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Article

Household-Level Variability of Nontarget Analytical Results for Drinking Water Provides a Tool for Uncovering Constituents Introduced by Distribution System Components

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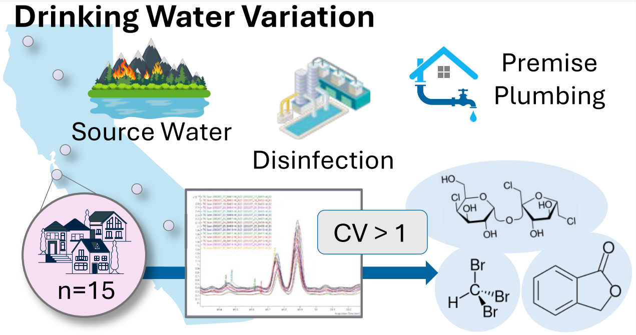
ABSTRACT: The variability in the nontarget chemical composition of tap water from 120 households and 15 brands of retail water was analyzed during two seasons. Fifteen households in eight separate community water systems were evaluated with the goal of identifying compounds with high within-source variability and investigating potential origins of the observed variation. High resolution mass spectrometry with liquid and gas chromatography was implemented and 10 chemical features from each water system with the highest coefficient of variation and a tentative library match were prioritized for investigation. This prioritization filter reduced the number of considered features from the 16,929 originally isolated to 282. High confidence structural annotations could be assigned to 134 compounds, which were then categorized based on plausible contaminant inputs. The most common source category was plastic (potentially originating from piping, fittings or packaging), with 47/50 of the GC compounds and 22/40 of the LC compounds having possible plastic-related origins. Other important source categories included other distribution system components (polychlorinated biphenyls, historically used in caulking), disinfection byproducts (trihalomethanes), and contaminants present in source waters at varying levels (sucralose, PFAS). The findings highlight the diverse constituents introduced into drinking water from the distribution system and the importance of assessing chemical exposures via drinking water at the point of use.



KEYWORDS: *water distribution, plastic, piping, per- and poly fluorinated alkyl substances (PFAS), polychlorinated biphenyl (PCB), disinfection byproduct (DBP), point-of-use, chemical exposure*

INTRODUCTION

There are more than 148,000 public water systems in the United States and 90% of residents receive water from such systems.[1] Drinking water chemistry can exhibit significant variability among households served by a single public water distribution system for three primary reasons:

1. Constituents are present in different concentrations in the water sources supplying the distribution system (e.g., multiple groundwater supply wells or surface water reservoirs) and they reach individual households in varied proportions
2. Constituents are formed or degraded by reactions occurring during transit through the distribution system (e.g., disinfection byproducts such as trihalomethanes), or
3. Constituents leach from components of the distribution system in differing amounts because:
    a. Varied construction materials were used across a public distribution system (e.g., because system components were built or upgraded at different times), or
    b. On-premise plumbing materials and fixtures differ among households.

Variability of disinfection byproducts (DBPs) such as trihalomethanes at the household level has long been recognized.[2] This variability is the basis for regulatory DBP testing at households in the system that have the longest travel times from the point of treatment. These locations typically represent the highest DBP concentrations and microbial risks, and the lowest chlorine residuals.[3,4] Recent work has confirmed a similar level of variability for emerging, unregulated classes of disinfection byproducts including iodinated halomethanes and haloacetonitriles and has shown that this can result in significant

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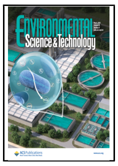

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household-level variation in the health risks associated with DBPs.[5,6]

Published work that documents the household-level variability of constituents beyond DBPs is far scarcer. Trace element variability was addressed by a study in Canada that showed a high degree of spatial (but not temporal) variability in manganese concentrations.[7] The most significant body of work on the variability of trace organic constituents at the household level has been conducted in the last five years by a group of researchers from the USGS, who have documented significant variability in chemical concentrations in tap water and estimated the associated health risks in Minneapolis, MN,[8] Puerto Rico,[9] Cape Cod, MA,[10] the Northern Great Plains, USA,[11] and California.[12,13] Although that work has involved an extensive list of target compounds and wide geographic coverage, almost none of it has examined the variability in exposures to chemicals not found on target lists.

Nontargeted chemical analysis (NTA) has emerged as a powerful tool for identifying a wide array of chemicals in drinking water supplies, providing insights into contaminants that traditional targeted methods might overlook. Studies utilizing NTA techniques have successfully detected a multitude of emerging contaminants in drinking water, including pharmaceuticals, personal care products, and industrial chemicals, thus highlighting the complexity of household exposure.[14−16] While NTA is a valuable technique for uncovering a broad suite of chemical constituents, a substantial degree of expert user input is still required. Numerous algorithms have been developed to improve annotation workflows, but schemes that prioritize chemical features to best answer key research questions, while minimizing expert curation time are still needed.[17]

In this work, we focused NTA identification efforts on constituents with the highest variability within a water system because we hypothesized that these constituents would yield critical insights into compounds that were formed or degraded during transport or were leached from distribution system components or household plumbing materials. The data for this study come from an extensive targeted and nontargeted chemical analysis of tap water from 8 community water systems with 15 participating households per system and 15 brands of retail water sampled in winter and in summer ($n = 270$). Patterns and commonalities in high variability nontarget features were examined to gain insights into their chemical identities and their putative sources.

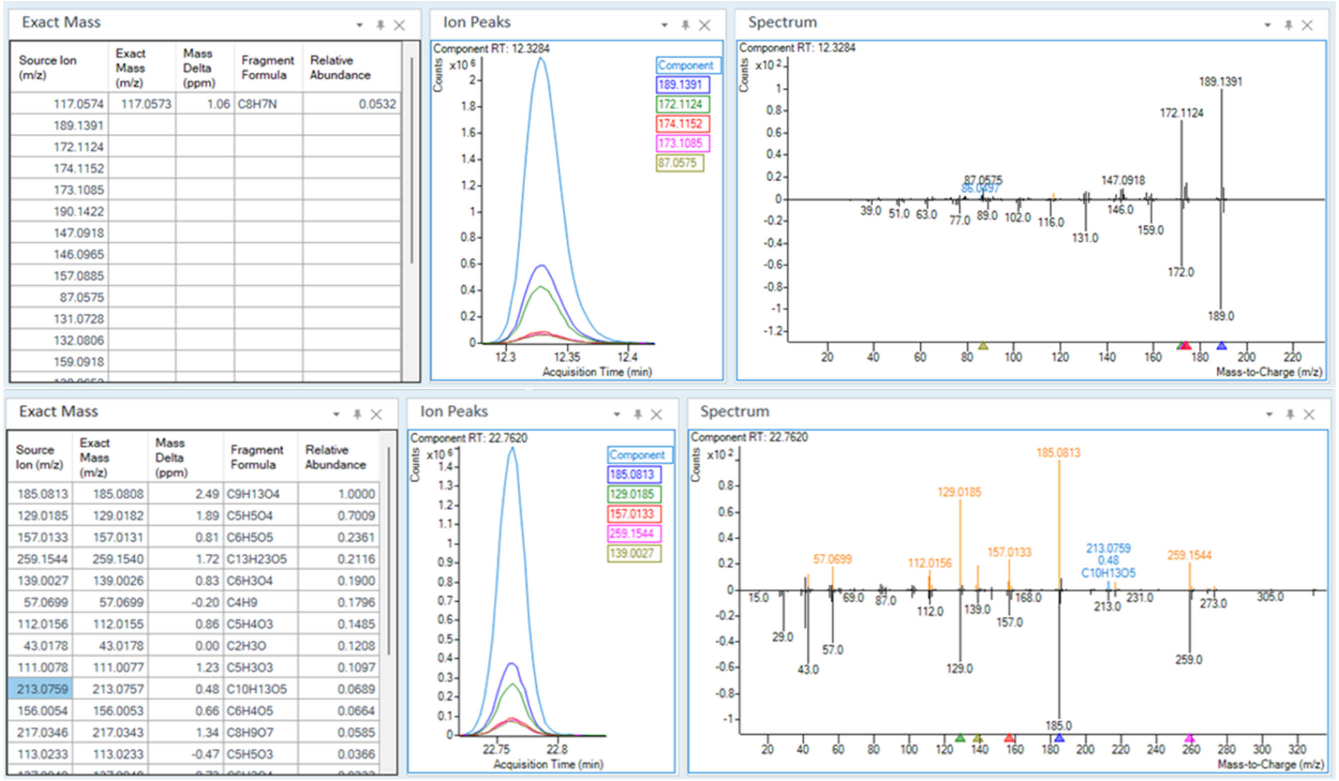
■ EXPERIMENTAL SECTION

Study Design. Eight community public water supplies and water purchased from 15 retail sources (collectively referred to as water sources throughout the paper) were sampled as part of this study (Supporting Information Tables S1 and S2). Within each community public supply system, residential households were recruited using direct mailings supplemented by additional outreach to community organizations as necessary; 15 households were selected in each community. Sampling occurred twice for each water source, once during winter of 2020 (January−March) and once during summer of 2020 (June−Sept). A map indicating the locations of the community water systems and the locations of participating households is available in Figure S1 of the Supporting Information for Anderson et al.[5] Briefly, four communities were located in northern California: East San Francisco Bay Area (EB), the city of San Mateo (SM), the town of Weaverville (WV), and the Yurok Tribe Reservation (YT); two communities were in central California: the towns of Merced (MC) and Madera (MD); and two communities were in southern California: greater Los Angeles (LA) and the city of Irvine (IR). All households within a community water system were sampled on the same day during each sampling event and were transported to UC Davis the day of collection. Across all eight communities, disinfection was achieved via either chlorination (WV, YT, MD, MC) or chloramination (EB, SM, LA, IR). Additionally, retail sourced water (BW) included 7 plastic bottled water brands, two wax-coated boxed waters, 2 aluminum canned waters, and 4 refill stations at retail stores in Davis, CA.

Analytical Methods. The analytical methods employed in the study have been documented in a previous publication[18] and are only briefly summarized here. Water samples (2.4 L) were pH adjusted (6.5−7) and passed through preconditioned lab-prepared solid phase extraction (SPE) cartridges containing Oasis HLB, Strata XAW, Strata XCW, and Isolute ENV+.[19,20] SPE cartridges were sequentially eluted with (1) 5% MTBE in MeOH, (2) dichloromethane, (3) 1:1 EtAc/MeOH with 0.5% NH_3, and last, (4) 1:1 EtAc/MeOH with 1.7% formic acid. Eluents were evaporated to 1 mL under nitrogen, and an aliquot (200 μL) was removed for bioassays. The remainder was evaporated to 400 μL and divided into a liquid chromatography (LC) fraction (MeOH/DDI water, 1:5, v/v) and a gas chromatography (GC) fraction (EtAc). Although the initial extract is divided evenly, subsequent concentration and solvent exchange may create uneven divisions in particular chemicals between the extracts, potentially causing compounds that should be detectable on both instruments to only be detected on either GC or LC. Internal standard calibration was used for both analyses. Recoveries of 24/26 surrogate compounds averaged 57−124%. To minimize holding times, analysis and data processing for winter and summer sample sets were performed separately.

LC analysis was performed using an Agilent 1260 Infinity HPLC coupled with an Agilent 6530 Quadrupole Time-of-Flight mass spectrometer (QTOF-MS; Table S3) in both positive and negative electrospray ionization modes (ESI+/ESI−) using the *All-Ions* acquisition method with collision cell voltages cycling through 0, 10, 20, and 40 eV. GC analysis was performed using an Agilent 8890 GC coupled to an Agilent 7250 QTOF-MS in electron ionization mode using two chromatographic methods (Table S4). Compounds with high ion abundances were analyzed in split mode (200:1 split ratio) to avoid overloading the detector,.while those with lower abundances were analyzed in splitless mode Both QTOF systems consistently produced mass errors below 5 ppm for annotated compounds.

Alignment. Data produced using each platform was aligned using MS-DIAL (version 3.66 for LC-QTOF-MS data and version 4.90 for GC-QTOF-MS data).[21] Initial annotations within MS-DIAL for GC data were made by matching experimental spectra to the NIST17 database accompanied by retention index calibration using *n*-alkane standards (C8−C32). Initial annotations for LC data were made in MS-DIAL by matching experimental *All-Ions* spectra against two MS/MS databases: (i) a merged Agilent Pesticides, Water Contaminants and Forensics/Toxicology library, and (ii) libraries downloaded from the Mass Bank of North America (MoNA) for LC-MS/MS Positive Mode (99,261 spectra) and LC-MS/MS Negative Mode (47,058 spectra). Secondary annotations were acquired using the vendor supplied software packages Unknowns



Exact Mass

Source Ion (m/z)	Exact Mass (m/z)	Mass Delta (ppm)	Fragment Formula	Relative Abundance
117.0574	117.0573	1.06	C8H7N	0.0532
189.1391				
172.1124				
174.1152				
173.1085				
190.1422				
147.0918				
146.0965				
157.0885				
87.0575				
131.0728				
132.0806				
159.0918				

Exact Mass

Source Ion (m/z)	Exact Mass (m/z)	Mass Delta (ppm)	Fragment Formula	Relative Abundance
185.0813	185.0808	2.49	C9H13O4	1.0000
129.0185	129.0182	1.89	C5H5O4	0.7009
157.0133	157.0131	0.81	C6H5O5	0.2361
259.1544	259.1540	1.72	C13H23O5	0.2116
139.0027	139.0026	0.83	C6H3O4	0.1900
57.0699	57.0699	-0.20	C4H9	0.1796
112.0156	112.0155	0.86	C5H4O3	0.1485
43.0178	43.0178	0.00	C2H3O	0.1208
111.0078	111.0077	1.23	C5H3O3	0.1097
213.0759	213.0757	0.48	C10H13O5	0.0689
156.0054	156.0053	0.66	C6H4O5	0.0664
217.0346	217.0343	1.34	C8H9O7	0.0585
113.0233	113.0233	-0.47	C5H5O3	0.0366

Figure 1. Example of poor (top panel) and good (bottom panel) exact mass matches for NIST database annotations. Annotated compounds are 1,5-naphthalenediol, 2-nitroso-, GC splitless, LA-10W (top panel) and Tributyl acetylcitrate, GC Splitless, SM-03W (bottom panel).

Analysis (v. 10, Agilent Technologies, Inc.) for GC data and Qualitative Analysis (v. 10, Agilent Technologies, Inc.) for LC data. Ion abundance for each feature (peak height of the ion selected as the quantifier ion) was exported for subsequent statistical analysis. A complete list of the aligned feature sets, before and after application of method blank and signal-to-noise filters is included in the Supporting Information (Tables S5–S10).

Feature Variability. The metric of variability used in this study was the coefficient of variation (CV) of feature height, which was calculated for each aligned feature within each water source as

$$\mathrm{CV} = \frac{\text{standard deviation}}{\text{average}}$$

across all samples within each water source in each season. We selected an arbitrary value of CV > 1 as a cutoff for high variability features. In some cases, a feature was present at low abundance in all samples within a water source, producing large, but not environmentally meaningful CV values. To be considered as a high CV compound for a particular water source, therefore, required that a feature had a CV > 1 and a maximum abundance of >3000 (for GC) or >5000 (for LC) within that water source. These abundance thresholds are the same as those applied across the entire data set when selecting peaks for inclusion in the initial alignment of the data from each instrument platform. As a point of comparison, standard compound mixtures injected approximately every 20 samples for quality assurance during the analytical runs typically displayed CV values below 0.3 and exhibited no discernible patterns in abundance variation over the run. As a result, no abundance corrections were implemented during the subsequent data analysis.

Confirmation and Retrospective Quantification. For selected high variability compounds with tentative library annotations, standards were purchased and samples with the highest ion abundances were reanalyzed to confirm retention time and spectral matches. External standard curves (two points, prepared by dilution of stock solutions) for confirmed compounds were prepared and used to retrospectively estimate sample concentrations using Agilent Quantitative Analysis (v. 10.0).

■ RESULTS

A significant fraction of the aligned features met the definition of "high variability" adopted in this study (Supporting Information, Table S11). For LC-QTOF data the high variability features represented 58% of the total feature list after blank and signal-to-noise filters were applied, while for the GC-QTOF, over 75% of the features (averaged across seasons and split/splitless analyses) met the selected high variability criterion. The observed variability represents a combination of "true variability", caused by the processes hypothesized to create variability in compound abundances across households, and "artifactual variability", caused by alignment or integration errors. High variability features were not evenly distributed across water sources, with the largest number of high variability features found in the retail "bottled" water source for four out of the six workflows (LC-ESI summer and winter, GC-EI split winter, GC-EI splitless summer, Table S12) while for the other two workflows (GC-EI split summer and GC-EI splitless winter) it was the second most variable water source. This result is not surprising because the retail water samples come from more

Table 1. List of GC Nontarget Compounds with the Greatest Variability within Water Sources[a]

compound	water source	potential inputs
9,10-anthracenedione (anthraquinone)	MD_S	DBP, DS-P[24,25]
methane, dibromochloro- (DBCM)	BW_S, EB_S, WV_W	DBP, DS-P[24,26]
methane, tribromo- (bromoform)	BW_S, BW_W, EB_S, MD_S, WV_W, YT_W	DBP, DS-P[24,26]
1,1′-biphenyl, 2,2′,5,5′-tetrachloro- (PCB 52)	EB_W, EB_S	DS-O[25]
2,2′,3-trichloro-1,1′-biphenyl (PCB 16)	EB_W	DS-O
1(3*H*)-isobenzofuranone (phthalide)	BW_W	DS-P[24]
1,3,5-triazine-2,4-diamine, 6-phenoxy-	BW_W, BW_S	DS-P
1-decanol, 2-hexyl-	EB_S	DS-P[24,25]
1-dodecanol (lauryl alcohol)	MD_W, YT_S	DS-P[24,25]
1-dodecene	YT_S	DS-P[24,25]
methyl isopimarate	BW_S, MC_S	DS-P[24,25]
1-propene-1,2,3-tricarboxylic acid, tributyl ester (tributyl aconitate)	EB_W, LA_W, MC_W, MD_W, SM_W, WV_W, YT_W	DS-P[24,25]
2(3*H*)-benzothiazolone	LA_W[b]	DS-P[24,27]
2-naphthyl benzoate	EB_S, IR_S	DS-P[24,25]
3,5-di-*tert*-butyl-4-hydroxybenzaldehyde	BW_W, WV_W	DS-P[24−27]
3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol	BW_S	DS-P[24,27]
4-piperidinone, 2,2,6,6-tetramethyl-	MD_W, SM_S	DS-P[24,25]
acetamide	LA_W, MC_W, MD_W, SM_W, YT_W	DS-P[24,27]
azulene	BW_S	DS-P[24,25]
benzaldehyde, 3-methoxy-	BW_W	DS-P
benzenamine, 2,4-dimethyl-(2,4-dimethylaniline)	SM_W	DS-P[24,25]
benzoic acid	EB_W, MC_W, SM_W	DS-P[24,25]
bis(2-ethylhexyl) phthalate (DEHP)	MD_W, WV_W	DS-P[24−26]
butanoic acid, 2,3-dimethyl-2-(1-methylethyl)-	BW_S	DS-P[24]
butylated hydroxytoluene (BHT)	BW_W, BW_S	DS-P[24−26]
decanal	BW_W	DS-P[24−26]
docosane	EB_S	DS-P[24,25]
dodecane, 1-bromo-	IR_S, LA_S, MD_S, WV_S	DS-P[24]
dodecane, 4,6-dimethyl-	SM_S	DS-P[24,25]
ethanone, 1,1′-(1,4-phenylene) bis- (1,4-diacetylbenzene)	LA_S	DS-P[24,25,27]
hexadecanoic acid, methyl ester (methyl palmitate)	EB_S	DS-P[24,25]
hexanoic acid, 2-ethyl-2-propyl-, methyl ester	BW_W	DS-P
naphthalene, 1-(phenylmethoxy)-	EB_S, IR_S, IR_W[b], LA_S, LA_W[b], MD_S, MD_W, SM_S, WV_W, YT_W	DS-P[25]
naphthalene, 2-ethenyl- (2-vinylnaphthalene)	EB_W	DS-P[24,25]
n-Hexadecanoic acid (palmitic acid)	MD_W	DS-P[24,25]
pentanoic acid, 5-hydroxy-, 2,4-di-*t*-butylphenyl esters	BW_S	DS-P
phenol, 2,2′-methylenebis[6-(1,1-dimethylethyl)-4-methyl-	LA_S, MD_S, SM_W, SM_S	DS-P[24,25]
phenol, 2,6-bis(1,1-dimethylethyl)-(2,6-Di-*tert*-butylphenol)	EB_W	DS-P[24−26]
p-octylacetophenone	LA_S, MC_S, MC_W, MD_S, MD_W, SM_W, YT_S	DS-P[24]
propanoic acid, 3,3′-thiobis-, didodecyl ester (dilauryl thiodipropionate)	SM_S	DS-P[24,25]
tributyl acetylcitrate	BW_S, EB_W, EB_S, IR_W, LA_W, MC_W, MC_S, MD_W, SM_W, WV_W, WV_S, YT_W, YT_S	DS-P[24,25]
tamoxifen	EB_W	SW
9*H*-fluorene, 9-methylene-	BW_S, IR_S, MD_S, IR_W	SW, DS-P[24]
caffeine	BW_S	SW, DS-P[24]
cyclopentasiloxane, decamethyl-	MC_W	SW, DS-P[24,25]
diphenyl sulfone	MC_W	SW, DS-P[24,25]
fluoranthene	IR_W, MC_W, MD_S	SW, DS-P[24]
p,p′-DDD	MC_W	SW, DS-P[24,25]
p,p′-DDE	MD_S, LA_S, MC_S	SW, DS-P[24,25]
p,p′-DDT	LA_W, MC_W, MD_S	SW, DS-P[24,25]

[a] Compounds included were annotated at confidence Levels 1 (bold type) or 2 and could be assigned potential sources. DBP = disinfection byproduct, DS-P = distribution system-plastic, DS-O = distribution system-other, SW = source water. A complete list of the high variability compounds, including those without potential source assignments, is available in the Supporting Information files.
[b] Detected with high variability in both split and splitless methods.

diverse sources compared with the other source types considered. The category includes spring waters with varying degrees of treatment and municipal water supplies with some additional treatment (typically ultraviolet radiation and activated carbon filtration), with the variability accentuated by the diverse packaging types employed (e.g., plastic bottles, aluminum cans, wax coated cardboard boxes) across the category.

To refine the prioritization strategy, and to reduce the fraction of the aligned features that required manual curation, we chose to narrow our focus to the 10 most variable features for which tentative library annotations were available within each source type and analytical approach. Complete lists of all high variability features with annotations separated by workflow and sampling season are presented in Tables S13−S18. These tables also identify which (if any) of the water sources had the feature included on their respective top 10 lists and indicate the confidence level assignment[22,23] based on the curation process described below. Focusing on the top 10 high variability features for each water source significantly reduced (by up to 73%) the number of features subject to manual curation. In total, 282 top-10 CV annotated features across all analysis platforms and seasons were subject to manual curation.

For GC data, the curation process focused on inspecting the MS-DIAL annotation and comparing it with the results from Unknowns Analysis for the samples with the five highest abundances for the feature in question. The comparison required that at least the five most abundant fragment ions in the annotated structure had assigned formulas that were consistent with the formula of that structure. An example of a prioritized feature that did not pass this curation step is provided in Figure 1 (top panel) A feature with the annotation 2-nitroso-

1,5-naphthalenediol ($C_{10}H_7NO_3$) had high variability in both GC modes in both seasons. It was an especially notable feature with respect to variability in the GC split samples from summer, where it was one of the top 10 most variable features for four water sources (EB, IR, SM, WV). However, despite the relatively high match score with the reference spectrum in the NIST database (typically over 70% for samples with above the median abundance), virtually none of the fragments had an accurate mass that was consistent with the formulas of the fragments in the NIST library. Specifically, the fragment masses were all consistent with a formula of the form $C_aH_bN_c$, and in no case did the generated molecular formula include one or more oxygen atoms as would be expected for the given annotation. Efforts to find a better match within the NIST database were unsuccessful, so this feature was assigned a confidence level of 5. When a fragment in the experimental spectrum is not consistent with the presumed molecular formula of the fragment in the NIST database, that fragment is shown in black in the experimental (top) spectrum in Figure 1 and in the Supporting Information (Figures S1−S70). An example of a high variability feature that passed the exact mass curation is Acetyl Tributyl Citrate (ATBC; Figure 1, bottom panel). This feature was on the high variability list for GC splitless samples for all 9 water sources in both seasons, and was on the top 10 CV list for 8 water sources in winter samples and 5 water sources in the summer samples. Not only does this spectrum have a high match score relative to the unit-mass NIST17 database, the experimentally observed fragments nearly all have exact mass matches to the fragment formulas expected for this annotation (peaks with exact mass matches are indicated in red in the experimental spectra in Figures 1 and S1−S70). For LC data, curation involved manual inspection of the peak shape and coelution of fragments and direct observation of the MS/MS spectral match to the combined Agilent database obtained on a similar instrument. Compounds that passed these thresholds were assigned confidence level 2, while features that did not pass were assigned a confidence level of 5 (for GC data, which lacks a clear molecular ion) or level 4 (for LC data). In some cases, the compound was either already on a target list for this project or a standard was subsequently purchased for confirmation; those compounds are classified as level 1 annotations.

The top 10 CV lists for each source type were combined by workflow for compounds with confident annotations (levels 1 or 2) and were consolidated to create two lists of high variability identified features, one for GC and one for LC compounds (Tables S19 and S20). Level 2 annotations for GC required that both retention indexes and mass spectra matched the NIST database. Even applying these filters, there is uncertainty in level 2 annotations, particularly for the alkanes (both linear and branched) because of high similarity of both RI and spectra for these compounds. A literature review was conducted to identify potential sources of these compounds in municipal and retail water supplies and compounds were assigned to one (or more) broad categories. The categories applied were: disinfection byproducts (DBP) for compounds known to be formed during disinfection processes, source water (SW) for compounds known to be present in finished drinking waters because of their well-documented occurrence in surface and groundwater supplies, or distribution system (DS) for compounds that have documented sources in water distribution systems (both public systems and on-premises plumbing) or in packaging materials (in the case of retail waters). Because many compounds potentially related to plastic were discovered in this analysis, the distribution system category was subdivided into compounds associated with plastic materials (DS-P) and those associated with other components of a distribution system (DS-O). Any compound that could not be assigned to one of these categories based on literature sources was assigned to the category unknown (U). Many compounds with potential distribution system sources are contaminants historically found in source waters (e.g., DDT and its transformation products) or are natural products likely to be widespread in surface waters impacted by human activities (e.g., 7-Desoxycholic acid or Cortisone). We have attempted to indicate compounds in this group by using the code SW, DS-P in Tables 1 and 2.

All compounds within the top 10 CVs for at least one water source with confident annotations that could be assigned a potential source are listed in Table 1 (detected by GC) and Table 2 (detected by LC). Putative sources could be assigned for 50/68 GC compounds and 40/66 LC compounds. The most prevalent assignment was to the category DS-P (either solely or in combination with another category like SW). This category includes 47 of the 50 high variability GC compounds and 22 of the 40 high variability LC compounds. Examples of compounds of interest within the various categories are discussed below.

Disinfection Byproducts. Because disinfection byproducts form in part from reactions between organic compounds (either natural or anthropogenic) and residual disinfectant during transport from the treatment plant to households, they are known to vary across the distribution system. The exact amount of inter-household variability within a system is therefore expected to depend on the difference in travel time to reach each household. Within the group of compounds measured via the split GC method, dibromochloromethane (DBCM) and tribromomethane (TBM) were identified as compounds having high variability. During the winter, TBM, an unregulated trihalomethane, was on the top 10 variability list for BW, WV, and YT and DBCM, a regulated trihalomethane, was listed for WV. In the summer TBM was listed for BW, EB, and MD and DBCM for BW and EB. The systems with high DBP variability have diverse characteristics and include both surface water (EB, WV, YT and some BW) and groundwater (MD) sources and both chlorinated (WV, YT, MD) and chloraminated (EB) treated waters. The high DBP variability observed for retail water supplies (BW) is likely caused, in part, by the inclusion of both prepackaged water (e.g., factory packed in plastic bottles, boxes or cans) and treated waters produced at retail sites to be taken home in customer supplied containers. Since all retail treated waters were purchased in Davis, California, the municipal supply was City of Davis water. Treated waters from these distribution sites contained higher levels of TBM and DBCM than the prepackaged retail waters. Trihalomethanes with higher volatility than TBM and DBCM such as dichloromethane and trichloromethane were not expected to be recovered well in our extraction workflow because the concentration procedures involve significant blowdown of the extracts. Consequently, disinfection byproducts were measured separately using targeted methods and the results have been reported previously[5] and are discussed further below. The identification of known DBPs as compounds that vary significantly across the distribution system by our approach of ranking nontarget features by their CV provides support for extending the method to other compound classes.

Another high variability compound with a probable source as a disinfection byproduct is 9,10-anthracenedione (anthraquinone). Retrospective quantification of anthraquinone revealed

Table 2. List of LC Nontarget Compounds with the Greatest Variability within Water Sources[a]

compound	water source	potential inputs
2,4-dinitrophenol	IR$_S$, LA$_S$	DS-P[24]
3,4-methylenedioxybenzoic acid	IR$_W$	DS-P[24,25]
4-nitrophenol	LA$_S$	DS-P
adipic acid	SM$_S$	DS-P[24,25]
arachidonic acid	LA$_S$, EB$_W$, SM$_W$	DS-P[24,25]
benzoic acid	IR$_W$, LA$_S$, MC$_W$, MD$_W$, MD$_S$, SM$_W$, WV$_W$, YT$_W$, YT$_S$	DS-P[24,25]
benzylamine	LA$_W$	DS-P[24]
benzotriazole (BTA)	MD$_S$	DS-P[24,27]
butylbenzyl phthalate	MC$_S$, WV$_S$, YT$_S$	DS-P[24,25]
Dexpanthenol (panthenol)	EB$_S$ MD$_W$	DS-P[24]
glycerol	EB$_S$	DS-P[25]
p-nonylphenol	BW$_S$, MC$_S$	DS-P[24,25]
salicylic acid	IR$_S$, LA$_W$, SM$_W$, WV$_S$	DS-P[24,25]
6beta-hydroxytestosterone	SM$_W$	SW
alprenolol	IR$_W$	SW
atrazine-2-hydroxy	MD$_W$	SW
dicamba	WV$_S$	SW
estriol	MC$_S$, MD$_S$	SW
imidacloprid	YT$_W$	SW
inosine	EB$_W$, EB$_S$, IR$_W$, IR$_S$, LA$_W$, MC$_W$, MC$_S$, MD$_W$, WV$_S$, YT$_W$, YT$_S$	SW
methamphetamine	MC$_W$, WV$_W$	SW
napropamide	MC$_W$, MD$_S$	SW
norethindrone acetate	EB$_W$, SM$_W$	SW
phendimetrazine	MC$_W$, MD$_W$, YT$_S$	SW
phenylpyruvic acid	EB$_W$, EB$_S$, LA$_S$, WV$_W$, YT$_W$, YT$_S$	SW
prednisolone trimethyl acetate	MD$_S$	SW
proline	EB$_W$, LA$_W$, SM$_W$, YT$_S$	SW
sucralose	IR$_W$, LA$_W$, LA$_S$	SW
tamoxifen	YT$_S$	SW
temazepam	BW$_S$	SW
triamcinolone	MD$_S$, WV$_S$	SW
7-desoxycholic acid	IR$_S$, MD$_S$, WV$_S$	SW, DS-P[24]
caffeine	EB$_S$, SM$_S$	SW, DS-P[24]
cortisone	BW$_W$, BW$_S$	SW, DS-P[24]
dehydroabietic acid	BW$_W$	SW, DS-P[24,25]
estrone (E1)	MC$_S$	SW, DS-P[24]
perfluorodecanoic acid (PFDA)	BW$_W$, BW$_S$	SW, DS-P[24,25]
perfluorooctanoic acid (PFOA)	MC$_S$	SW, DS-P[24,25]
perfluorooctanesulfonic acid (PFOS)	MC$_S$, WV$_S$	SW, DS-P[24,25]
pulegon	SM$_S$	SW, DS-P[24]

[a] Compounds included were annotated at confidence Levels 1 (bold type) or 2 and could be assigned potential sources. DBP = disinfection byproduct, DS-P = distribution system-plastic, DS-O = distribution system-other, SW = source water. A complete list of the high variability compounds is available in the SI.

that almost 10% of the samples (24/270) contained quantifiable levels ranging from 16.7 to 371 ng/L. Most detections occurred in samples from SM, followed by EB and IR. Anthraquinone is a primary byproduct when anthracene containing waters are disinfected using chlorine,[28] so its presence in the summer sample set, where numerous anthracene detections were recorded, is not surprising. Further supporting the idea that anthraquinone is a DBP is the strong correlation with anthracene observed, with a Pearson's linear correlation coefficient of 0.978 ($p < 0.001$) across all summer samples. Anthraquinone has been documented to induce liver, kidney and bladder cancers in rodents[29] and is already the focus of some regulatory scrutiny by its inclusion on the US Environmental Protection Agency Contaminant Candidate List (CCL5). A corresponding oxidation product for phenanthrene, which is present in the samples at ion abundances 26 times (summer) and 34 times (winter) higher than anthracene was not observed. This is consistent with experimental results that show that phenanthrene is not oxidized during typical disinfection processes using chlorine.[28]

Distribution System Components. Between the point of water disinfection and household water taps, water can contact a diverse array of materials, including metals (iron, copper, lead) and organic substances (polymers, elastomers); our nontarget GC and LC methods focus on the latter group. The presence of known plasticizers on the high variability lists (e.g., Bis(2-ethylhexyl)phthalate and Butylbenzyl phthalate) motivated a more systematic review of the occurrence of plastic-derived compounds in drinking water supplies. Four sources identified in this review contained extensive lists of plastic and packaging related chemicals of potential water quality concern. The first was the PlastChem database developed from a literature survey supported by the Norwegian Research Council,[24] the second was a white paper based on a literature review that examined the organic compounds that are leached from six different types of plastic piping materials,[26] the third was a recent experimental nontargeted analysis of water passed through high-density polyethylene piping,[27] and the fourth was a compilation of compounds leached from food packaging materials.[25] The high variability chemicals with confident annotations listed in Tables S9 and S10 were searched for in these four lists using InChIKey matching, and any matched compounds were assigned a DS-P source, with a footnote provided to indicate the matched list(s). Several of these compounds are discussed further below.

As noted earlier, one of the most consistently detected and most significantly variable compounds identified in this study was acetyl tributyl citrate (ATBC, CV = 1.03−3.64), a compound with widely varied applications including use as a plasticizer in PVC piping. Although initially a tentative library annotation within our nontarget method, it was subsequently confirmed and retrospectively quantified. ATBC was quantifiable in 51 of the 270 samples analyzed, with a maximum concentration of 1.7 μg/L. The average concentration of ATBC observed in the 51 samples with detectable concentrations was 316 ng/L. Over half of the ATBC detections occurred in repeated samples from the same household or water source, suggesting localized sources of the compound. Ninety-seven of the households or retail water sources had no detections of ATBC in either season. Although it is possible that ATBC was introduced during our sample processing (it is also an ingredient in nail polish and some cosmetics), the strong patterns in its occurrence and high variability across samples suggests that the primary sources were distribution system components or household plumbing fixtures. The significance of the ATBC detections for human health is unclear. It has been approved as a food contact additive by the US Food and Drug Administration,

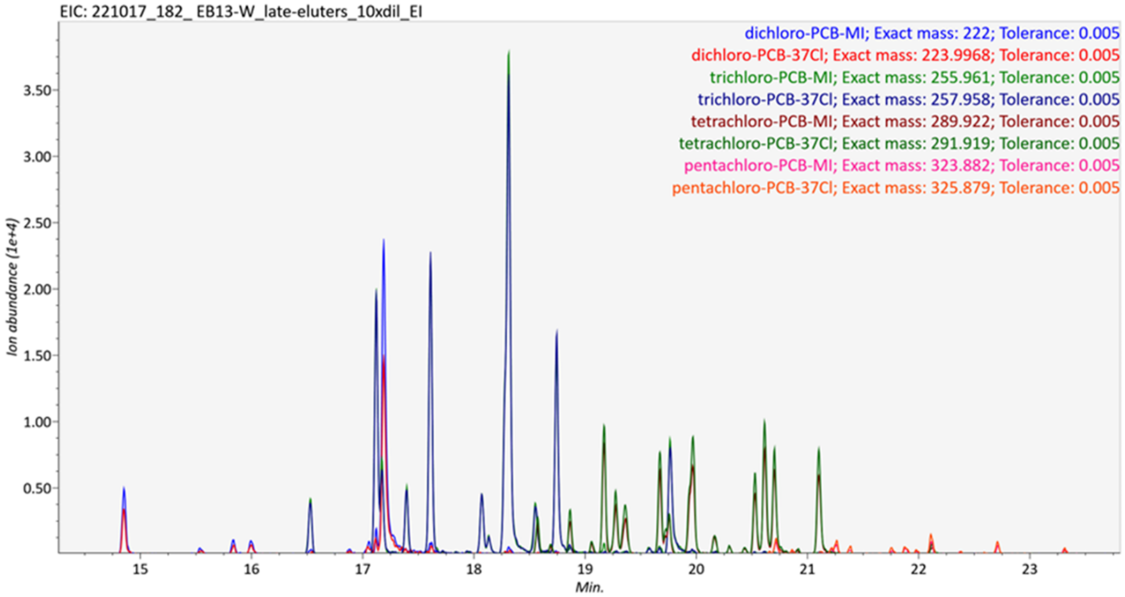


Figure 2. Extracted ion chromatograms for the molecular ion (M$^+$) and the ^{37}Cl analog of the molecular ion for di-, tri-, tetra- and penta-chloro biphenyl congeners reveal the presence of numerous congeners of each chlorination level in sample EB-13W.

and it is often used in plastics like poly(vinyl chloride) (PVC) to replace phthalate substances with known endocrine disrupting effects. Some studies have, however, called into question the safety of ATBC. For example, type 2 diabetic mice dosed at levels of ATBC well below the presumed safe dose exhibited cognitive deficits and a variety of other tissue specific effects leading to the conclusion that prolonged ATBC exposure may aggravate diabetes symptoms and cause brain tissue damage in sensitive populations.[30] Among alternative plasticizers to phthalates, ATBC was found to induce the most significant activation of the steroid and xenobiotic receptor (SXR) which regulates expression of cytochrome P450 3A4 (CYP3A4) in the liver and intestines.[31] CYP3A4 in turn affects the metabolism of contaminants and endogenous steroid hormones suggesting that the compound may affect estrogen receptor levels in vivo. A compound potentially related to ATBC that was detected with high variability in all samples in winter was tributyl aconitate (1-propene, tricarboxylic acid tributyl ester). The compound was only sporadically detected in summer samples and was not isolated as a feature in the MS-DIAL alignment process. Although this compound is not listed in the three plastic chemical databases reviewed here, it can be formed via hydrolysis of ATBC with a loss of acetic acid and is therefore assigned to the DS-P source category.[32]

Several of the plastic-related compounds with high variability were observed primarily or exclusively in retail water samples in both sampling seasons, driving the high variability for these compounds. For example, 6-phenoxy-1,3,5-triazine-2,4-diamine was detected with high abundance in BW-11 (W and S), 2-ethyl-2-propyl-Hexanoic acid, methyl ester and 2,3-dimethyl-2-(1-methylethyl)-butanoic acid were detected with high abundance in BW-09 (W and S), and 2-ethenyl-Naphthalene was detected with high abundance in BW-06 (W and S). These repeated occurrences of high variability and high abundance compounds in specific brands of retail water strongly suggest the presence of constituents added during processing at the packaging facility and/or leached from the containers in which the water was shipped and stored. Although 6-phenoxy-1,3,5-triazine-2,4-diamine is not listed in the plastic constituent databases searched, several closely related compounds including 6-phenyl-1,3,5-triazine-2,4-diamine are included, suggesting this is either another triazine compound contained in plastic materials or is a transformation product of one of these compounds.

Components of distribution systems other than plastics were also observed as causes of variability. Four polychlorinated biphenyl (PCB) congeners, two trichlorobiphenyl isomers and two tetrachlorobiphenyl isomers, had the highest coefficients of variation in the winter samples from EB. One of these congeners was also on the top 10 CV list for EB in summer. PCB variability was largely driven by a single household (EB13) with unusually high levels of PCB isomers containing between two and five chlorine substituents relative to all other EB households. Although a full investigation of the PCBs present in the samples from EB13 is beyond the scope of this study, screening analysis indicates that 10 of 24 possible trichlorobiphenyl congeners and 12 of 42 possible tetrachlorbiphenyl congeners were present in sample EB-13W (Figure 2) Retrospective quantification of the tri- and tetra-chlorobiphenyl congeners indicated concentrations of 119 and 124 ng/L in the winter and 48 and 64 ng/L in the summer, respectively. These collectively place the samples below the US EPA maximum contaminant limit for total PCBs of 500 ng/L but are still of concern. Earlier research by the EB water supplier estimated that as of 1995, up to 47% (84/178) of their water reservoirs were potentially contaminated with PCBs originating from polysulfide caulking materials containing between 10 and 15 wt % PCBs that had been used during their construction in the 1970s.[33] Although remedial actions were taken at the time, only 12 samples were analyzed to confirm the absence of PCBs (below a detection limit of 100 ng/L) from the distribution system.[33] The finding of persistent PCB contamination (winter and summer) at one of the 15 EB households, while the same congener groups were below detection limits for all other EB households, suggests that not all portions of the distribution system have been fully remediated.

Source Water Contributions. Some of the high variability compounds are well established markers of wastewater inputs to water supplies, including sucralose[34] and caffeine.[35] Sucralose, in particular, has been shown to persist through both conventional wastewater and water treatment operations and is widely detected in finished drinking waters and in household level samples.[34] The high variability list also includes numerous compounds of current concern in drinking water supplies including the perfluorinated alkyl acids (PFAAs) PFDA, PFOA and PFOS. A likely source of variability in a water distribution system is differential mixing of water from different sources that contains particular contaminants at differing concentration levels. For example, if multiple wells are used to supply all or a portion of water needs of a system, (as is typical for a public groundwater system such as those in MC, MD, LA and IR, or bottled waters that are supplied by such systems) then households in various locations may receive water with significantly different concentrations of these contaminants. A recent study has highlighted significant interhousehold variability in PFAA concentrations in Southeast Los Angeles where a total of 22 Southeast Los Angeles households, served by multiple community water suppliers were investigated (including one household served by the utility that supplied our LA households).[13] Although only a few households served by any one community system (≤4) were included in this study, all the households relied on local groundwater drawn from the same regional aquifer providing some degree of comparability with the present study. Coefficients of variation were calculated using data from the Supporting Information from von Behren et al.[13] (with the assumption that nondetect (nd) values were equal to zero) and all detected PFAAs (PFOA, PFOS, PFNA, PFHxS, PFBA, PFHpA, PFPeA) had CV values larger than one, similar the findings in our study.

Comparison with Target Compound Variability. The nontarget results that are the focus of this paper were collected as part of a larger study that included measurement of 98 target constituents using traditional quantitative approaches and the targeted compound concentrations have been previously reported.[5,18] In some cases target concentrations were measured using independent instrumental methods (e.g., DBPs, metals, PFAS), while in other cases they involved quantification of target compounds using the same underlying HRMS data using extracted target quantifier ions at known retention times instead of the deconvolution algorithms in nontargeted workflows. To examine household-level variability of target constituents using a process analogous to the one used for nontarget data, we replaced all values below the method detection limit with zero and used the reported values above the method detection limit to calculate coefficients of variation. Target compounds with a CV > 1 and at least one sample per water source with a concentration that exceeded the minimum quantification limit for that constituent were flagged as high variability compounds (Tables S22 and S23). Consistent with the idea that on-premise plumbing contributes to high variability for certain constituents, materials widely used in household piping were on the list, including copper (EB(s,w), MC(s,w), MD(s,w), LA(s,w), SM(s), IR(s), BW(w)), iron (MD(w), LA(w), WV(s)) and zinc (IR(s,w), MC(w), MD(w), LA(w), YT(w) WV(s)). Manganese was on the high variability list for BW in both winter and summer. This result is driven primarily by sample BW09 (boxed, filtered spring water), which had Mn concentrations above 20 μg/L in both seasons. The next highest Mn concentration in the data set is 3.3 μg/L, almost an order of magnitude lower.

Although there were a limited number of overlapping compounds listed on the high variability nontarget and target lists, there is reasonable qualitative agreement between the lists (Table S24). The high variability target list includes a large number of disinfection byproducts as would be expected from previous research. Some of the DBPs are not well recovered or are detected with low sensitivity using our nontarget methods (e.g., more volatile THMs, haloacetic acids, haloacetonitriles), so these compounds are not found on the high variability nontarget list. For DBPs that were detectable within our nontarget workflow (DBCM and tribromomethane) nearly all of the water source/season combinations categorized as high variability using the target approach were categorized similarly using the nontarget data. The nontarget method identified high variability in DDT concentrations in winter data from LA and MC and in summer data from MD; DDT did not appear on the high variability target list because no sample exceeded our method detection limit of 0.5 ng/L. The potential source of DDT in these water samples is not clear, but all of the high variability DDT samples were collected in regions with a history of intensive agriculture (MC and MD) or DDT production (LA). Both target and nontarget variability lists contained PFAS compounds including PFHxA, PFOA, PFDA, PFHxS, and PFOS and there is some agreement across water source/season combination. In some cases where there is no agreement in the water source/season across the two techniques for a specific compound, such as PFOA, the difference is likely caused by the arbitrary CV cutoff. For example, EB(s) is listed as a high variability PFOA sample on the target list but not on the nontarget list. Closer examination reveals that the nontarget CV of 0.998 for PFOA is just below the cutoff of 1 and so this compound is (barely) not on the nontarget list. Over the set of PFAS that overlapped between the target and nontarget methods, there were a total of 7 water source/season combinations identified by the nontarget workflow that matched a finding in the target data out of a total of 17 water source/season combinations determined for these compounds by the target workflow. This level of agreement is considered good given the fact that the target data were obtained with a PFAS specific analytical method designed for improved performance for this compound class. In general, the qualitative agreement between the target and nontarget lists of high variability compounds provides support for the analysis of nontarget feature abundance variability as a proxy for concentration (and exposure) variability.

Implications. The examination of variability in nontarget compound abundances successfully isolated numerous compounds, some not reported in drinking water in past studies, that had plausible relationships to the potential causes of variation. Variability-based prioritization revealed examples of compounds known to be formed during water treatment operations (e.g., DBPs), that are associated with piping materials, fittings or sealants (e.g., chemicals in plastics, PCBs) and chemicals that may be present in multiple source waters used by a utility at different concentrations and combined in varying ratios to supply particular households (e.g., sucralose, PFAS). Some of the chemicals identified are also found in numerous household products and in food supplies, and widespread human exposure to some of them has been documented.[36] The portion of human exposure accounted for by drinking water is not known but should be the subject of further inquiry. The findings clearly indicate that water users supplied by typical community water systems may be exposed to very different concentrations of a diverse set of organic chemicals beyond the regulated DBPs. It is possible that some of the high variability chemicals may contribute to the high variability of estrogen receptor agonism at the household level previously reported for the same set of water samples, where CV > 1 was observed for all water sources in summer sampling and 6/9 sources in winter sampling.[18] Additionally, the results presented here make a case for more careful assessment and selection of the materials that contact drinking water between water treatment or packaging facilities and the ultimate consumer, including public water distribution systems and private premise plumbing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.4c14749.

Mass spectra compared to reference spectra for GC detected compounds (PDF)

Results of filtering operations; lists of high variability annotated nontarget features and comparisons with target variability results (XLSX)

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Notes

The authors declare no competing financial interest.

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