotenv.2016.12.004).
- 106 A. D. Woolf, B. D. Stierman, E. D. Barnett, L. G. Byron, C. O. E. Health, C. Change and C. O. I. Disease, Technical report: Drinking water from private wells and risks to



- children, *Pediatrics*, 2023, **151**, 21, DOI: [10.1542/peds.2022-060645](https://doi.org/10.1542/peds.2022-060645).
- 107 D. P. Divine, The Groundwater Atlas of Saunders County, Nebraska, Report Resource Atlas 9, Conservation and Survey Division, School of Natural Resources, University of Nebraska-Lincoln, 2015, <https://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1040&context=conservationsurvey>.
- 108 V. L. Souders, Availability of water in eastern Saunders County, Nebraska, Report U. S. Geological Survey Hydrologic Atlas 266, 1967, DOI: [10.3133/ha266](https://doi.org/10.3133/ha266).
- 109 S. M. Meppelink, K. M. Romanok, P. M. Bradley, K. L. Smalling, C. E. Givens, M. L. Hladik, M. S. Gross, J. L. Gray, L. K. Kanagy, B. R. McCleskey and D. A. Roth, Chemical Concentrations and Microbiological Results for Assessment of Mixed-Organic/Inorganic Chemical Exposures in Tapwater in Mead, Nebraska, June 2022 and January 2023, Report U.S. Geological Survey data release, 2023, DOI: [10.5066/P94FUNI9](https://doi.org/10.5066/P94FUNI9).
- 110 U.S. Environmental Protection Agency, 40 C.F.R. § 141 and § 142: National Primary Drinking Water Regulations for Lead and Copper: Improvements (LCRI), 2024, <https://www.federalregister.gov/documents/2024/10/30/2024-23549/national-primary-drinking-water-regulations-for-lead-and-copper-improvements-lcri>.
- 111 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](https://www.epa.gov/system/files/documents/2024-10/final_lcri_fact_sheet_general_public.pdf).
- 112 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](https://doi.org/10.3133/ofr20181098).
- 113 K. L. Smalling, K. M. Romanok, P. M. Bradley, M. L. Hladik, J. L. Gray, L. K. Kanagy, R. B. McCleskey, D. A. Stavreva, A. K. Alexander-Ozinskas, J. Alonso, W. Avila, S. E. Breitmeyer, R. Bustillo, S. E. Gordon, G. L. Hager, R. R. Jones, D. W. Kolpin, S. Newton, P. Reynolds and G. M. Solomon, Mixed Contaminant Exposure in Tapwater and the Potential Implications for Human-Health in Disadvantaged Communities in California, *Water Res.*, 2024, **122485**, DOI: [10.1016/j.watres.2024.122485](https://doi.org/10.1016/j.watres.2024.122485).
- 114 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](https://doi.org/10.3133/ofr99193).
- 115 U.S. Environmental Protection Agency, 40 C.F.R. § 136: Guidelines establishing test procedures for the analysis of pollutants, 2020, <http://www.ecfr.gov/cgi-bin/text-idx?SID=3c78b6ce8952e5e79268e429ed98bad84&mc=true&node=pt40.23.136&rgn=div5>.
- 116 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](https://doi.org/10.3133/tm4C4).
- 117 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](https://doi.org/10.1016/j.talanta.2021.122139).
- 118 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).
- 119 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).
- 120 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>.
- 121 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](https://doi.org/10.1897/07-474.1).
- 122 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](https://doi.org/10.1016/j.envint.2018.02.013).
- 123 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](https://doi.org/10.1016/j.taap.2011.09.005).
- 124 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](https://doi.org/10.1039/C9EW00988D).
- 125 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](https://doi.org/10.1016/j.cotox.2023.100418).
- 126 G. Braun, G. Herberth, M. Krauss, M. König, N. Wojtyasiak, A. C. Zenclussen and B. I. Escher, Neurotoxic mixture effects of chemicals extracted from blood of pregnant



- women, *Science*, 2024, **386**, 301–309, DOI: [10.1126/science.adq0336](https://doi.org/10.1126/science.adq0336).
- 127 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](https://doi.org/10.1016/S0166-445X(02)00133-9).
- 128 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](https://doi.org/10.1002/etc.5620190927).
- 129 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](https://doi.org/10.1023/A:1020592802989).
- 130 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](https://doi.org/10.1016/j.scitotenv.2017.11.081).
- 131 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](https://doi.org/10.1289/EHP11051).
- 132 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](https://doi.org/10.1016/j.envint.2020.106206).
- 133 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](https://www.ecfr.gov/current/title-40/chapter-I/subchapter-D/part-141#_top).
- 134 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>.
- 135 World Health Organization (WHO), Guidelines for drinking-water quality, Fourth edition incorporating the first and second addenda, 2022, <https://iris.who.int/bitstream/handle/10665/352532/9789240045064-eng.pdf?sequence=1>.
- 136 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).
- 137 J. E. Norman, P. L. Toccalino and S. A. Morman, Health-Based Screening Levels for evaluating water-quality data (2nd ed.), (accessed February 10, 2020), DOI: [10.5066/F71C1TWP](https://doi.org/10.5066/F71C1TWP).
- 138 D. L. Filer, P. Kothiya, R. W. Setzer, R. S. Judson and M. T. Martin, tepl: the ToxCast pipeline for high-throughput screening data, *Bioinformatics*, 2017, **33**, 618–620, DOI: [10.1093/bioinformatics/btw680](https://doi.org/10.1093/bioinformatics/btw680).
- 139 M. Feshuk, L. Kolaczowski, K. Dunham, S. E. Davidson-Fritz, K. E. Carstens, J. Brown, R. S. Judson and K. Paul Friedman, The ToxCast pipeline: updates to curve-fitting approaches and database structure, *Front. Toxicol.*, 2023, **5**, 1275980, DOI: [10.3389/ftox.2023.1275980](https://doi.org/10.3389/ftox.2023.1275980).
- 140 U.S. Environmental Protection Agency, CompTox Chemicals Dashboard, <https://comptox.epa.gov/dashboard>, (accessed January 22, 2024).
- 141 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, *ACS ES&T Water*, 2022, **2**, 1772–1788, DOI: [10.1021/acsestwater.2c00293](https://doi.org/10.1021/acsestwater.2c00293).
- 142 U.S. Environmental Protection Agency, National Center for Computational Toxicology, ToxCast Database InvitroDBv3.5, <https://clowder.edap-cluster.com/spaces/62bb560ee4b07abf29f88fef>, (accessed May 26, 2023).
- 143 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](https://doi.org/10.1016/j.taap.2022.116141).
- 144 D. L. Villeneuve, K. Coady, B. I. Escher, E. Mihaich, C. A. Murphy, T. Schlekot 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](https://doi.org/10.1002/etc.4315).
- 145 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  $\alpha$  at the Crossroads of Toxicokinetics and Toxicodynamics, *Basic Clin. Pharmacol. Toxicol.*, 2018, **123**, 42–50, DOI: [10.1111/bcpt.13004](https://doi.org/10.1111/bcpt.13004).
- 146 L. A. Schaidler, J. M. Ackerman and R. A. Rudel, Septic systems as sources of organic wastewater compounds in domestic drinking water wells in a shallow sand and gravel aquifer, *Sci. Total Environ.*, 2016, **547**, 470–481, DOI: [10.1016/j.scitotenv.2015.12.081](https://doi.org/10.1016/j.scitotenv.2015.12.081).
- 147 L. A. Schaidler, R. A. Rudel, J. M. Ackerman, S. C. Dunagan and J. G. Brody, Pharmaceuticals, perfluorosurfactants, and other organic wastewater compounds in public drinking water wells in a shallow sand and gravel aquifer, *Sci. Total Environ.*, 2014, **468**, 384–393, DOI: [10.1016/j.scitotenv.2013.08.067](https://doi.org/10.1016/j.scitotenv.2013.08.067).
- 148 H. Zhang, R. Zhang, X. Zeng, X. Wang, D. Wang, H. Jia, W. Xu and Y. Gao, Exposure to neonicotinoid insecticides and their characteristic metabolites: Association with human liver cancer, *Environ. Res.*, 2022, **208**, 112703, DOI: [10.1016/j.envres.2022.112703](https://doi.org/10.1016/j.envres.2022.112703).



- 149 A. M. Vuong, C. Zhang and A. Chen, Associations of neonicotinoids with insulin and glucose homeostasis parameters in US adults: NHANES 2015–2016, *Chemosphere*, 2022, **286**, 131642, DOI: [10.1016/j.chemosphere.2021.131642](https://doi.org/10.1016/j.chemosphere.2021.131642).
- 150 D. Zhang and S. Lu, Human exposure to neonicotinoids and the associated health risks: A review, *Environ. Int.*, 2022, **163**, 107201, DOI: [10.1016/j.envint.2022.107201](https://doi.org/10.1016/j.envint.2022.107201).
- 151 G. N. Saari, W. C. Scott and B. W. Brooks, Global scanning assessment of calcium channel blockers in the environment: Review and analysis of occurrence, ecotoxicology and hazards in aquatic systems, *Chemosphere*, 2017, **189**, 466–478, DOI: [10.1016/j.chemosphere.2017.09.058](https://doi.org/10.1016/j.chemosphere.2017.09.058).
- 152 E. T. Furlong, A. L. Batt, S. T. Glassmeyer, M. C. Noriega, D. W. Kolpin, H. Mash and K. M. Schenck, Nationwide reconnaissance of contaminants of emerging concern in source and treated drinking waters of the United States: Pharmaceuticals, *Sci. Total Environ.*, 2017, **579**, 1629–1642, DOI: [10.1016/j.scitotenv.2016.03.128](https://doi.org/10.1016/j.scitotenv.2016.03.128).
- 153 M. J. Benotti, R. A. Trenholm, B. J. Vanderford, J. C. Holady, B. D. Stanford and S. A. Snyder, Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water, *Environ. Sci. Technol.*, 2009, **43**, 597–603, DOI: [10.1021/es801845a](https://doi.org/10.1021/es801845a).
- 154 A. Ido, Y. Hiromori, L. Meng, H. Usuda, H. Nagase, M. Yang, J. Hu and T. Nakanishi, Occurrence of fibrates and their metabolites in source and drinking water in Shanghai and Zhejiang, China, *Sci. Rep.*, 2017, **7**, 45931, DOI: [10.1038/srep45931](https://doi.org/10.1038/srep45931).
- 155 K. Zhang, Y. Zhao and K. Fent, Cardiovascular drugs and lipid regulating agents in surface waters at global scale: Occurrence, ecotoxicity and risk assessment, *Sci. Total Environ.*, 2020, **729**, 138770, DOI: [10.1016/j.scitotenv.2020.138770](https://doi.org/10.1016/j.scitotenv.2020.138770).
- 156 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 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](https://doi.org/10.1016/j.scitotenv.2023.161672).
- 157 K. S. Mohammed Abdul, S. S. Jayasinghe, E. P. S. Chandana, C. Jayasumana and P. M. C. S. De Silva, Arsenic and human health effects: A review, *Environ. Toxicol. Pharmacol.*, 2015, **40**, 828–846, DOI: [10.1016/j.etap.2015.09.016](https://doi.org/10.1016/j.etap.2015.09.016).
- 158 A. H. Smith and C. M. Steinmaus, Health effects of arsenic and chromium in drinking water: recent human findings, *Annu. Rev. Public Health*, 2009, **30**, 107–122, DOI: [10.1146/annurev.publhealth.031308.100143](https://doi.org/10.1146/annurev.publhealth.031308.100143).
- 159 A. Navas-Acien, A. R. Sharrett, B. S. Schwartz, E. Guallar, E. K. Silbergeld, K. E. Nachman and T. A. Burke, Arsenic exposure and cardiovascular disease: A systematic review of the epidemiologic evidence, *Am. J. Epidemiol.*, 2005, **162**, 1037–1049, DOI: [10.1093/aje/kwi330](https://doi.org/10.1093/aje/kwi330).
- 160 G. Pichler, M. Grau-Perez, M. Tellez-Plaza, J. Umans, L. Best, S. Cole, W. Goessler, K. Francesconi, J. Newman, J. Redon, R. Devereux and A. Navas-Acien, Association of arsenic exposure with cardiac geometry and left ventricular function in young adults, *Circ.: Cardiovasc. Imaging*, 2019, **12**, e009018, DOI: [10.1161/CIRCIMAGING.119.009018](https://doi.org/10.1161/CIRCIMAGING.119.009018).
- 161 Y.-H. Shih, T. Islam, S. K. Hore, G. Sarwar, M. H. Shahriar, M. Yunus, J. H. Graziano, J. Harjes, J. A. Baron, F. Parvez, H. Ahsan and M. Argos, Associations between prenatal arsenic exposure with adverse pregnancy outcome and child mortality, *Environ. Res.*, 2017, **158**, 456–461, DOI: [10.1016/j.envres.2017.07.004](https://doi.org/10.1016/j.envres.2017.07.004).
- 162 M. Argos, T. Kalra, P. J. Rathouz, Y. Chen, B. Pierce, F. Parvez, T. Islam, A. Ahmed, M. Rakibuz-Zaman, R. Hasan, G. Sarwar, V. Slavkovich, A. van Geen, J. Graziano and H. Ahsan, Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study, *Lancet*, 2010, **376**, 252–258, DOI: [10.1016/S0140-6736\(10\)60481-3](https://doi.org/10.1016/S0140-6736(10)60481-3).
- 163 E. García-Esquinas, M. Pollán, J. G. Umans, K. A. Francesconi, W. Goessler, E. Guallar, B. Howard, J. Farley, L. G. Best and A. Navas-Acien, Arsenic exposure and cancer mortality in a US-based prospective cohort: The Strong Heart Study, *Cancer Epidemiol., Biomarkers Prev.*, 2013, **22**, 1944–1953, DOI: [10.1158/1055-9965.Epi-13-0234-t](https://doi.org/10.1158/1055-9965.Epi-13-0234-t).
- 164 A. Navas-Acien, E. K. Silbergeld, R. Pastor-Barriuso and E. Guallar, Arsenic exposure and prevalence of type 2 diabetes in US adults, *JAMA, J. Am. Med. Assoc.*, 2008, **300**, 814–822, DOI: [10.1001/jama.300.7.814](https://doi.org/10.1001/jama.300.7.814).
- 165 State of New Jersey, New Jersey Administrative Code. 7:10–5.2: Safe Drinking Water Act; State Primary Drinking Water Regulations, Discretionary Changes to National Regulations, 2023, § 7:10–5.2, <https://advance.lexis.com/container?config=00JAA50TY5MTdjZi1lMzYxLTQxNTetOWFkNi0xMmU5ZTViODQ2M2MKAfBvZENhdGFsb2coFSYEAfv22IKqMT9DIHrf&rid=b2a14677-af29-47fa-83cb-e0d0f0c1f364>.
- 166 New Hampshire Department of Environmental Services, Arsenic in New Hampshire Well Water, 2021, <https://www.des.nh.gov/sites/g/files/ehbemt341/files/documents/2020-01/dwgb-3-2.pdf>.
- 167 D. B. Smith, F. Solano, L. G. Woodruff, W. F. Cannon and K. J. Ellefsen, Geochemical and mineralogical maps, with interpretation, for soils of the conterminous United States, Report U. S. Geological Survey Scientific Investigations Report 2017–5118, Reston, VA, 2019, DOI: [10.3133/sir20175118](https://doi.org/10.3133/sir20175118).
- 168 Nebraska Department of Environment and Energy, 2023 Nebraska Groundwater Quality Monitoring Report, 2023, [https://nebraskalegislature.gov/FloorDocs/108/PDF/Agencies/Environment\\_and\\_Energy\\_\\_Nebraska\\_Department\\_of\\_/702\\_20231127-113929.pdf](https://nebraskalegislature.gov/FloorDocs/108/PDF/Agencies/Environment_and_Energy__Nebraska_Department_of_/702_20231127-113929.pdf).
- 169 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](https://doi.org/10.1289/ehp.9707).
- 170 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](https://doi.org/10.1016/j.envres.2009.02.002).
- 171 G. Björklund, 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](https://doi.org/10.1007/s00204-020-02676-8).
- 172 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](https://doi.org/10.1016/j.envint.2020.106107).
- 173 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](https://doi.org/10.1053/j.ajkd.2006.03.002).
- 174 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](https://doi.org/10.1289/ehp.7475).
- 175 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](https://doi.org/10.3390/ijerph17030712).
- 176 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](https://doi.org/10.1016/j.taap.2015.11.017).
- 177 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](https://doi.org/10.1289/ehp.9910).
- 178 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](https://doi.org/10.1007/s12011-019-01920-2).
- 179 M. S. Spaur, Drinking Water Arsenic and Uranium: Associations With Urinary Biomarkers and Diabetes Across the United States, *Doctoral Thesis*, Columbia University, 2023, DOI: [10.7916/7y8r-hz45](https://doi.org/10.7916/7y8r-hz45).
- 180 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](https://doi.org/10.1155/2021/2358060).
- 181 A. Menke, E. Guallar and C. C. Cowie, Metals in Urine and Diabetes in U.S. Adults, *Diabetes*, 2015, **65**, 164–171, DOI: [10.2337/db15-0316](https://doi.org/10.2337/db15-0316).
- 182 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](https://doi.org/10.1542/peds.2016-1493).
- 183 U.S. Environmental Protection Agency, Lead and Copper Rule: A quick reference guide, Report EPA 816-F-08-018, 2008, <https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockkey=60001N8P.txt>.
- 184 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](https://doi.org/10.1080/10643389.2011.556556).
- 185 U.S. Environmental Protection Agency, Quick Guide to Drinking Water Sample Collection, <https://www.epa.gov/sites/production/files/2017-04/documents/quick-guide-drinking-water-sample-collection-2ed-update-508.pdf>, (accessed February 26, 2018).
- 186 U.S. Environmental Protection Agency, National Primary Drinking Water Regulations, (accessed March 16, 2020).
- 187 P. G. Georgopoulos, A. Roy, M. J. Yonone-Lioy, R. E. Opiekun and P. J. Lioy, Environmental copper: its dynamics and human exposure issues, *J. Toxicol. Environ. Health, Part B*, 2001, **4**, 341–394, DOI: [10.1080/109374001753146207](https://doi.org/10.1080/109374001753146207).
- 188 B. R. Stern, Essentiality and Toxicity in Copper Health Risk Assessment: Overview, Update and Regulatory Considerations, *J. Toxicol. Environ. Health, Part A*, 2010, **73**, 114–127, DOI: [10.1080/15287390903337100](https://doi.org/10.1080/15287390903337100).
- 189 B. R. Stern, M. Solioz, D. Krewski, P. Aggett, T.-C. Aw, S. Baker, K. Crump, M. Dourson, L. Haber, R. Hertzberg, C. Keen, B. Meek, L. Rudenko, R. Schoeny, W. Slob and T. Starr, Copper and Human Health: Biochemistry, Genetics, and Strategies for Modeling Dose-response Relationships, *J. Toxicol. Environ. Health, Part B*, 2007, **10**, 157–222, DOI: [10.1080/10937400600755911](https://doi.org/10.1080/10937400600755911).
- 190 A. A. Taylor, J. S. Tsuji, M. R. Garry, M. E. McArdle, W. L. Goodfellow, W. J. Adams and C. A. Menzie, Critical Review of Exposure and Effects: Implications for Setting Regulatory Health Criteria for Ingested Copper, *Environ. Manage.*, 2020, **65**, 131–159, DOI: [10.1007/s00267-019-01234-y](https://doi.org/10.1007/s00267-019-01234-y).
- 191 Nebraska Department of Environment and Energy, 2024 Nebraska Groundwater Quality Monitoring Report, 2024, <https://dec.nebraska.gov/sites/default/files/publications/2024%20Nebraska%20Groundwater%20Quality%20Monitoring%20Report.pdf>.
- 192 P. A. Fail, R. E. Chapin, C. J. Price and J. J. Heindel, General, reproductive, developmental, and endocrine toxicity of boronated compounds, *Reprod. Toxicol.*, 1998, **12**, 1–18, DOI: [10.1016/S0890-6238\(97\)00095-6](https://doi.org/10.1016/S0890-6238(97)00095-6).
- 193 U.S. Environmental Protection Agency, Drinking water health advisory for boron, Report 822-R-08-013, U.S.



- Environmental Protection Agency, Washington, D.C., 2008, [https://www.epa.gov/sites/production/files/2014-09/documents/drinking\\_water\\_health\\_advisory\\_for\\_boron.pdf](https://www.epa.gov/sites/production/files/2014-09/documents/drinking_water_health_advisory_for_boron.pdf).
- 194 Minnesota Department of Health, Toxicological summary for: Boron, 2017, <https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/boronsumm.pdf>.
- 195 California State Water Resources Control Board, Hexavalent Chromium (Chromium-6), [https://www.waterboards.ca.gov/drinking\\_water/certlic/drinkingwater/Chromium6.html](https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/Chromium6.html), (accessed February 27, 2025).
- 196 U.S. Environmental Protection Agency, RIS Toxicological Review of Hexavalent Chromium [Cr(VI)] CASRN 18540-29-9, Report EPA/635/R-24/164Fc, 2024, [https://iris.epa.gov/static/pdfs/0144\\_summary.pdf](https://iris.epa.gov/static/pdfs/0144_summary.pdf).
- 197 U.S. Environmental Protection Agency, Regional Screening Levels (RSLs), <https://www.epa.gov/risk/regional-screening-levels-rsls>, (accessed February 27, 2025).
- 198 J. S. Rosenblum, A. Liethen and L. Miller-Robbie, Prioritization and Risk Ranking of Regulated and Unregulated Chemicals in US Drinking Water, *Environ. Sci. Technol.*, 2024, **58**, 6878–6889, DOI: [10.1021/acs.est.3c08745](https://doi.org/10.1021/acs.est.3c08745).
- 199 J. Zhang and S. Li, Cancer Mortality in a Chinese Population Exposed to Hexavalent Chromium in Water, *J. Occup. Environ. Med.*, 1997, **39**, 315–319.
- 200 National Toxicology Program (NTP), NTP monograph on the state of the science concerning fluoride exposure and neurodevelopment and cognition: a systematic review, Report NTP Monograph 08, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina, 2024, DOI: [10.22427/NTP-MGRAPH-8](https://doi.org/10.22427/NTP-MGRAPH-8).
- 201 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](https://doi.org/10.1016/j.scitotenv.2020.139217).
- 202 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](https://doi.org/10.3133/cir1360).
- 203 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](https://doi.org/10.1542/peds.2009-0751).
- 204 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](https://doi.org/10.1177/003335491513000408).
- 205 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](https://doi.org/10.1016/j.neuro.2019.02.013).
- 206 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](https://doi.org/10.1021/acs.est.0c08065).
- 207 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](https://www.who.int/docs/default-source/wash-documents/wash-chemicals/gdwq-manganese-background-document-for-public-review.pdf?sfvrsn=9296741f_5).
- 208 M. Musgrove, The occurrence and distribution of strontium in U.S. groundwater, *Appl. Geochem.*, 2021, **126**, 104867, DOI: [10.1016/j.apgeochem.2020.104867](https://doi.org/10.1016/j.apgeochem.2020.104867).
- 209 Agency for Toxic Substances and Disease Registry (ATSDR), Strontium CAS #7440-24-6, <https://www.atsdr.cdc.gov/toxfaqs/tfacts159.pdf>, (accessed March 5, 2025).
- 210 S. Ozgür, H. Sümer and G. Koçoğlu, Rickets and soil strontium, *Arch. Dis. Child.*, 1996, **75**, 524–526, DOI: [10.1136/adc.75.6.524](https://doi.org/10.1136/adc.75.6.524).
- 211 U.S. Environmental Protection Agency, Fact Sheet: Preliminary Regulatory Determinations for the Third Drinking Water Contaminant Candidate List (CCL 3), Report 815-F-14-001, 2044, <https://www.epa.gov/sites/default/files/2014-10/documents/epa815f14001.pdf>.
- 212 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 March 5, 2025).
- 213 S.-K. Eng, P. Pusparajah, N.-S. Ab Mutalib, H.-L. Ser, K.-G. Chan and L.-H. Lee, Salmonella: A review on pathogenesis, epidemiology and antibiotic resistance, *Front. Life Sci.*, 2015, **8**, 284–293, DOI: [10.1080/21553769.2015.1051243](https://doi.org/10.1080/21553769.2015.1051243).
- 214 J. Silva, D. Leite, M. Fernandes, C. Mena, P. Gibbs and P. Teixeira, *Campylobacter* spp. as a foodborne pathogen: A review, *Front. Microbiol.*, 2011, **2**, 200, DOI: [10.3389/fmicb.2011.00200](https://doi.org/10.3389/fmicb.2011.00200).
- 215 J. M. Kunz, H. Lawinger, S. Miko, M. Gerdes, M. Thuneibat, E. Hannapel and V. A. Roberts, Surveillance for Waterborne Disease Outbreaks Associated with Drinking Water — United States, 2015–2020, *Morb. Mortal. Wkly. Rep.*, 2024, **73**, 1–23, DOI: [10.15585/mmwr.ss7301a1](https://doi.org/10.15585/mmwr.ss7301a1).
- 216 J. O. Falkinham, A. Pruden and M. Edwards, Opportunistic Premise Plumbing Pathogens: Increasingly Important Pathogens in Drinking Water, *Pathogens*, 2015, **4**, 373–386, DOI: [10.3390/pathogens4020373](https://doi.org/10.3390/pathogens4020373).
- 217 M. Cazals, E. Bédard, S. P. Faucher and M. Prévost, Factors Affecting the Dynamics of *Legionella pneumophila*, Nontuberculous Mycobacteria, and Their Host *Vermamoeba vermiformis* in Premise Plumbing, *ACS ES&T Water*, 2023, **3**, 3874–3883, DOI: [10.1021/acsestwater.3c00288](https://doi.org/10.1021/acsestwater.3c00288).
- 218 R. Laxminarayan, A. Duse, C. Wattal, A. K. Zaidi, H. F. Wertheim, N. Sumpradit, E. Vlieghe, G. L. Hara, I. M. Gould and H. Goossens, Antibiotic resistance—the need for global solutions, *Lancet Infect. Dis.*, 2013, **13**, 1057–1098, DOI: [10.1016/S1473-3099\(13\)70318-9](https://doi.org/10.1016/S1473-3099(13)70318-9).
- 219 N. J. Ashbolt, A. Amézquita, T. Backhaus, P. Borriello, K. K. Brandt, P. Collignon, A. Coors, R. Finley, W. H. Gaze, T. Heberer, J. R. Lawrence, D. G. J. Larsson, S. A. McEwen, J. J. Ryan, J. Schönfeld, P. Silley, J. R. Snape, C. V. d. Eede and



- E. Topp, Human Health Risk Assessment (HHRA) for environmental development and transfer of antibiotic resistance, *Environ. Health Perspect.*, 2013, **121**, 993–1001, DOI: [10.1289/ehp.1206316](https://doi.org/10.1289/ehp.1206316).
- 220 U.S. Environmental Protection Agency, Literature review of contaminants in livestock and poultry manure and implications for water quality, Report EPA 820-R-13-002, U. S. Environmental Protection Agency, 2013, <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100H2NI.txt>.
- 221 T. R. Burch, J. P. Stokdyk, S. K. Spencer, B. A. Kieke, A. D. Firnstahl, M. A. Muldoon and M. A. Borchardt, Quantitative microbial risk assessment for contaminated private wells in the fractured dolomite aquifer of Kewaunee County, Wisconsin, *Environ. Health Perspect.*, 2021, **129**, 067003, DOI: [10.1289/EHP7815](https://doi.org/10.1289/EHP7815).
- 222 M. A. Borchardt, J. P. Stokdyk, B. A. Kieke, M. A. Muldoon, S. K. Spencer, A. D. Firnstahl, D. E. Bonness, R. J. Hunt and T. R. Burch, Sources and risk factors for nitrate and microbial contamination of private household wells in the fractured dolomite aquifer of northeastern Wisconsin, *Environ. Health Perspect.*, 2021, **129**, 067004, DOI: [10.1289/EHP7813](https://doi.org/10.1289/EHP7813).
- 223 J. C. Chee-Sanford, R. I. Aminov, I. J. Krapac, N. Garrigues-Jeanjean and R. I. Mackie, Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities, *Appl. Environ. Microbiol.*, 2001, **67**, 1494–1502, DOI: [10.1128/AEM.67.4.1494-1502.2001](https://doi.org/10.1128/AEM.67.4.1494-1502.2001).
- 224 C. E. Givens, D. W. Kolpin, M. A. Borchardt, J. W. Duris, T. B. Moorman and S. K. Spencer, Detection of hepatitis E virus and other livestock-related pathogens in Iowa streams, *Sci. Total Environ.*, 2016, **566-567**, 1042–1051, DOI: [10.1016/j.scitotenv.2016.05.123](https://doi.org/10.1016/j.scitotenv.2016.05.123).
- 225 M. A. Fox, K. E. Nachman, B. Anderson, J. Lam and B. Resnick, Meeting the public health challenge of protecting private wells: Proceedings and recommendations from an expert panel workshop, *Sci. Total Environ.*, 2016, **554-555**, 113–118, DOI: [10.1016/j.scitotenv.2016.02.128](https://doi.org/10.1016/j.scitotenv.2016.02.128).
- 226 K. Wait, A. Katner, D. Gallagher, M. Edwards, W. Mize, C. L. P. Jackson and K. J. Pieper, Disparities in well water outreach and assistance offered by local health departments: A North Carolina case study, *Sci. Total Environ.*, 2020, **747**, 141173, DOI: [10.1016/j.scitotenv.2020.141173](https://doi.org/10.1016/j.scitotenv.2020.141173).
- 227 A. D. Woolf, B. D. Stierman, E. D. Barnett and L. G. Byron, Policy statement: Drinking water from private wells and risks to children, *Pediatrics*, 2023, **151**, 10, DOI: [10.1542/peds.2022-060644](https://doi.org/10.1542/peds.2022-060644).
- 228 A. E. Nigra, Environmental racism and the need for private well protections, *Proc. Natl. Acad. Sci. U. S. A.*, 2020, **117**, 17476–17478, DOI: [10.1073/pnas.2011547117](https://doi.org/10.1073/pnas.2011547117).
- 229 L. H. Nowell, P. W. Moran, T. S. Schmidt, J. E. Norman, N. Nakagaki, M. E. Shoda, B. J. Mahler, P. C. Van Metre, W. W. Stone and M. W. Sandstrom, Complex mixtures of dissolved pesticides show potential aquatic toxicity in a synoptic study of Midwestern US streams, *Sci. Total Environ.*, 2018, **613-614**, 1469–1488, DOI: [10.1016/j.scitotenv.2017.06.156](https://doi.org/10.1016/j.scitotenv.2017.06.156).
- 230 R. F. Spalding, M. E. Burbach and M. E. Exner, Pesticides in Nebraska's Ground Water, *Groundwater Monit. Rem.*, 1989, **9**, 126–133, DOI: [10.1111/j.1745-6592.1989.tb01021.x](https://doi.org/10.1111/j.1745-6592.1989.tb01021.x).
- 231 G. Wehtje, J. R. C. Leavitt, R. F. Spalding, L. N. Mielke and J. S. Schepers, Atrazine contamination of groundwater in the platte valley of Nebraska from non-point sources, *Sci. Total Environ.*, 1981, **21**, 47–51, DOI: [10.1016/0048-9697\(81\)90136-4](https://doi.org/10.1016/0048-9697(81)90136-4).
- 232 C. M. Wieben, Estimated annual agricultural pesticide use by major crop or crop group for states of the conterminous United States, 1992–2019 (including preliminary estimates for 2018–19), Report U.S. Geological Survey data release, 2024, DOI: [10.5066/P900FZ6Y](https://doi.org/10.5066/P900FZ6Y).
- 233 D. Sushch, M. L. Hladik, M. D. De Parsia, B. G. Perrotta, C. J. Kotalik and D. M. Walters, Pesticide concentrations in multiple stream matrices collected near Mead, Nebraska, 2022, Report U.S. Geological Survey data release, 2024, DOI: [10.5066/P1MG7T7X](https://doi.org/10.5066/P1MG7T7X).
- 234 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](https://doi.org/10.1016/j.cotox.2023.100388).
- 235 P. Price, S. Hagiwara and F. Momoli, Using data on the uncertainty of LOAELs to model the probability of observing adverse effects in low-dose studies of the toxicity of chemical mixtures, *Regul. Toxicol. Pharmacol.*, 2025, **161**, 105843, DOI: [10.1016/j.yrtph.2025.105843](https://doi.org/10.1016/j.yrtph.2025.105843).
- 236 L. L. Pham, S. M. Watford, P. Pradeep, M. T. Martin, R. S. Thomas, R. S. Judson, R. W. Setzer and K. Paul Friedman, Variability in in vivo studies: Defining the upper limit of performance for predictions of systemic effect levels, *Comput. Toxicol.*, 2020, **15**, 100126, DOI: [10.1016/j.comtox.2020.100126](https://doi.org/10.1016/j.comtox.2020.100126).
- 237 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](https://doi.org/10.1093/toxsci/kfz201).
- 238 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](https://doi.org/10.1002/etc.3309).
- 239 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](https://doi.org/10.1038/s41545-021-00128-z).
- 240 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](https://doi.org/10.1016/j.watres.2019.115455).
- 241 M. Powers, J. Yracheta, D. Harvey, M. O'Leary, L. G. Best, A. Black Bear, L. MacDonald, J. Susan, K. Hasan, E. Thomas, C. Morgan, P. Olmedo, R. Chen, A. Rule, K. Schwab,



A. Navas-Acien and C. M. George, Arsenic in groundwater in private wells in rural North Dakota and South Dakota: Water

quality assessment for an intervention trial, *Environ. Res.*, 2019, **168**, 41–47, DOI: [10.1016/j.envres.2018.09.016](https://doi.org/10.1016/j.envres.2018.09.016).

