Changes in Sewage Sludge Chemical Signatures During a COVID-19 Community Lockdown, Part 1: Traffic, Drugs, Mental Health, and Disinfectants

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Abstract: The early months of the COVID-19 pandemic and the associated shutdowns disrupted many aspects of daily life and thus caused changes in the use and disposal of many types of chemicals. While records of sales, prescriptions, drug overdoses, and so forth provide data about specific chemical uses during this time, wastewater and sewage sludge analysis can provide a more comprehensive overview of chemical changes within a region. We analyzed primary sludge from a wastewater-treatment plant in Connecticut, USA, collected March 19 to June 30, 2020. This time period encompassed the first wave of the pandemic, the initial statewide stay at home order, and the first phase of reopening. We used liquid chromatography–high-resolution mass spectrometry and targeted and suspect screening strategies to identify 78 chemicals of interest, which included pharmaceuticals, illicit drugs, disinfectants, ultraviolet (UV) filters, and others. We analyzed trends over time for the identified chemicals using linear trend analyses and multivariate comparisons (p < 0.05). We found trends related directly to the pandemic (e.g., hydroxychloroquine, a drug publicized for its potential to treat COVID-19, had elevated concentrations in the week following the implementation of the US Emergency Use Authorization), as well as evidence for seasonal changes in chemical use (e.g., increases for three UV-filter compounds). Though wastewater surveillance during the pandemic has largely focused on measuring severe acute respiratory syndrome–coronavirus-2 RNA concentrations, chemical analysis can also show trends that are important for revealing the public and environmental health effects of the pandemic. Environ Toxicol Chem 2022;41:1179–1192. © 2021 SETAC

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INTRODUCTION

The COVID-19 pandemic has dramatically increased the practice of wastewater-based epidemiology, with scientists and public health practitioners worldwide monitoring levels of severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) RNA in untreated wastewater (Pulicharla et al., 2021). Measurements of SARS-CoV-2 in wastewater and sludge are associated with daily case rates from testing and COVID-19-related hospitalizations and can provide early information about potential clusters and outbreaks of COVID-19 (Medema et al., 2020; Peccia et al., 2020). Historically, wastewater-based epidemiology has focused primarily on chemical contaminants, which can provide information about the habits of the population within the catchment area of a treatment plant. Chemical analysis of wastewater has been used to track use of licit and illicit drugs and pharmaceuticals such as antidepressants, benzodiazepines, opioids, and asthma medications, as well as exposure to pesticides and plasticizers (Choi et al., 2018; González-Mariño et al., 2017; Rousis et al., 2017). Wastewater analysis can be a highly efficient way to gather information about topics such as use of illegal drugs and psychoactive medications, without identification of individual persons. In addition, wastewater analysis has been used to track antiviral and antibiotic use during influenza pandemics throughout the world (Azuma et al., 2015; Singer et al., 2014; Zhang et al., 2019). However, previous studies evaluating chemical concentrations in wastewater during the COVID-19 pandemic have focused primarily on licit and illicit drugs.
Our objectives were to detect a wide range of anthropogenic contaminants in sewage sludge, to characterize their temporal variation during the initial COVID-19 outbreak and associated lockdown, and to relate our findings to the health and activities of local residents and broader global trends. We used both targeted and suspect screening methods to cover a broad range of chemicals including common analytes such as pharmaceuticals and illicit drugs (Choi et al., 2018) but also more unusual compounds for wastewater epidemiology studies such as disinfectants, ultraviolet (UV) filters, and pesticides. The COVID-19 pandemic has affected many aspects of daily life beyond the direct effects of the virus, and those changes affect the organic chemicals present in wastewater.

MATERIALS AND METHODS

Primary sludge samples were collected daily from March 19 to June 30, 2020, between 8:00 and 10:00 a.m. at the East Shore Water Pollution Abatement Facility (New Haven, CT USA), as described in Peccia et al. (2020). This treatment plant serves an estimated population of 200,000 in New Haven, Hamden, East Haven, and Woodbridge (CT, USA); part of the service area contains combined sewers. Samples included both liquid and solid fractions (2–5% solids w/w) of sludge and were stored at −80 °C until analysis. We analyzed daily samples from March 19 to April 15 and weekly composite samples from March 19 to June 30. Weekly sample extracts were further combined into 5-week composite samples, which were used for compound identification analysis only. Figure 1 shows the sampling timeline relative to key dates for the pandemic and related shutdown.

Our analytical approach was based on in-house methods used on food samples and other matrices. Our goal was to detect a broad range of contaminants. Because we did not know what chemicals were present prior to sample analysis, we opted for minimal sample processing to avoid removing any unknowns. First, liquid and solid fractions of the primary sludge were separated via centrifugation. For weekly composite samples, 75 µl of liquid phase from each day was combined (7-day composite). In a separate tube, 150 ± 5 mg solids from each day were combined. Solids were sonicated with 3.5 ml acetonitrile, then centrifuged. Acetonitrile extract (525 µl) was mixed with the composite liquids for each week. For daily sludge samples, 150 ± 10 mg solids were sonicated with 0.5 ml acetonitrile. Supernatant from extracted solids (300 µl) was combined with 300 µl of liquid phase from the centrifuged sample. Details on methods and materials and recovery information are available in Supporting Information, Sections S.1.1, S.1.2, and S.2.1.

FIGURE 1: Timeline showing key pandemic-related events and the timing of sample collection. We analyzed daily samples for 4 weeks during the initial increase in local COVID-19 cases. We analyzed weekly composite samples for a total of 15 weeks, which covered the early stages of the pandemic and shut down as well as the initial stages of reopening. All dates are within the year 2020.
Samples were analyzed using an Ultimate 3000 liquid chromatograph coupled with a Q-Exactive mass spectrometer (MS; Thermo Scientific) and positive electrospray ionization. Mobile phases were 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). We used an Agilent SB-C18 RRHD 1.8 μm, 2.1 x 150 mm column and a 55-min method with a gradient of 5% B to 95% B. Calibration points, blanks, and daily, weekly, and 5-week composite samples were analyzed using an alternating full MS and all ion fragmentation (AIF) method. In addition, the 5-week composite samples were analyzed using data-dependent MS2 (ddMS2) analysis with an iterative inclusion approach, which has similar advantages to previously reported intelligent acquisition methods (Koelmel et al., 2018, 2020). Briefly, we used the full scan data to generate inclusion lists including all features after blank-filtering to ensure that ddMS2 spectra were collected for each peak in the three 5-week composite samples. Each 5-week composite was injected 10 or 11 times, each run with a separate inclusion list for ddMS2 data collection. Additional instrument method and iterative inclusion information may be found in Supporting Information, Sections S.1.2, S.1.3, and S.2.3.

We used three separate data processing methods to identify and (semi-)quantify compounds in the samples. Full method descriptions, confidence levels for compound identification, and information on accuracy and variability are provided in Supporting Information, Sections S.1.4–S.1.7, S.2.1, and S.2.4. First, we used a targeted approach with TraceFinder software, Ver 4.1 (Thermo Scientific), to conduct quantitative analysis based on standards for 62 compounds (listed in Supporting Information, Table S1). Analytes included a variety of toxins, pharmaceuticals, and illicit drugs known to be found in wastewater and/or sludge and several compounds chosen for their relevance to COVID-19 treatment and prevention. Concentrations in the sludge extracts were determined based on a seven-point calibration curve that ranged from 0.1 to 100 ng/ml. We used a separate method in TraceFinder to screen our data using an in-house database of approximately 1800 compounds. The database contains exact parent and product ion m/z values (multiple product ions) and retention times for many compounds that have previously been measured in house or by collaborators with the same (or very similar) instrument methods used in this project. The in-house database also contains parent and product ion mass to charge ratio values that are provided in the Thermo Scientific EF-S_HRAM database in TraceFinder (without retention times, multiple product ions included). Compound identifications using the screening method were based on exact mass matches for parent and product ions (5 ppm threshold), isotope pattern matching, and retention time matching where available. Only the full MS/AIF data were used in the TraceFinder methods. The third method used Compound Discoverer, Ver 3.1, software (Thermo Scientific) and identified compounds based on the ddMS2 data for the 5-week composite samples and spectral matches with the mzCloud database (5 ppm threshold for MS1 masses, 10 ppm threshold for MS2 masses). The full MS data for the daily and weekly samples were then screened for the identified compounds. Each identification was assigned a confidence level based on available evidence. In the main text, identifications based on analytical standards are referred to as “confirmed,” confident screening results (from TraceFinder and Compound Discoverer) are “probable,” and screening results where more ambiguity remains are listed as “tentative” (Schymanski et al., 2014). More information, including detailed, software-specific confidence levels for each identification, is available in Supporting Information, Sections S.1.4–S.1.7 and S.2.2.

Trends over time for each identified compound in daily and weekly samples were determined using two types of analysis: linear regression and multigroup analyses. Multi-group statistical tests were determined based on the normality and homoscedasticity of each data set. Concentrations based on an external calibration curve were used for trend analysis where available (compounds identified in quantitative analysis); peak area was used for all other trend analyses (compounds identified in screening methods). Compound relative standard deviations (RSDs) were calculated based on replicate extractions of an unspiked sample (n ≥ 3). The replicate samples were drawn from the same large sludge sample but were extracted and analyzed individually. Six replicates were analyzed in total, including three spiked with a selection of standards (Supporting Information, Table S1); all six were used to calculate RSDs for unspiked compounds, while only the three unspiked replicates were used for compounds in the standard mixture. Detailed statistical methods and results for trend determination are available in Supporting Information, Sections S.1.8 and S.2.2.

Ten additional standards were purchased and analyzed after data analysis took place in an effort to improve annotation confidence for interesting results. We found that 9 of 10 compounds were correctly identified (amitriptyline, citalopram, diphenhydramine, triclocarban, diclofenac, lamotrigine, acetaminophen, benzotriazol, sertraline, and oxybenzone). Results for these compounds are reported as “confirmed,” but trend analysis is based on peak area because of lack of quantitative standards run alongside the samples. All nine of these compounds were previously identified as “probable” using Compound Discoverer, and acetaminophen was also identified as “tentative” in TraceFinder. The misidentified compound (acamprosate) is not included in our results and was previously identified only as “tentative” in TraceFinder. This indicates that “tentative” identifications have high uncertainty and should be interpreted with care. Detailed quality control, confidence assessment, and methodological results are available in Supporting Information, Sections S.2.1, S.2.3, and S.2.4.

RESULTS AND DISCUSSION

Table 1 shows the full list of identified compounds, their uses, their detection information, and the observed trends over time. Probable trends are listed as “increase” or “decrease” in Table 1, which indicates a statistically significant linear regression (p ≤ 0.05), with R² ≥ 0.3, or a multigroup analysis where there were multiple statistically significant differences
| Compound | Use | Confidence level | Trends | Daily samples (3/19/20–4/15/20) | Weekly samples (3/19/20–6/30/20) | m/z Measured\(^b\) | Δ Mass (ppm)\(^bc\) | Retention time (min)\(^b\) | RSD\(^d\) |
|----------|-----|------------------|--------|----------------------------------|----------------------------------|---------------------|----------------------|--------------------------|-----------|
| **COVID-19 drugs and disinfectants** | | | | | | | | | |
| Hydroxychloroquine | Antiviral | Confirmed\(^a\) | Increase | 334.1835 | | -0.72 | 6.17 | 9 | |
| Azithromycin | Antibiotic | Confirmed\(^a\) | Decrease | 749.5152 | | -0.74 | 12.58 | 5 | |
| Ate伐otin | Analgesic | Confirmed | Increase-T | 152.0706 | | -0.28 | 5.22 | 7 | |
| Triclosan | Disinfectant | Confirmed | Increase-T | 314.9849 | | -1.34 | 32.98 | 35 | |
| Didecyldimethylammonium | Disinfectant | Confirmed | | 372.3778 | | -0.86 | 40.98 | 60 | |
| Cetrimide | Disinfectant | Probable | | 284.3308 | | -1.18 | 38.56 | 46 | |
| Didecyldimethylammonium | Disinfectant | Probable | Increase-T | 270.3154 | | -0.64 | 37.8 | 73 | |
| Dodecyltrimethylammonium (A) | Disinfectant | Tentative | | 228.2685 | | 0.11 | 30.88 | 45 | |
| Dodecyltrimethylammonium (B) | Disinfectant | Tentative | Increase-T | 228.2686 | | 0.15 | 27.32 | 15 | |
| **Opioids and drugs of abuse** | | | | | | | | | |
| Fentanyl | Opioid | Confirmed\(^a\) | Increase | 337.2273 | | -0.45 | 16.06 | 25 | |
| Levorphanol | Opioid | Confirmed\(^a\) | Decrease | 258.1853 | | 0.03 | 10.2 | 19 | |
| Methadone | Opioid | Confirmed\(^a\) | Increase | 310.2164 | | -0.45 | 20.3 | 17 | |
| Ocodeine | Opioid | Confirmed\(^a\) | | 300.1594 | | -0.17 | 16.8 | 2 | |
| Hydromorphone | Opioid | Confirmed\(^a\) | Increase | 286.1439 | | 0.53 | 4.05 | 9 | |
| Oxycodone | Opioid | Confirmed\(^a\) | | 316.1543 | | -0.22 | 7.07 | 5 | |
| Tildine | Opioid | Probable | | 274.1791 | | -3.71 | 41.26 | 24 | |
| Tramadol | Opioid | Probable | | 264.1957 | | -0.32 | 10.18 | 11 | |
| Cocaine | Cocaine | Confirmed\(^a\) | Increase-T | 304.1542 | | -0.35 | 12.16 | 6 | |
| Benzoylcodeine | Cocaine | Probable | | 290.1386 | | -0.43 | 9.54 | 10 | |
| Ecgonine methyl ester | Cocaine | Probable | | 200.1278 | | -1.38 | 2.30 | 28 | |
| Anhydroecgonine | Cocaine | Probable | Decrease | 168.1019 | | -0.25 | 7.08 | 20 | |
| THC | Cannabis | Probable | Decrease-T | 315.2315 | | -1.20 | 40.67 | 31 | |
| Cannabidiol\(^b\) | Cannabis | Probable | | 315.2315 | | -1.2 | 36.81 | 27 | |
| 11-Hydroxy-8(9)-THC | Cannabis | Probable | | 331.2264 | | -1.11 | 33.25 | 13 | |
| Nor-9-carboxy-9-THC | Cannabis | Probable | | 345.2059 | | -0.45 | 33.53 | 22 | |
| THC-A | Cannabis | Tentative | Increase-T | 359.2211 | | -1.70 | 42.66 | 27 | |
| Methamphetamine | Amphetamine | Confirmed\(^a\) | Increase | 150.1277 | | -0.08 | 7.49 | 13 | |
| TFMP | Party drug | Tentative | Decrease | 231.1106 | | 1.01 | 2.00 | 46 | |
| **Antidepressant and antiseizure drugs** | | | | | | | | | |
| Doxepin | Antidepressant | Confirmed\(^a\) | Increase | 280.1696 | | -0.16 | 17.04 | 25 | |
| Amitriptyline | Antidepressant | Confirmed | Increase | 278.1903 | | -0.1 | 20.49 | 19 | |
| Citalopram | Antidepressant | Confirmed | Increase | 325.1571 | | -0.31 | 17.4 | 17 | |
| Desmethyl-citalopram | Antidepressant | Probable | Increase-T | 311.1553 | | -0.47 | 17 | 10 | |
| Sertraline | Antidepressant | Confirmed | Increase | 306.081 | | -0.3 | 21.47 | 10 | |
| Trazodone | Antidepressant | Probable | | 372.1584 | | -0.44 | 14.87 | 19 | |
| Venlafaxine | Antidepressant | Probable | | 278.2114 | | -0.15 | 14.28 | 18 | |
| Clozapine | Antipsycotic | Probable | Increase | 327.137 | | -0.26 | 14.3 | 22 | |
| Carbamazepine | Anticonvulsant | Probable | | 237.1022 | | -0.8 | 18.93 | 11 | |
| Gabapentin | Anticonvulsant | Probable | | 172.1331 | | -0.5 | 6.89 | 4 | |
| Pregabalin | Anticonvulsant | Probable | | 160.133 | | -1.11 | 1.99 | 5 | |
| **Pharmaceuticals—other** | | | | | | | | | |
| Propafenone | Antiarrhythmic | Probable | | 342.2061 | | -0.8 | 34.23 | 23 | |
| Trimethoprim | Antibiotic | Probable | | 291.1450 | | -6.3 | 8.02 | 8 | |
| Diphenhydramine | Antihistamine | Confirmed | Increase | 256.1695 | | -0.43 | 17.04 | 19 | |
| Fexofenadine | Antihistamine | Probable | | 502.295 | | -0.36 | 20.53 | 12 | |
| Raltegravir | Antiviral | Probable | | 445.1629 | | -0.32 | 20.87 | 12 | |
| Darunavir | Antiviral | Probable | | 548.2424 | | -0.13 | 24.21 | 5 | |
| Zalcitabine | Antiviral | Tentative | Decrease | 212.1027 | | -0.130 | 2.02 | 8 | |
| Losartan | ARB inhibitor | Confirmed\(^a\) | Decrease | 423.1693 | | -0.4 | 20.47 | 7 | |
| Valsartan | ARB inhibitor | Probable | | 436.2341 | | -0.42 | 25.38 | 18 | |
| Atenolol | Beta-blocker | Probable | | 268.1542 | | 0.6 | 7.79 | 5 | |
| Carvedilol | Beta-blocker | Probable | | 407.1963 | | -0.5 | 19.19 | 17 | |
| Labetalol | Beta-blocker | Probable | | 329.1858 | | -0.4 | 14.33 | 23 | |
| Metoprolol | Beta-blocker | Probable | | 268.1906 | | -0.33 | 11.55 | 50 | |

(Continued)
COVID-19 drugs and disinfectants

In the early days of the pandemic the drug combination of hydroxychloroquine and azithromycin received consideration as a potential treatment for COVID-19. The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) on March 28, 2020 (Week 2 of our data), which remained in effect until June 15, 2020 (week 13; Thomson & Nachlis, 2020). An EUA allows treatments that have not been fully approved by the US FDA to be used to mitigate public health emergencies. As shown in Figure 2A, hydroxychloroquine concentrations increased in daily sludge samples in the third week of our study. While an overall hydroxychloroquine trend was not observed during the time that weekly samples were collected, a clear increase in concentration occurs in week 3 (Figure 2B).

Hydroxychloroquine has an elimination half-life in the human body of approximately 22 days for oral doses and >40 days for intravenous doses (Drug Bank Online, 2020a; Tett et al., 1989); thus, the increase in sludge concentrations is not as immediate or drastic as it would be for a drug with a shorter half-life. Our data indicate that the EUA and the large amount of publicity generated around hydroxychloroquine had significant impacts between groups \( (p \leq 0.05, \text{same trend direction}) \). Tentative trends, which have less certainty but are still statistically significant \( (p \leq 0.05) \), are listed for compounds with a replicate RSD of \( \geq 30\% \), linear regressions with \( R^2 < 0.3 \), and/or multigroup comparisons with only one statistically significant \( p \) level in the sludge. Trends in identified compounds are discussed categorically.

### TABLE 1: (Continued)

| Compound         | Use            | Confidence level | Daily samples (3/19/20–4/15/20) | Weekly samples (3/19/20–6/30/20) | m/z Measured\(^b\) | Δ Mass (ppm)\(^c\) | Retention time (min)\(^b\) | RSD\(^d\) |
|------------------|----------------|------------------|----------------------------------|-------------------------------|--------------------|-----------------|--------------------------|----------|
| Propranolol      | Beta-blocker   | Probable         | 260.1645                         | -0.08                         | 15.69             | 44              |
| Verapamil        | Blood pressure | Probable         | 455.2902                         | -0.48                         | 20.6              | 22              |
| Warfarin         | Blood thinner  | Probable         | 309.1120                         | -0.42                         | 24.72             | 22              |
| Metformin        | Diabetes       | Probable         | 130.1086                         | -0.76                         | 1.83              |                |
| Raiffezine       | Exogenous      | Probable         | 474.1733                         | -0.1                          | 17.41             | 51              |
| Cinchofen        | Gout           | Probable         | 250.086                          | -0.89                         | 42.24             | 18              |
| Cyclobenzaprine  | Muscle relaxant | Probable       | 276.1746                         | -0.16                         | 19.76             | 22              |
| Tolycaine        | Pain—topical   | Probable         | 279.1702                         | -0.52                         | 13.02             | 28              |
| Pramocaine       | Pain—topical   | Probable         | 294.2063                         | -0.2                          | 18.77             | 18              |
| Edaravone        | Stroke and ALS | Probable         | 175.0865                         | -0.25                         | 10.59             | 40              |
| Berberine        | Supplement     | Confirmed\(^*\) | 336.1229                         | -0.44                         | 16.17             | 20              |
| Piracetam        | Supplement     | Tentative        | 143.0814                         | -1.03                         | 1.90              | 12              |
| Betanechol       | Urinary retention | Tentative   | 161.1283                         | -0.72                         | 1.71              | 7               |

### Personal care products

| Compound         | Use            | Confidence level | Daily samples (3/19/20–4/15/20) | Weekly samples (3/19/20–6/30/20) | m/z Measured\(^b\) | Δ Mass (ppm)\(^c\) | Retention time (min)\(^b\) | RSD\(^d\) |
|------------------|----------------|------------------|----------------------------------|-------------------------------|--------------------|-----------------|--------------------------|----------|
| Oxybenzone       | UV-filter      | Decrease-T       | 229.0859                         | 0.06                          | 29.96             | 16              |
| Avobenzene       | UV-filter      | Probable         | 311.1636                         | -1.92                         | 41.52             | 28              |
| Octocylene       | UV-filter      | Probable         | 362.2111                         | -1.01                         | 42.25             | 18              |
| Galaxolidone     | Fragrance      | Probable         | 273.1847                         | -0.79                         | 35.95             | 15              |
| Nicotine         | Tobacco        | Probable         | 163.1228                         | -1.36                         | 2.16              | 11              |
| Caffeine         | Stimulant      | Probable         | 195.0876                         | 0.16                          | 7.81              | 5               |

### Other chemicals

| Compound         | Use            | Confidence level | Daily samples (3/19/20–4/15/20) | Weekly samples (3/19/20–6/30/20) | m/z Measured\(^b\) | Δ Mass (ppm)\(^c\) | Retention time (min)\(^b\) | RSD\(^d\) |
|------------------|----------------|------------------|----------------------------------|-------------------------------|--------------------|-----------------|--------------------------|----------|
| Benztelinazo     | Anticorrosion  | Decrease         | 120.0559                         | 2.08                          | 9.51              | 5               |
| Levamisole       | Veterinary drug | Probable         | 205.0793                         | -0.66                         | 7.48              | 44              |
| Ipronidazole     | Veterinary drug | Tentative        | 170.0922                         | -1.08                         | 1.71              | 4               |
| Imazalil         | Pesticide      | Decrease-T       | 297.0555                         | -0.26                         | 18.67             | 10              |
| Piperonyl-butoxide | Pesticide     | Decrease-T       | 356.2427                         | -1.35                         | 35.60             | 24              |
| Dinotefuran-metabolite-UF | Pesticide | Tentative | 159.1126                         | -1.33                         | 1.83              | 10              |
| Nithiazine       | Pesticide      | Tentative        | 161.0377                         | -1.28                         | 1.90              | 22              |

\(^a\) All trends are based on semiquantitative data and are reported here as probable and tentative trends. Tentative trends (indicated by -T) have lower confidence.

\(^b\) Detailed description provided in Supporting Information, Section S.2.1.

\(^c\) Relative standard deviation of concentration or peak area for replicate extractions of an unspiked sample (n = 3 or n = 6).

\(^d\) Semiquantitation performed using standards. Other compounds have semiquantitation based on peak area.

\(^e\) Elevated in Week 3 only.

\(^f\) Multidirectional changes in multivariate analysis.

\(^g\) In daily (but not weekly) solvent blanks at high levels.

RSD = relative standard deviation; THC = tetrahydrocannabinol; TFMPP = trifluoromethylphenylpiperazine; ARB = angiotensin receptor blocker; ALS = amyotrophic lateral sclerosis.
on the amount used in the New Haven area, which includes two major hospitals. Hydroxychloroquine is normally used to treat malaria, lupus, and rheumatoid arthritis (Drug Bank Online, 2020a), which are unlikely to have changed during the pandemic. Azithromycin concentrations decreased over the present study period (weekly samples; Figure 2B). Azithromycin is only sometimes used in combination with hydroxychloroquine (Rosenberg et al., 2020) and is more frequently used to treat bacterial respiratory infections, which typically decline in the spring. Corresponding seasonal changes in azithromycin concentrations in wastewater have been detected previously (Coutu et al., 2013).

Acetaminophen, which can be used to treat COVID-19 symptoms such as fever and headache, had limited availability during the pandemic, likely due to increased demand and use (Blankenship, 2020). Correspondingly, acetaminophen sludge concentrations had a tentative increase in our weekly sample analysis (Table 1; Supporting Information, Table S8).

Disinfectant use for cleaning both hands and surfaces has grown during the pandemic (Hora et al., 2020). Previous studies have shown pandemic-related increases in concentrations of quaternary ammonium disinfectants in household dust (Zheng et al., 2020) and higher risk of health effects due to increased exposure (Li et al., 2020). Levels of two quaternary ammonium disinfectant chemicals (dioctyldimethylammonium and dodecyltrimethylammonium [B]) showed tentative increases in sludge during the overall study period (weekly samples; Figure 1D; Supporting Information, Table S8). Triclocarban, an antibacterial compound used in consumer and medical-grade handwashes, tentatively increased in concentration in our daily sampling period (Figure 1C). Triclocarban was previously banned in medical-grade hand washes (2017) and rubs and consumer hand washes (2016) for its endocrine-disruption potential and other negative health effects (Halden et al., 2017; USFDA, 2016, 2017). However, the most recent ruling against triclocarban (regarding consumer antiseptic rubs) took place in 2019, with an effective date of April 13, 2020 (USFDA, 2019). Thus, it is likely that triclocarban product use had not yet been fully phased out during our study period. In addition, the pandemic is likely to have prompted increased use of soaps and hand sanitizers that were previously stored. There were

FIGURE 2: Trends for COVID-19-related drugs and disinfectants detected in daily and weekly primary sewage sludge samples. (A) Boxplot showing a significant increase in hydroxychloroquine concentrations in week 3 samples based on daily sample concentrations (analysis of variance with Tukey’s honestly significant difference post hoc analysis). (B) Scatterplot showing hydroxychloroquine and azithromycin concentrations in weekly composite samples. (C) Scatterplot showing increasing triclocarban levels in daily sludge samples. (D) Scatterplot showing data for two quaternary ammonium disinfectants in weekly composite sludge samples. Though p > 0.05 for dodecyltrimethylammonium-B, our multigroup analysis showed a significant trend (Supporting Information, Table S8). All scatterplot error bars show the relative standard deviation for each compound, calculated from one set of replicate samples.
no trends detected during the study period for didecyldimethylammonium, cetrimonium, or dodecyltrimethylammonium (A) (Table 1).

**Opioids and drugs of abuse**

The ongoing epidemic of opioid abuse across the United States has included the state of Connecticut (Allen, 2019). In addition, there are pandemic-related increases in legal use of opioids. In April of 2020, the US Drug Enforcement Administration authorized increased production quotas for fentanyl, morphine, hydromorphone, codeine, and methadone to meet COVID-19 treatment needs to ensure that addiction treatment centers were adequately supplied (US Drug Enforcement Administration, 2020). Sludge concentrations of fentanyl, methadone, and hydromorphone increased during our study period (weekly samples; Figure 3A). Fentanyl and methadone are commonly used both legally and illegally. Hydromorphone is itself a drug, but it is also a metabolite of morphine, codeine, and other opioids; thus, its increasing levels are an indication of an overall increase in opioid concentrations (Smith, 2009). Levorphanol, an opioid used for pain management and as a preoperative drug (Drug Bank Online, 2020b), decreased in both daily and weekly sludge samples (Figure 3A and Table 1). This decrease is potentially due to the reduction in elective procedures during the study period (Stannard, 2020). We did not observe trends over time for codeine, oxycodone, tildine, or tramadol (Table 1). We note that our method was not capable of measuring heroin at these low concentrations (Supporting Information, Section S.2.1).

Concentrations of cocaine and two of its metabolites (ecgonine methyl ester and benzoylecgonine) increased in the weekly

**FIGURE 3:** Trends for opioids and cocaine-related compounds detected in weekly composite primary sewage sludge samples. (A) Scatterplot showing opioid concentrations. (B) Scatterplot showing levels of cocaine and cocaine metabolites. All scatterplot error bars show the relative standard deviation for each compound, calculated from one set of replicate samples.
samples (Figure 3B; Supporting Information, Table S8). While the trend we found for cocaine has lower confidence, the trend for benzoylecgonine, the most common chemical for monitoring cocaine usage via wastewater analysis (Choi et al., 2018), was more clearly defined, with an $R^2$ value of 0.66 and an RSD of 10%. Anhydroecgonine, a metabolite specific for crack cocaine (Scheidweiler et al., 2000), decreased in the weekly samples, suggesting the possibility of a shift in local cocaine use patterns (Figure 3B). Crack cocaine use is more common in socially vulnerable populations, who were disproportionately affected by the COVID-19 pandemic (Palamar et al., 2015; Freese et al., 2021). We saw no trends for methamphetamine, though the party drug trifluoromethylphenylpiperazine decreased during the present study period (Table 1; Supporting Information, Table S8). Cannabis-related compounds did not show a consistent trend.

The pandemic has increased risk factors for the development of substance abuse disorders and overdoses, such as isolation and economic distress. High COVID-19-related worry has been shown to be a predictor of beginning substance use during the pandemic (Rogers et al., 2020), and increasing numbers of overdoses have been reported nationwide (Alter & Yeager, 2020). An increase in the amount of emergency responses necessary for opioid overdoses has occurred in some locations (Slavova et al., 2020). Locally, there were 36 fatal overdoses during the present study period in the towns and cities served by the East Shore Water Pollution Abatement Facility in New Haven (New Haven, East Haven, Woodbridge, and Hamden; Chief Medical Examiner, 2020). Thirty-two of these overdoses involved opioids, including 28 where fentanyl was detected. Cocaine was involved in 17 of the overdose deaths; most cases included multiple drugs (Chief Medical Examiner, 2020). Overall, the state of Connecticut had a 14.3% increase in accidental overdose deaths in 2020 compared to 2019, with the largest increase happening in April (Connecticut Department of Public Health, 2021). Both the drug overdose mortality rate and the increase in the number of deaths were highest for the non-Hispanic Black population (Connecticut Department of Public Health, 2021). In addition, the COVID-19 pandemic has caused many changes in treatments for both pain and substance abuse disorders, which usually depend heavily on in-person interactions and carefully controlled access to medications. New systems for opioid distribution and telemedicine appointments have been developed, but there is continued concern over their effectiveness (Alexander et al., 2020; El-Tallawy et al., 2020; Shanthanna et al., 2020).

**Antidepressants and other medications**

Many people have struggled with mental health challenges during the COVID-19 pandemic, and the incidence of depression has increased in the United States during the pandemic (Ettman et al., 2020). In addition, there is evidence that people with psychiatric disorders are at increased risk for COVID-19 infection (Q. Wang et al., 2021) and that COVID-19 infection is associated with new diagnoses of psychiatric illnesses (Taquet et al., 2020). Correspondingly, increased demand for the antidepressant drug sertraline has caused shortages throughout the United States (Edney, 2020; US Food and Drug Administration, 2020). Sertraline levels increased in our analysis of daily sludge samples (Figure 4A). In our weekly sample analysis, the levels of three additional antidepressants (citalopram, amitriptyline, and doxepin), one antidepressant metabolite (desmethylcitalopram, tentative trend), and the antipsychotic drug clozapine increased (Figure 4B and Table 1; Supporting Information, Table S8). No trends were observed for the antidepressants trazadone and venlafaxine and the anticonvulsants carbamazepine, gabapentin, and pregabalin (Table 1; Supporting Information, Table S8).

We also observed various trends for other pharmaceuticals identified in our analysis (Table 1; Supporting Information, Table S8 and Figures S3–S5). Some of these trends are likely related to pandemic-induced changes in behavior, while others are not. For example, tolcycaine, a local anaesthetic used in dental injections (National Center for Advancing Translational Sciences, 2021), decreased in the sludge samples, which corresponds to a decrease in dental appointments during the shutdown (Connecticut Department of Public Health, 2020). Pramocaine, a mild anaesthetic used in over-the-counter creams (Drug Bank Online, 2021), had increasing levels in sludge, which is more likely due to seasonal changes in exposure to insect bites and poison ivy than to pandemic-related changes. Diphenhydramine, an allergy medication, also increased during the present study period (Table 1; Supporting Information, Table S8).

**Personal care product ingredients and other chemicals**

We found that benzotriazole, a corrosion inhibitor frequently used on cars and a known contaminant in road dust (Asheim et al., 2019), had trends in sludge that corresponded to the shutdown and Phase 1 reopening that occurred during our study period (Figure 5A). There was a decrease in the daily and weekly composite sample concentrations at the beginning of the study period and then an increase in weekly composite sample levels starting in the weeks before Phase 1 reopening. We hypothesize that the benzotriazole trends are due to changes in the amount of traffic. Doucette et al. (2020) found that traffic in Connecticut decreased 43% during the stay-at-home order that began in the first week of our study period, and air pollutants related to traffic decreased during stay-at-home orders in other locations (Chowdhuri et al., 2020; Xiang et al., 2020). With fewer cars on the road, less benzotriazole washes off cars onto the road, and thus less is dissolved in the runoff water that enters the combined sewer system. Benzotriazole is also used on aircraft as a deicer and corrosion inhibitor (Sulej et al., 2012). There is one small airport in the study area that, like many other airports, experienced decreased traffic during the stay-at-home order. Benzotriazole is also used in household dishwasher detergents, which is likely a smaller source to combined sewer wastewater systems.
All of the UV-filter compounds detected increased in the weekly composite samples (Figure 5B). This trend is likely due to the increase in sunscreen use that corresponds to the seasonal change that occurs in Connecticut between March and June. A tentative decrease in oxybenzone levels was observed in the daily samples and the first weekly samples, which may be reflective of decreased cosmetic usage during the stay-at-home order, while there was still winter weather. We suspect that the other trends we found in this category were not affected by the pandemic or stay-at-home order (Table 1; Supporting Information, Table S8).

**Broader relevance, limitations, and future directions**

Though our results are specific to the New Haven, Connecticut, area, many of the trends that we found are more broadly relevant. We observed increased concentrations for medications whose demand increased during the pandemic (USFDA, 2020) and increasing trends for illegal drugs that align with the increasing number of overdoses locally and nationwide (Alter & Yeager, 2020). Wastewater monitoring can be a way to monitor drug usage during this time when other monitoring strategies have been disrupted by the pandemic (National Institute on Drug Abuse, 2020; US Drug Enforcement Administration, 2020). Moreover, if wastewater trends can be associated with public health monitoring data, wastewater-based information can play an important role in providing real-time estimates or early warnings of a variety of infectious and non-infectious disease. We note that our results on drugs of abuse differ from those reported by wastewater monitoring programs in Europe, where there has been an overall decrease in illicit drug use (European Monitoring Centre for Drugs and Drug Addiction, 2020). Specifically, a study in Austria
found decreased use of cocaine, amphetamine, and 3,4-methylenedioxymethamphetamine during the initial COVID-19 lockdown, which was partially compensated for by increased methamphetamine use (Reinstadler et al., 2021). They saw no changes in cannabis or methadone-related compounds relative to other years (Reinstadler et al., 2021). In addition, wastewater monitoring and drug use surveys in Australia have revealed record low levels of fentanyl and oxycodone but regional increases in cocaine, heroin, methamphetamine, and cannabis (Australian Criminal Intelligence Commission, 2020). The differing trends may be related to differences in pandemic severity and local political responses but are also reflective of existing trends from before COVID-19; the opioid crisis that is prominent throughout the United States has not affected Australia or Europe to the same extent (Australian Criminal Intelligence Commission, 2020; European Monitoring Centre for Drugs and Drug Addiction, 2020). Trends we observed for pharmaceuticals are more similar to those reported by the Austrian study; though there is some variation in individual compound results, both studies show consistent levels of long-term medications such as beta-blockers and anticonvulsants and lowered levels of short-term medications such as analgesics (Reinstadler et al., 2021).

In addition to human health-related trends, our results reveal trends in chemical releases that may affect the environment. Though our samples did not undergo the complete wastewater-treatment process, many of the compounds we

**FIGURE 5:** Trends for additional chemicals detected in daily and weekly primary sewage sludge samples. (A) Scatterplot showing benzotriazole levels in daily and weekly samples. (B) Scatterplot showing ultraviolet-filter levels in weekly composite samples. Scatterplot error bars show the relative standard deviation for each compound, calculated from one set of replicate samples (n = 6). UV = ultraviolet.
detected are not fully removed by standard treatment trains (Kostich et al., 2014; Petrie et al., 2014; J. Wang & Wang, 2016) and are released with the effluent water or sewage sludge. We detected endocrine-disrupting compounds including triclocarban, oxybenzone, and sertraline that can have negative impacts on marine organisms and cycle back to humans via consumption of local seafood (Arpin-Pont et al., 2016; Karthikeyan et al., 2019). Much concern has been expressed about the potential ecological impacts of increased pharmaceutical loads in wastewater, particularly in developing areas where wastewater treatment is limited and access to antibiotic and antiviral medications is not controlled by prescriptions (Espejo et al., 2020; Farias et al., 2020; Hom et al., 2020; Usman et al., 2020); and modeling studies have demonstrated the potential for high risk from environmental releases of antiviral drugs used to treat COVID-19 (Kumari & Kumar, 2021; Kuroda et al., 2021). Spread of resistance to antibiotic and antiviral medications is also a potential concern (Hom et al., 2020; Usman et al., 2020). Antibiotic resistance was found to increase with levels of SARS-CoV-2 RNA in a study on wastewater and surface water in India (Kumar et al., 2021).

While our analytical method was designed to include a wide range of chemicals, the scope of any analysis is inherently limited. We intentionally included both liquid and solid portions of primary sludge to measure both hydrophilic and hydrophobic chemicals. However, this prohibited the exact quantification of chemicals in either phase. We therefore are not able to use our data to back-calculate per capita consumption as has been done in other wastewater studies (Choi et al., 2018; Reinstadler et al., 2021; S. Wang et al., 2020). In addition, we designed our sample preparation method for the relatively small volume of sample available from corresponding research on levels of SARS-CoV-2 RNA in primary sludge; we could not use solid-phase extraction to preconcentrate the liquid portion of our samples, as is common in wastewater studies (Kostich et al., 2014; J. Wang & Wang, 2016). This likely caused a decrease in the number of liquid-phase contaminants we detected. In addition, our unique method makes our quantitative results difficult to relate to other studies, though trends over time can still be compared. We note that our analytical methods were highly effective and that our sample collection and preparation methods were simple and fast and did not require specialized supplies. Sewage sludge is a well-mixed, concentrated source that does not require complex sampling equipment. Though we collected data over a relatively long period of time in 2020, our sampling campaign did not begin until the pandemic was underway; therefore, we cannot directly compare our results to those from previous years.

The data described in the present study represent only a small fraction of what was collected using our high-resolution MS methods. In part 2 of this series, we further investigate chemicals in the sludge that were not easily identifiable using our databases and examine chemical correlations with measured levels of SARS-CoV-2 RNA and other COVID-19 metrics (Nason et al., 2022). Because both SARS-CoV-2 RNA analysis and liquid chromatography–high-resolution MS analysis were conducted on the same samples, these complex analyses are an excellent opportunity to identify chemical signals that may provide information about COVID-19 levels within the community.

CONCLUSIONS

Overall, the first wave of the COVID-19 pandemic and the related shutdown had a significant influence on the chemical fingerprint of primary sludge in New Haven, Connecticut. To our knowledge, the present study is the first to report trends in wastewater concentrations for chemicals with direct significance to the COVID-19 pandemic including hydroxychloroquine and disinfectants. We found upward trends in hydroxychloroquine and disinfectant concentrations in sludge, reflecting increased use during the initial wave of the COVID-19 pandemic. We also saw increases in drugs of abuse and antidepressants and seasonal changes for chemicals such as UV filters that are used in sunscreens. Importantly, we found that benzotriazole concentrations showed different trends during and after the local stay-at-home order, an indication that benzotriazole is a potential marker for the influence of traffic on wastewater and sludge in combined sewer systems. Overall, our findings relate strongly to trends in public and environmental health worldwide and show specific trends that may not have been picked up in other types of analysis. Sewage sludge surveillance is a promising strategy to monitor a variety of human behavioral changes during the pandemic that have public health consequences.

Supporting Information

The Supporting Information are available on the Wiley Online Library at https://doi.org/10.1002/etc.5217.

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Conflicts of Interest—The authors declare that there are no conflicts of interest.

Author Contributions Statement—S. L. Nason led sample analysis, data analysis, and manuscript writing; E. Lin assisted with sample analysis and data analysis; B. Eitzer assisted with method development for instrumental writing; E. Lin assisted with sample analysis and data analysis; B. Eitzer assisted with method development for instrumental analysis and compound identification; J. Koelmel assisted with method development for instrumental analysis; J. Peccia led sample collection and provided access to the samples. All contributed to manuscript edits and revisions.

Data Availability Statement—A version of this manuscript and associated Supporting Information has been uploaded to the preprint server ChemRxiv (https://doi.org/10.26434/chemrxiv.13562525.v2). The RAW instrument data files used in the present study are available as a data set on MassIVE.
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