Science of the Total Environment 742 (2020) 140546

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

The effective design of sampling campaigns for emerging chemical and microbial contaminants in drinking water and its resources based on literature mining

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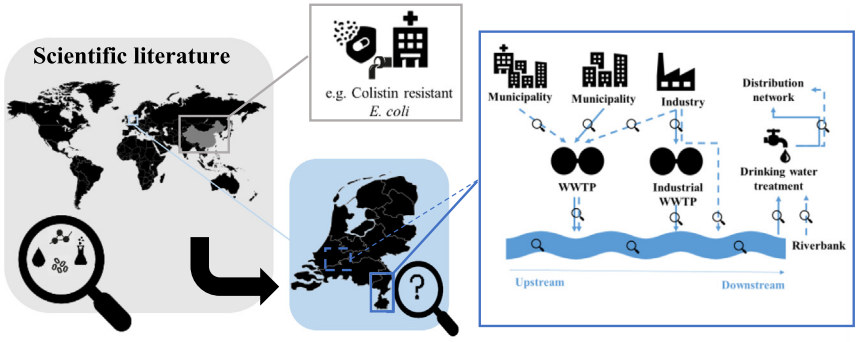
HIGHLIGHTS

- Sampling campaign based on literature mining is effective for early warning purposes
- Integrated assessment of potential chemical and microbial risks to drinking water
- Four out of six analysed contaminants detected in surface water and wastewater
- First report of Bu_4P^+, mycophenolic acid and MCR-1 *E. coli* in Dutch wastewater

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 24 April 2020
Received in revised form 15 June 2020
Accepted 25 June 2020
Available online 26 June 2020

Editor: Damia Barcelo

Keywords:
Pathogen
Emerging
Early warning
Contaminants

ABSTRACT

As well as known contaminants, surface waters also contain an unknown variety of chemical and microbial contaminants which can pose a risk to humans if surface water is used for the production of drinking water. To protect human health proactively, and in a cost-efficient way, water authorities and drinking water companies need early warning systems. This study aimed to (1) assess the effectiveness of screening the scientific literature to direct sampling campaigns for early warning purposes, and (2) detect new aquatic contaminants of concern to public health in the Netherlands. By screening the scientific literature, six example contaminants (3 chemical and 3 microbial) were selected as potential aquatic contaminants of concern to the quality of Dutch drinking water. Stakeholders from the Dutch water sector and various information sources were consulted to identify the potential sources of these contaminants. Based on these potential contamination sources, two sampling sequences were set up from contamination sources (municipal and industrial wastewater treatment plants), via surface water used for the production of drinking water to treated drinking water. The chemical contaminants, mycophenolic acid, tetrabutylphosphonium compounds and Hexafluoropropylene Oxide Trimer Acid, were detected in low concentrations and were thus not expected to pose a risk to Dutch drinking water. Colistin resistant *Escherichia coli* was detected for the first time in Dutch wastewater not influenced by hospital wastewater, indicating circulation of bacteria resistant to this last-resort antibiotic in the open Dutch population. Four out of six

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https://doi.org/10.1016/j.scitotenv.2020.140546

contaminants were thus detected in surface or wastewater samples, which showed that screening the scientific literature to direct sampling campaigns for both microbial and chemical contaminants is effective for early warning purposes.

1. Introduction

To provide all humans with clean drinking water by 2030 is our goal (UN, 2015). For this, we need to effectively govern and manage the quality of our drinking water resources and focus scarce resources on aquatic contaminants that pose the greatest threat to human health when water is used for drinking water production. In large parts of the world, surface water is used for the production of drinking water (Sullivan et al., 2005a; Sullivan et al., 2005b). However, surface water serves multiple functions in addition to being a drinking water resource, such as receiving industrial and municipal wastewater, being home to aquatic ecosystems and serving recreational and transportation purposes (Sullivan et al., 2005a; Sullivan et al., 2005b). These functions result in a wide variety of different chemical and microbial contaminants being present in surface water (Damania et al., 2019). Furthermore, although contaminants (both microbial and chemical) might be absent in the water source used for drinking water production, they may be introduced during treatment (e.g. disinfection by-products) or distribution (e.g. biofilms) (Mian et al., 2018; Liu et al., 2013). All of these aspects contribute to the complexity of effective risk governance of drinking water and its resources (Damania et al., 2019; Wuijts et al., 2018; Carvalho et al., 2019).

The potential human health effect of some contaminants has been well studied (for example arsenic (Ahmad et al., 2020) and *Cryptosporidium* (Medema, 2013)). Health based targets for drinking water have been implemented for these contaminants in national and international legislation. In Europe, the European Drinking Water Directive (DWD, 98/83/EC) is in place to protect citizens from adverse health effects caused by contamination of water intended for human consumption. The requirements for the chemical and microbial quality set by the European DWD are implemented into national legislation by Member States and need to be met by drinking water companies (European Commission, 2016). European drinking water companies are detecting chemical and microbial contaminants in drinking water and its resources that are not listed in the European DWD (Moreno-Mesonero et al., 2017; Vouga and Greub, 2016; Houtman et al., 2014). The potential (long-term) risk posed by (mixtures of) these emerging contaminants in drinking water is often unknown (Houtman, 2010; Schriks et al., 2010; Baken et al., 2018; Sanganyado and Gwenzi, 2019).

Examples of emerging chemical contaminants in drinking water and its resources that have attention over the past years are industrial chemicals such as per- and polyfluoroalkyl substances (PFAS) (Wang et al., 2019), microplastics (Eerkes-Medrano et al., 2015), ionic liquids and new groups of disinfection by-products such as halogenated methanesulfonic acids (Richardson and Ternes, 2018). Many of these chemicals have been in the aquatic environment for years, but have only recently been identified due to the increasing sensitivity of analytical techniques (Richardson and Kimura, 2017). The emergence of concern about contaminants such as PFAS has shown that, by the time scientific and regulatory agreement has been reached on the risk that these chemicals pose to humans and aquatic ecosystems, they are already ubiquitously present in the environment and remediation actions are costly and time-consuming (Stepien et al., 2014).

Recent examples of emerging microbial contaminants relevant to drinking water are: *Waddlia chondrophila* (Van Dooremalen et al., 2020), antibiotic resistant bacteria (Sanganyado and Gwenzi, 2019) and sapoviruses (Kauppinen et al., 2019). Pathogens are not directly included in the current European DWD, but are governed through quality standards for faecal contamination (*E. coli* and *enterococci*) which are used to indicate the adequate disinfection performance of the drinking-water supply. However, viruses and protozoa (such as *Cryptosporidium* and *Giardia*) can be of risk to public health even in the absence of these quality standards (Gunnarsdottir et al., 2020). Also, pathogens present in drinking water might remain undetected due to imperfect detection methods (Signor and Ashbolt, 2006). The revision of the European DWD will focus on risk-based monitoring based on (1) risk assessment and risk management of the catchment areas of the abstraction points, (2) risk management of water supply systems including abstraction, treatment, storage and distribution to the point of supply, and (3) risk assessment of the domestic distribution system (European Commission, 2018). But even with a risk-based approach, risk governance is still based on knowledge of known pathogens, including treatment efficiencies for these, which might be inaccurate for emerging pathogens (Schijven et al., 2011).

To protect humans from adverse health effects from both microbial and chemical contaminants in drinking water and to prevent costly remediation actions, water authorities and drinking water companies need early warning systems. Here, early warning systems are defined as processes aimed at reducing the impact of hazards by providing timely and relevant information in a systematic way (Khankeh et al., 2019). It has been shown that new hazards are reported in scientific articles long before the contaminant is globally recognised as an emerging risk for water functions (Halden, 2015; Lodder et al., 2013). Scientific articles may thus be used as part of an early warning system for proactive risk governance by water authorities and drinking water companies.

In a previous study, the authors developed a methodology to identify the first scientific article that reported the presence of a specific contaminant in the aquatic environment (Hartmann et al., 2019). The semi-automated methodology uses literature mining to enable the simultaneous analysis of a large number of scientific publications and is freely accessible. Using retrospective validation (period 2001–2015), the developed methodology was found to be effective in picking up early signals of aquatic contaminants of concern (Hartmann et al., 2019). However, this was a theoretical exercise and the practical effectiveness of the methodology still needs to be proven. The methodology was therefore applied to studies published between 1 January 2016 and 27 August 2018. This resulted in a list of 359 articles which reported one or more chemical (173 articles) and microbial (186 articles) contaminants for the first time (see Appendix A).

In this study, the results from this literature screening were used to direct a sampling campaign for chemical and microbial contaminants in the Netherlands. The integrated analysis of both emerging chemical and microbial contaminants in the aquatic environment is an innovative feature of this study and is considered valuable as chemical and microbial contaminates often arise from similar sources of contamination (e.g. municipal and industrial wastewater). The objective of this study was twofold, namely (1) to validate the practical effectiveness of screening the scientific literature for early warning purposes, and (2) to detect new aquatic contaminants of concern to public health in the Netherlands. First, the list of contaminants reported in the 359 articles was assessed to select both aquatic chemical and microbial hazards not yet recognised as such in the Netherlands. Then, possible sources of these contaminants in the Netherlands were identified, and based on these sources a monitoring campaign was set up to target the contaminants in municipal and industrial wastewater, drinking water resources, and/or drinking water. Monitoring results as well as

information sources and stakeholders consulted are described, to conclude with suggestions for successfully developing a sampling campaign based on literature mining.

2. Material and methods

2.1. Drinking water production in the Netherlands

In the Netherlands, 58% of the drinking water is produced from groundwater, 35% from surface water, 6% from riverbank filtration and 1% from natural dune water (Vewin, 2017). The main surface water resources for the production of drinking water are the rivers Rhine and Meuse and the lake IJsselmeer (Vewin, 2017). Dutch drinking water is of very high quality due to good asset management, the use of preventive risk assessment and risk management from source to tap, and the application of a multi-barrier approach in drinking water treatment (Schijven et al., 2011; Rosario-Ortiz et al., 2016; van den Berg et al., 2019). Despite the high quality of drinking water, emerging contaminants in drinking water and its resources, such as microplastics and PFAS, have led to considerable regulatory challenges and media attention in the Netherlands (Hartmann et al., 2018; Brandsma et al., 2019; Koelmans et al., 2019).

2.2. Contaminant selection

The result of applying the literature mining methodology developed by Hartmann et al. (2019) to recent scientific literature is shown in Appendix A. The result is a list of 359 articles that report the detection of one or more contaminants for the first time in the aquatic environment. A list of all the (groups of) contaminants reported by these articles is also included in Appendix A. For details on the text mining methodology, see Hartmann et al. (2019).

To validate the practical effectiveness of screening the scientific literature for early warning purposes, three chemical and three microbial contaminants were selected from the list of contaminants in Appendix A. These contaminants were selected as examples of potential new aquatic contaminants of concern to Dutch drinking water. Selecting six and not more contaminants was done for practical reasons. As this study integrates the chemical and microbial assessment of water samples, the word 'contaminant' is used to indicate both chemical and microbial water constituents. All six contaminants met the following hazard and exposure related criteria, namely:

- The contaminant is an unknown water constituent in surface water in the Netherlands or is a known water constituent but the relevance to drinking water quality is unknown;
- The contaminant could potentially be present in Dutch surface water resources used for drinking water production based on the presence of potential sources of pollution (e.g. industrial use of the contaminant, presence of the contaminant in human wastewater);
- The contaminant has a potential to be toxic or pathogenic, or the toxicity and pathogenicity of the contaminant are unknown;
- An analytical methodology is available for the analysis of the contaminant in water samples.

The three chemical contaminants selected were mycophenolic acid (MPA, Chemical Abstracts Service (CAS) number 24280-93-1), tetrabutylphosphonium compounds (Bu_4P^+, hereafter referred to as TBP, CAS number 2304-30-5) and Hexafluoropropylene Oxide Trimer Acid (HFPO-TA, CAS number 13252-14-7). The three microbial contaminants selected were mobilised colistin resistance-1 positive *Escherichia coli* (MCR-1 *E. coli*), a novel variant of *Vibrio cholerae* O1 El Tor ctxB and *Legionella longbeachae*. We consciously opted to investigate 6 constituents as the sampling campaign itself was not the aim of the paper. The aim was to test the effectiveness of designing sampling campaigns based on literature mining, and for this purpose 6 constituents were sufficient. The manner in which the six contaminants fit within the selection criteria for potential new aquatic contaminants of concern to Dutch drinking water is discussed in detail in Sections 2.2.1–2.2.6 and in brief in Table 1.

2.2.1. Mycophenolic acid (MPA)

MPA was identified by Franquet-Griell et al. (2016) as a potential emerging risk to drinking water quality in Spain. MPA is prescribed in the Netherlands predominantly as an immunosuppressant. At the time of this study, MPA had not been considered a contaminant of concern for the aquatic environment in the Netherlands. Neither the number of users (14,182 in 2018), nor the total number of Defined Daily Dosages (DDDs) prescribed per year (2,924,500 in 2018) were very high compared to other commonly-used pharmaceuticals (e.g. Naproxen was used by 674,260 people in 2018 with a total of 34,543,200 DDDs prescribed) (https://www.gipdatabank.nl/databank#/g//B_01-basis/vg/L04AA06, 2019).

However, as 1 DDD of MPA is 2 g according to the World Health Organization (2019), it can be estimated that 5849 kg of MPA was consumed in the Netherlands in 2018. After ingestion, 60% of the drug is excreted via urine as mycophenolic acid glucuronide and 3% remains unchanged (Franquet-Griell et al., 2016). The glucuronide metabolite is deconjugated and the parent compound is formed again in wastewater treatment plants (WWTPs) (Franquet-Griell et al., 2016). Consequently, an estimated 3685 kg MPA was discharged via effluents of WWTPs to surface water in the Netherlands in 2018. The estimated load of MPA is high (mainly due to the expected limited removal in WWTPs) compared to the widely-used Naproxen (864 kg, estimated removal in Dutch WWTPs is 95%) and similar to Irbesartan (3221 kg, no expected removal in Dutch WWTPs) (Vissers and van Gelderen, 2018). MPA was thus considered a potential contaminant of concern to drinking water quality in the Netherlands.

2.2.2. Tetrabutylphosphonium compounds (Bu_4P^+, TBP)

Brand et al. (2018) detected TBP for the first time in the River Elbe in Germany. TBP compounds are used as phase-transfer catalysts in the synthesis of organic compounds. Two different tetrabutylphosphonium compounds were registered by companies located in the Netherlands as part of the regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). These registrations suggest the potential emission of TBP to the environment in the Netherlands. Furthermore, Brand et al. (2018) showed that TBP is persistent in the environment and observed cytotoxic potential in human cells of $Bu_4P^+Cl^-$. Therefore, the analysis of the potential presence of TBP in surface waters in the Netherlands was considered valuable.

2.2.3. Hexafluoropropylene Oxide Trimer Acid (HFPO-TA)

Per- and polyfluoroalkyl substances (PFAS) are an increasing cause of concern due to their persistence in the environment and their potential to cause adverse effects in humans. PFAS have been widely used since the 1950s in many industrial applications such as in the production of polytetrafluoroethylene and paints (Xiao, 2017; Post et al., 2012). After the phase out of PFOA, a widely used PFAS, alternative PFAS have been developed. Hexafluoropropylene Oxide Trimer Acid (HFPO-TA), one of the alternatives, was recently detected for the first time in the aquatic environment by Pan et al. (2017). HFPO-TA was detected in concentrations up to 68.5 μg/L in the Xiaoqing River in China as a result of wastewater discharges from a fluoropolymer manufacturing plant. Sheng et al. (2018) showed that HFPO-TA has a higher bioaccumulation potential than PFOA and is more hepatotoxic. Little is known about the annual production and environmental occurrence of HFPO-TA in Europe's surface waters.

HFPO-TA is not registered under REACH by any company located in the Netherlands, indicating that if HFPO-TA is used or produced in the Netherlands it is below 1000 kg per year. This indicates low emission

Table 1
Fulfilment of the selection criteria for potential new aquatic contaminants of concern to Dutch drinking water by MPA, TBP, HFPO-TA, MCR-1 *E. coli*, *Vibrio cholerae* O1 El Tor ctxB and *Legionella longbeachae*.

Contaminant	Signal reported by	Study detected contaminant in	Potential relevance to drinking water production in the Netherlands
MPA	Franquet-Griell et al. (2016)	River Llobregat in Spain	Pharmaceutical estimated to be discharged in high amounts to surface water due to high daily dose (2 g), minor metabolic impact and limited removal in wastewater treatment plants. No environmental concentrations available for the Netherlands.
TBP	Brand et al. (2018)	River Elbe in Germany	Industrial chemical used as phase-transfer catalyst in the synthesis of organic compounds. Potential industrial source present in the Netherlands. Observed cytotoxic potential in human cells. Presence in the (aquatic) environment in the Netherlands unknown.
HFPO-TA	Pan et al. (2017)	Xiaoqing River in China and the common carp (*Cyprinus carpio*)	Industrial chemical (PFAS) used by fluorochemical industry. Potential industrial source present (fluorochemical company) in the Netherlands. Potential hepatotoxic effects. Limited environmental concentrations available for the Netherlands (Pan et al., 2018).
MCR-1 *E. coli*	Jin et al. (2017)	Hospital wastewater in Beijing, China	Colistin is considered a last-resort antibiotic. Dissemination of resistance to last resort antibiotics poses a major public health risk. Unknown whether MCR-1 *E. coli* is present in wastewater to the aquatic environment in the Netherlands.
Vibrio cholerae O1 El Tor with mutation in *ctxB*	Bhattacharya et al. (2016)	Faecal specimen from various Cholera outbreaks in India	*Vibrio* detected in salt and brackish water in the Netherlands, freshwater less frequently. Vibrio species are known to be effectively removed by drinking water treatment in the Netherlands. However, the genetic mutation found by Bhattacharya et al. (2016) of *V. cholerae* O1 El in *ctxB* (gene sequence that encodes cholera toxin B) could be transferred via Horizontal Gene Transfer (HGT) to other bacteria, thereby posing a threat to public health.
Legionella longbeachae	Thornley et al. (2017)	Manmade water system (cooling tower) in New Zealand	Increase in endemic cases of Legionellosis in the Netherlands. Infection source remains often unknown. Whether infection with *L. longbeachae* via manmade water systems could be a source of infection is unknown.

potential to the aquatic environment. Pan et al. (2018) detected trace levels of HFPO-TA in water samples taken from the Dutch and German part of the River Rhine as well as in water samples from other European countries, such as Sweden and the United Kingdom, indicating potential emission of HFPO-TA in Europe.

The presence of another PFOA alternative, Hexafluoropropylene Oxide Dimer Acid (HFPO-DA), in surface and drinking water in the Netherlands has caused considerable public and regulatory concern over the past years. Since July 2019, HFPO-DA has been categorised as a Substance of Very High Concern by the European Chemicals Agency (ECHA) following a Dutch proposition (*MSC unanimously agrees that HFPO-DA is a substance of very high concern (ECHA/NR/19/23)*, 2019).

Pan et al. (2018) sampled locations on the River Waal (a Dutch branch of the River Rhine) upstream of a fluorochemical production plant in the Netherlands. Whether the concentrations of HFPO-TA found by Pan et al. (2018) were the result of wastewater discharged by the fluorochemical production plant in the Netherlands has not yet been investigated. Due to the concern about HFPO-DA and the limited knowledge about HFPO-TA, it was considered valuable to analyse the potential presence of HFPO-TA in surface water and wastewater of the fluorochemical production plant in the Netherlands.

2.2.4. Mobilised colistin resistance-1 positive Escherichia coli (MCR-1 E. coli)

Jin et al. (2017) reported the presence of mobilised colistin resistance-1 positive Escherichia coli (MCR-1 *E. coli*) in hospital wastewater for the first time in China. They detected MCR-1 *E. coli* in both the influent and effluent of the wastewater treatment plant, thereby indicating the introduction of MCR-1 *E. coli* into the aquatic environment via hospital wastewater. MCR-1 *E. coli* has also been detected in isolates obtained from hospitalised patients and in retail chicken meat in the Netherlands (Schrauwen et al., 2017; Nijhuis et al., 2016). Dissemination of resistance to colistin is considered a serious threat to public health as it is used to treat human infections caused by multidrug-resistant and carbapenem-resistant bacteria that cannot be treated by conventionally used antibiotics (Zając et al., 2019). No information is available on the dissemination of MCR-1 *E. coli* to the aquatic environment through wastewater in the Netherlands.

Drinking water treatment is effective in removing bacteria and resistance does not limit the removal efficiency (Sanganyado and Gwenzi, 2019; Schijven et al., 2011). However, antibiotic resistant genes (ARG) have been shown to persist drinking water treatment (Dodd, 2012). Zhang et al. (2018) detected an increase in antibiotic resistance in drinking water due to the detachment of biofilm. ARG could be transferred to pathogens via Horizontal Gene Transfer (HGT), thereby posing a threat to public health. Therefore, the potential presence of MCR-1 *E. coli* in the aquatic environment in the Netherlands is relevant from a drinking water perspective.

2.2.5. Vibrio cholerae O1 E1 Tor with mutation in cholera toxin B subunit gene (ctxB)

Vibrio bacteria are found abundantly in the aquatic environment, especially in the marine environment, and play an important role in maintaining the health of the aquatic ecosystem (Thompson et al., 2005; Miyoshi, 2013). Of the 100 *Vibrio* species known to humans, 11 are known pathogens (Miyoshi, 2013). Infection with *V. cholerae* O1/O139 can cause cholera, a severe diarrheal disease, which is responsible for an estimated 95,000 deaths worldwide per year (Ali et al., 2015). Bhattacharya et al. (2016) were the first to report a new variant of *Vibrio cholerae* O1 E1 Tor in South India with a mutation in the cholera toxin B subunit gene (*ctxB*).

In the Netherlands, *Vibrio* infections caused by swimming in contaminated waters have been reported (Schets et al., 2006). Furthermore, the presence of *V. alginolyticus*, *V. parahaemolyticus*, *V. cholerae non O1/O139* and *V. fluvialis* in coastal waters has been shown but, to date, has rarely been detected in freshwater (Schets et al., 2011). *Vibrio* species are known to be effectively removed by drinking water treatment in the Netherlands. However, the potential presence of the newly identified *Vibrio cholerae* O1 E1 variant in surface water was initiated as *ctxB* could be transferred to other pathogens by HGT which might be less effectively removed by drinking water treatment.

2.2.6. Legionella longbeachae

Thornley et al. (2017) first reported the transmission of *Legionella longbeachae* (aerobic Gram-negative bacteria) from cooling towers citing it as a potential cause for Legionnaires' disease (LD). In general, the watering of contaminated compost or soil is expected to be the major source of infection for *L. longbeachae* (Den Boer et al., 2007; Potočnjak et al., 2016). The Thornley et al. (2017) study highlights the relevance of waterborne transmission in investigations to find the source of *L. longbeachae* infection.

Since 2012, an increase in endemic LD cases has been observed in the Netherlands which might be related to an increase in in the number of warm, humid and showery weather days (Reukers et al., 2018;

Karagiannis et al., 2009). For most of the *Legionella* infections, the infection source remains unknown. Recently, the infection risk posed by Dutch wastewater treatment plants was investigated, but whether cases of LD caused by *L. longbeachae* in the Netherlands could be related to WWTPs is currently unknown (Bartels et al., 2019). Therefore, an investigation into the potential presence of *L. longbeachae* in wastewater in the Netherlands was considered relevant to protect public health.

2.3. Development of the sampling campaign: consulted stakeholders and information sources

In order to develop the sampling campaign, different stakeholders from the Dutch water sector as well as several information sources were consulted. Two questions were taken into consideration: (1) what could be the potential source of the contaminant and (2) which drinking water production location would be potentially impacted by this source of pollution.

First, a vast array of stakeholders, including Dutch drinking water companies and their laboratories, the association of River water companies for both the River Rhine and Meuse (RIWA) as well as the national water authority (Rijkswaterstaat), were asked whether the selected chemical contaminants had ever been detected in surface water in the past. Both target and non-target screening data (when available) were checked. None of the contaminants had been detected in the available monitoring data. Also, no next generation sequencing data were available for the microbial contaminants from the labs. Therefore, no indication for potential sources or drinking water production sites at risk could be abstracted from this information.

Based on the literature information, it was concluded that human wastewater could be a potential source of MPA and MCR-1 *E. coli* (Franquet-Griell et al., 2016; Jin et al., 2017). This could also be the case for *L. longbeachae*, as indicated by Thornley et al. (2017). As surface waters receive discharges from municipal WWTPs and *Vibrio* species are their natural inhabitants, surface waters used for the production of drinking water were considered for this study.

Based on the information from the REACH registrations for TBP, a company was contacted that could potentially produce or use TBP. The company has two locations in the Netherlands. One in the city of Bergen op Zoom, which is the location mentioned in the REACH registration, and one on an industrial site in the southern part of the Netherlands where an industrial WWTP collects and treats wastewater from 150 chemical companies. The effluent from this industrial WWTP is discharged into a branch of the River Meuse which is an important drinking water resource in the Netherlands. The potential emission of TBP by this location of the company could thus potentially influence the production of drinking water. The company appreciated the early signal and investigated whether any of the products used on site, including chemical cleaning products, contained TBP. To the best of their knowledge, TBP was not used on their site (personal communication May 2019). It was decided to investigate the wastewater from the chemical industry site to confirm the absence of TBP.

The fluorochemical manufacturer near the city of Dordrecht was considered a potential industrial source of HFPO-TA (also referred to in a recent study by Brandsma et al. (2019)). At the time of this study, because of the national and international concern about HFPO-DA, the Dutch national water authority (Rijkswaterstaat) was already closely monitoring the wastewater from the fluorochemical manufacturer for the presence of HFPO-DA. Through Rijkswaterstaat, sites that would have been otherwise restricted could be sampled. The company appreciated the early signal, and declared that it was not aware of any use of HFPO-TA at their company. Whether HFPO-TA was formed as a by-product during the process was unknown and triggered the investigation of their wastewater. The wastewater of this company is directly and indirectly (via a municipal WWTP) discharged into the River Beneden Merwede, a river which influences the River Noord that is used for the production of drinking water downstream (see Fig. 1).

2.4. Sample collection

Based on the potential sources of contamination, receiving surface waters and possibly influenced drinking water production sites, two different sampling campaigns were initiated in the Netherlands. The first campaign was located around the city of Dordrecht and the second one in the southern part of the Netherlands. In both campaigns samples were collected from industrial wastewater, municipal wastewater, surface water and drinking water.

Samples for Campaign 1 were collected from May until October 2019. In October 2019 all samples for Campaign 2 were collected. The sampling locations are shown in Fig. 1. Sampling locations are based on previous research by drinking water companies and water authorities, detailed information is provided in Appendix B.

Table 2 provides details on sample locations and on the number of samples in which a contaminant was analysed at the particular location.

If possible, composite samples were collected at the municipal WWTPs. However, for practical reasons (e.g. samples needed for quality monitoring by the WWTP and the time of collection), composite sampling was not done at all locations. Where it was not possible, grab samples were collected. Wastewater samples were taken at a WWTPs receiving hospital and municipal wastewater (C1L25 and C1L26), a WWTP that did not treat hospital wastewater (C2L5–C2L8) and at an industrial WWTP that collects and treats wastewater from 150 chemical companies and their sanitary installations (C2L9 and C2L10). Runoff from the industrial site (C1L18–C1L22) was sampled at designated collection locations were concentrated rainwater was discharged. Drinking water samples were collected before water entered the distribution network. Surface water samples taken during Campaign 1 were collected at multiple locations in the river by boat with the help of Rijkswaterstaat. During Campaign 2 no boat was available, these samples were thus collected from shore. The samples used for the analysis of HFPO-TA, MPA and TBP were stored at 4 °C until the time of analysis. The samples used for the analysis of *V. cholerae*, MCR-1 *E. coli* and *L. longbeachae* were analysed within 24 h.

2.5. Sample analysis

The analyses of MPA, TBP, *V. cholerae*, MCR-1 *E. coli* and *Legionella longbeachae* were performed at the Dutch National Institute for Public Health and the Environment (RIVM) and the analysis of HFPO-TA was carried out by Wageningen Food Safety Research.

2.5.1. Mycophenolic acid (MPA)

Before sample preparation, isotopically labelled MPA was added to all samples and quality control samples. Blank matrix samples were used for quality control and were prepared following the same procedure as the water samples. 15 mL of the samples was concentrated in duplicate using *solid phase extraction* (SPE) and run through a Waters OASIS HLB 6 cm^3/200 mg column. The column was washed with 40% methanol and water. MPA was eluted from the column by 4 mL methanol and the eluate was evaporated at 45 °C. Finally, the residue was dissolved in 300 μL methanol.

The analysis of MPA was carried out using liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS) in positive heated ESI mode. 10 μL was injected on a Waters Acquity UPLC HSS C18 column of 150 × 2.1 mm, 1.8 μm particles. MPA was eluted using a 14 minute gradient: mobile phase A, 10 mM ammonium formate; mobile phase B, acetonitrile.

The mass spectrometer (QTrap 6500, AB Sciex) was operated at 400 °C with an ion spray voltage of 5500 V and a decluttering potential of 26 V. The curtain gas was 40 psi, the ion source nebuliser gas was 90 psi and the ion source heater gas 50 psi. MPA was identified using the transition of m/z 321 > 207 for quantification, and m/z 321 > 159 for qualification. For quantification of the deuterated MPA the transition of m/z 324 > 210 was used, following Franquet-Griell et al. (2016). The

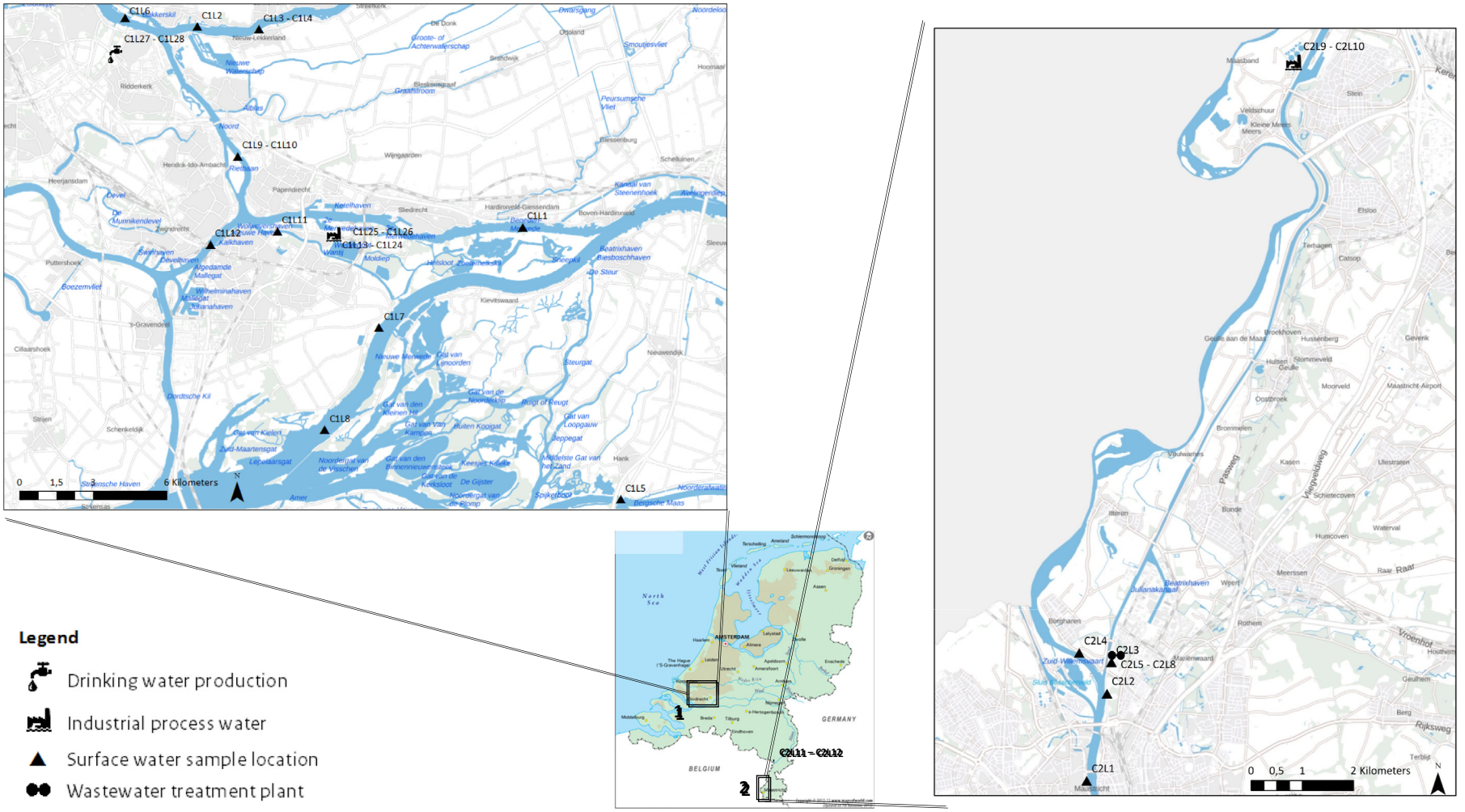

Fig. 1. Map of the Netherlands giving an overview of the sampling sites. A more detailed view of both sampling campaigns is also shown.

Table 2
Overview of samples collected during Campaign 1 (location codes = C1L1–C1L28) and Campaign 2 (location codes = C2L1–C2L13).

Location code	Type of water	Type of sample	Shore side	Number of samples for specific contaminant analysis collected at particular locations					
				HFPO-TA	MPA	TBP	*V. cholerae*	MCR-1 *E. coli*	*L. longbeachae*
C1L1	Surface water	GS	Middle	4	-	-	-	-	-
C1L2	Surface water	GS	Right	4	-	-	-	-	-
C1L3	Surface water	GS	Middle	4	-	-	-	-	-
C1L4	Surface water	GS	Left	4	-	-	-	-	-
C1L5	Surface water	GS	Middle	2	6	6	1	-	-
C1L6	Surface water	GS	Right	5	3	3	1	-	-
C1L7	Surface water	GS	Right	5	-	-	-	-	-
C1L8	Surface water	GS	Middle	5	-	-	-	-	-
C1L9	Surface water	GS	Left	5	1	1	-	-	-
C1L10	Surface water	GS	Right	5	2	2	1	-	-
C1L11	Surface water	GS	Middle	5	-	-	-	-	-
C1L12	Surface water	GS	Right	5	-	-	-	-	-
C1L13	Cooling water used in industrial processes	GS	-	2	3	3	-	-	-
C1L14	Wastewater fluorochemical company	GS	-	3	3	3	-	-	-
C1L15	Wastewater fluorochemical company	GS	-	3	-	-	-	-	-
C1L16	Wastewater fluorochemical company	GS	-	3	2	2	-	-	-
C1L17	Wastewater fluorochemical company	GS	-	3	3	2	-	-	-
C1L18	Runoff from industrial site	GS	-	2	-	-	-	-	-
C1L19	Runoff from industrial site	GS	-	2	-	-	-	-	-
C1L20	Runoff from industrial site and process water	GS	-	3	1	1	-	-	-
C1L21	Runoff from industrial site	GS	-	2	-	-	-	-	-
C1L22	Runoff from industrial site	GS	-	2	-	-	-	-	-
C1L23	Wastewater fluorochemical company	CS[a]	-	-	2	2	-	-	-
C1L24	Wastewater fluorochemical company	GS	-	-	1	1	-	-	-
C1L25	Influent municipal WWTP	GS	-	1	3	3	-	1	
C1L26	Effluent municipal WWTP	GS	-	5	2	2	-	-	-
C1L27	Intake water	GS	-	1	4	4	-	-	-
C1L28	Drinking water	GS	-	1	4	4	-	-	-
C2L1	Surface water	GS	Left	-	2	2	-	-	-
C2L2	Surface water	GS	Right	-	3	3	1	-	-
C2L3	Surface water	GS	Right	-	3	3	1	-	-
C2L4	Surface water	GS	Right	-	3	3	1	-	-
C2L5	Influent municipal WWTP	GS	-	-	1	1	-	1	1
C2L6	Influent municipal WWTP	CS[b]	-	-	2	2	-		
C2L7	Effluent municipal WWTP	GS	-	-	1	1	-	-	1
C2L8	Effluent municipal WWTP	CS[b]	-	-	2	2	-	-	-
C2L9	Influent industrial WWTP	GS	-	-	3	3	-	1	1
C2L10	Effluent industrial WWTP	GS	-	-	3	3	-	-	1
C2L11	Intake water	GS	-	-	2	2	-	-	-
C2L12	Drinking water	GS	-	-	2	2	-	-	-

Explanation of abbreviations and symbols used: - = not applicable, GS = grab sample, CS = composite sample, WWTP = wastewater treatment, HFPO-TA = Hexafluoropropylene Oxide Trimer Acid, MPA = mycophenolic acid, TBP = tetrabutylphosphonium compounds, *V. cholerae* = *Vibrio cholerae* O1 E1 Tor with mutation in cholera toxin B subunit gene (ctxB), MCR-1 *E. coli* = mobilised colistin resistance-1 positive *Escherichia coli* (MCR-1 *E. coli*).

[a] Time-proportional composite sample over 24 h.

[b] Flow-proportional composite sample (40 mL sample per 180 m^3 water).

limit of detection (LOD) was 0.01 ng/L and limit of quantification (LOQ) was 0.04 ng/L.

2.5.2. Tetrabutylphosphonium compounds (Bu_4P^+, TBP)

For the analysis of TBP, samples were not concentrated by SPE, but were only centrifuged. Isotopically labelled TBP was added to the samples before analysis, which was carried out using the same gradient conditions and column on the LC-MS/MS system as was the case for the MPA analysis (Section 2.5.1). The mass spectrometer (QTrap 6500, AB Sciex) was operated at 500 °C, with an ion spray of 5500 V and a decluttering potential of 66 V. The curtain gas was 40 psi, the ion source nebuliser gas was 90 psi and the ion source heater gas 50 psi. TBP was identified using the transition of m/z 259 > 76 for quantification and the transitions of m/z 259 > 61 and m/z 259 > 90 for qualification. The LOD and LOQ were 0.01 ng/L and 0.04 ng/L respectively.

2.5.3. Hexafluoropropylene Oxide Trimer Acid (HFPO-TA)

HFPO-TA was analysed using a Wageningen Food Safety Research in-house method. Before sample preparation, isotopically labelled HFPO-DA was added to all samples and quality control samples. A blank matrix and a blank chemical sample were used for quality control and were prepared following the same procedure as the water samples. 200 mL of the samples was concentrated by using weak anion exchange solid phase extraction (WAX-SPE). The samples were run through activated WAX columns (Strata-X, Phenomenex). HFPO-TA was eluted from the column by alkaline acetonitrile after washing with sodium acetate buffer and methanol. The eluate was evaporated at 40 °C under nitrogen. The residue was dissolved in 300 μL acetonitrile and diluted with 2 mM ammonium acetate in water to 1 mL.

The analysis of HFPO-TA was carried out using liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS). 20 μL of the extract was injected on an Acquity UPLC BEH C18 analytical column of 50 × 2.1 mm, 1.7 μm particles. An isolator column was used to prevent any interference by substances from the mobile phase. HFPO-TA was eluted using a 12.5 minute gradient: mobile phase A, 2 mM ammonium acetate buffer in water; mobile phase B, acetonitrile.

The mass spectrometer (Q-Trap 5500, Sciex) was equipped with an electrospray interface in the negative ion mode. HFPO-TA was detected based on the ion transition m/z 495 > 185 and 185 > 119, the latter originating from an in-source fragment of HFPO-TA. The LOD was 1 ng/L unless a sample proved to be highly contaminated with other PFAS (e.g. PFOA or HFPO-DA). In that case no concentration step was carried out to prevent contamination of the laboratory equipment, yielding an LOD of 300 ng/L. Quantification of all samples was performed with a

linear 7 point calibration curve with concentrations ranging from 5 ng/L up to 125 ng/L. To check for an adequate performance of the instrumentation, isotopically labelled PFOA was added just before injection into the LC-system.

2.5.4. Mobilised colistin resistance-1 positive Escherichia coli (MCR-1 E. coli)

Three wastewater samples were analysed within 6 h of sample collection for the presence of MCR-1 *E. coli*. The protocol published by Biomérieux (CHROMID®, 2019) for the screening of Colistin-resistant *Enterobacteriaceae* was used.

Each sample was tested in two dilutions after filtration using a 0.45 μm Millipore® filter. The two dilutions were prepared with 1 mL or 10 mL of the sample and 9 mL or 10 mL of Brain Heart Infusion broth (BHI), respectively. After incubation for 4 h at 37 °C, 50 μL of each of the dilutions and 10 and 100 μL of the filtered samples were transferred to CHROMID® Colistin R disks containing 10 μg colistin each. This resulted in 12 disks that were incubated for 18 to 24 h at 44 °C (a deviation from the protocol by Biomérieux (CHROMID®, 2019) which calls for incubation at 37 °C). NCTC 13864 CR-*E. coli* and ATCC 25922 *E. coli* were used as positive and negative controls, respectively.

After incubation, pink coloured colonies were transferred to Tryptone Soy Agar (TSA) plates (Oxoid®). Polymerase chain reaction (PCR) was used for confirmation following the multiplex PCR methodology published by Rebelo et al. (2018).

2.5.5. Vibrio cholerae O1 E1 Tor with mutation in cholera toxin B subunit gene (ctxB)

The methodology used for the identification of *Vibrio cholerae* in water is based on ISO 21872-1:2017 (2017). On day 1, 1 mL, 10 mL and 100 mL of the samples were filtered over a 0.45 μm Millipore® cellulose nitrate filter. The filters were incubated at 37 °C overnight in 50 mL Alkaline Peptone Water (APW, Biotrading®). The next day, 10 μL from the subsurface layer of each APW suspension were transferred to thiosulfate citrate bile-salts sucrose (TCBS) agar plates and again incubated overnight at 37 °C (Huq et al., 2012). *Vibrio cholerae* are known to appear as translucent, flat, yellow or green colonies on TCBS agar (Huq et al., 2012). Therefore, on day 3, five yellow and five green colonies were transferred to TSA plates (Oxoid®) and incubated overnight at 37 °C. The next day, all isolates were identified using API20E Biochemical Tests and confirmed using APIWEB™ by Biomerieux. In order to investigate the strains of the isolates identified as *V. cholerae* by APIWEB™, PCR was used.

The *V. cholerae* identified colonies were diluted in 500 μL 0.85% NACL in a 1.5 mL clean Eppendorf Tube®. The tubes were put in a water bath for 4 to 6 min at 95 °C and then centrifuged at 10,000*g* for 1 min. Two PCR tests were carried out for confirmation, one for *V. cholerae* O:1 Ogawa and one for *V. cholerae* non O1. In both cases, 0.85% NACL was used as negative control. Table 3 shows primers and probes used. The PCR mix consisted of 12.5 μL of master mix, 0.4 μL each of forward and reverse primer, 0.2 μL of probe, 6.5 μL water and 5 μL of DNA. The realtime PCR program used for *V. cholerae* identification was one cycle of 3 min at 95 °C for initial denaturation and polymerase activation and 45 cycles each of 15 s at 95 °C for denaturation and 60 s at 60 °C for annealing.

Table 3
Primers and probes used to identify Vibrio cholerae using PCR (Rebelo et al., 2018).

Ctx	Forward	TTTGTTAGGCACGATGATGGAT
Ctx	Reverse	ACAGACAATATAGTTTGACCACTAAG
Ctx	Probe	TGTTTCCACCTCAATTAGTTTGAGAAGTCCC
Tox R	Forward	GTGCCTTCATCAGCCACTGTAG
Tox R	Reverse	AGCAGTCGATTCCCCAAGTTTG
Tox R	Probe	CACCGCAGCCAGCCAATGTCGT

2.5.6. Legionella Longbeachae

Four wastewater samples, two influent and two effluent samples, were analysed for the presence of *L. longbeachae* using NEN-EN-ISO 11731:2017 (2017). For practical reasons, the analysis was only possible for samples taken during Campaign 2. The methodology used for analysis of *Legionella* deviated from NEN-EN-ISO 11731:2017 in two aspects. Firstly, all samples were tested with and without acid and with and without heat treatment. This is in line with other published methodologies for the detection of *Legionella* bacteria in environmental samples (Ditommaso et al., 2011). Secondly, all samples were transferred to three different media to maximise the probability of culturing *Legionella* bacteria, namely buffered charcoal yeast (BCYE) agar (Oxoid®) with, and without, added antibiotics and BCYE supplemented with glycine (3 g/L), vancomycin (1 mg/L), polymyxin B (50,000 UI/L) and anisomycin (MWY, Oxoid®). The Oxoid® *Legionella* Latex test was used to serogroup isolated colonies suspected to be *Legionella* bacteria.

3. Results

In total, 166 samples were analysed. MPA was detected in 41 out of 67 samples, TBP was found in 48 out of 66 samples, HFPO-TA in 1 out of 86 samples and MCR-1 *E. coli* was found in all three tested samples. *V. cholerae* was identified in 2 out of 6 samples. However, the novel variant of *V. cholerae* O1 E1 Tor and *L. longbeachae* were not detected in the analysed samples. The results are shown in Figs. 2 and 3 for sampling Campaigns 1 and 2, respectively, and are discussed in detail below. For the statistical analysis of MPA, TBP and HFPO-TA concentrations, the numerical value of the LOD was used for non-detects.

3.1. Mycophenolic acid (MPA) detected in 41/67 samples

The highest MPA concentrations were found in influent samples of WWTPs, with a maximum of $1.46 \times 10^3 \pm 369$ ng/L found in the influent of the WWTP sampled during Campaign 1 (7.899×10^2–2.01×10^3 ng/L in all analysed influent samples). In order to compare the MPA concentrations to other pharmaceuticals in wastewater in the Netherlands, the Watson Database was consulted (http://www.emissieregistratie.nl/erpubliek/erpub/wsn/default.aspx, 2019). Fig. 4 shows the average detected concentrations of MPA and twelve other prescription drugs that have been detected in influent and effluent of Dutch WWTPs in 1990–2019. These are all pharmaceuticals with expected high loads to the aquatic environment based on the DDD and prescription data (https://www.gipdatabank.nl/databank#/g//B_01-basis/vg/L04AA06, 2019). The average influent concentration of MPA found in this study is in the same order of magnitude as Sotalol (treats and prevents abnormal heart rhythms) and Hydrochlorothiazide (high blood pressure medication). The MPA concentration found in the effluent is comparable to pharmaceuticals such as Naproxen and Ibuprofen (both nonsteroidal anti-inflammatory drugs).

3.2. Tetrabutylphosphonium compounds (Bu_4P^+, TBP) detected in 48/66 samples

TBP was detected in industrial and municipal wastewater and in surface water. The maximum concentration was detected in WWTP influent and was 5.47 ng/L. The average of all tested WWTP influent samples was 3.47 ng/L (standard deviation = 2.01 ng/L). In surface water, the concentrations detected ranged from 0.10 to 0.56 ng/L (average = 0.28 ng/L, standard deviation = 0.18 ng/L).

3.3. Hexafluoropropylene Oxide Trimer Acid (HFPO-TA) detected in 1/86 samples

In total, 86 samples were analysed for the presence of HFPO-TA. In all but one sample, HFPO-TA was not detected above the limit of detection. HFPO-TA was detected at 11.7 ng/L in one sample taken from a

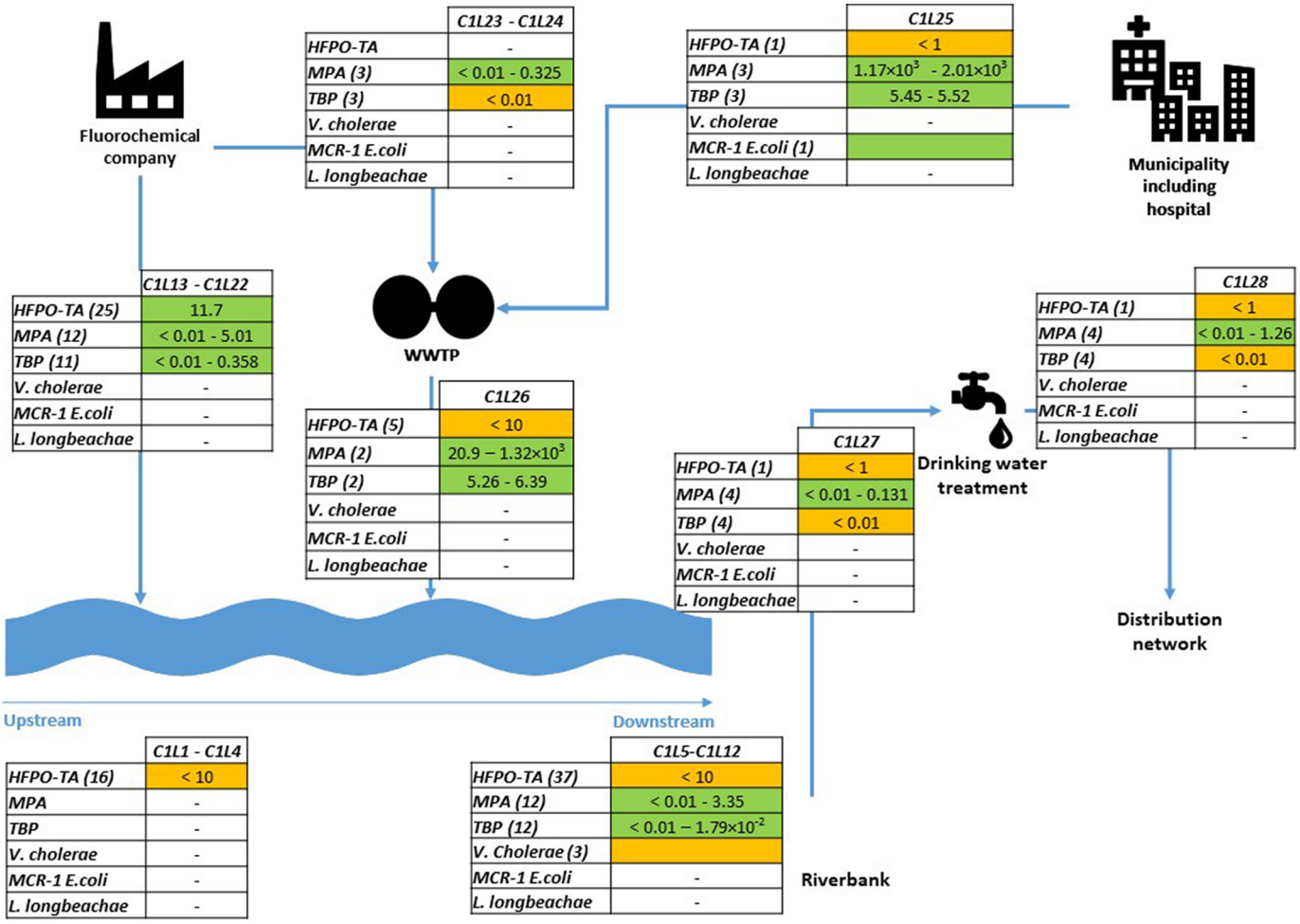

Fig. 2. Results of HFPO-TA, MPA, TBP, V. cholerae, MCR-1 *E. coli* and *Legionella longbeachae* analyses in surface water, wastewater and drinking water samples collected during Campaign 1. Green = detected, orange = not detected, - = not analysed. For chemical contaminants the detected concentration is shown in ng/L (minimum–maximum). Detection limits are, depending on the sample 1 or 10 ng/L for HFPO-TA and 0.01 ng/L for both MPA and TBP. In case of V. cholerae, MCR-1 *E. coli* and *L. longbeachae*, the concentration in the samples could not be determined based on the performed analyses. For details on sampling locations see Fig. 1. The number between brackets behind each contaminant is the number of samples the contaminant is analysed in at the specific location(s). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

collection point of runoff from an industrial site which is discharged directly into the River Beneden Merwede. The source of HFPO-TA in this water could not be determined.

3.4. Mobilised colistin resistance-1 positive Escherichia coli (MCR-1 E. coli) isolated from 3/3 samples

Table 4 shows the number of colonies suspected to be MCR-1 *E. coli* on the CHROMID® Colistin R disks. Of these colonies, 35 colonies were isolated and transferred to TSA plates for confirmation (15 of C1L25, 10 of C2L9 and 10 of C2L6). The results of the multiplex PCR are shown in Appendix C. MCR-1 *E. coli* colonies were confirmed in all three wastewater samples.

3.5. Vibrio cholerae O1 E1 Tor with mutation in cholera toxin B subunit gene (ctxB) isolated from 0/6 samples

After 3 days, green and yellow colonies were found on all TCBS agar plates. APIWEB™ confirmed the presence of *Vibrio cholerae* in surface water sample locations C1L10 (all tested volumes) and C1L6 (only in 100 mL). Table 5 shows all confirmed *Vibrio* species found in the studied samples.

PCR confirmation tests showed that the detected *Vibrio cholerae* species were non-O1/O139. Therefore, the detected *V. cholerae* species did not belong to the novel strain identified by Bhattacharya et al. (2016).

3.6. Legionella longbeachae isolated from 0/4 samples

Table 6 shows the results of *Legionella*. After 10 days, colonies suspected to be *Legionella* were found on 2 out of 184 plates. The first presumptive colony was found on BCYE agar prepared with the sample from location C2L6. The second presumptive colony was cultured on MYC agar with a sample from location C2L10. The two colonies were then subcultured on BCYE agar and serogrouped using the Oxoid® Legionella Latex test. The Oxoid® Legionella Latex test was not able to unambiguously confirm the isolates as *Legionella* bacteria.

4. Discussion

This study aimed to validate the practical effectiveness of screening scientific literature for early warning purposes. Four out of six analysed contaminants were detected in Dutch surface and wastewater samples, namely mycophenolic acid, tetrabutyl phosphonium compounds, HFPO-TA and colistin resistant *E. coli*, which showed that directing sampling campaigns based on literature mining is effective in finding unknown aquatic contaminants. The second objective was to detect new aquatic contaminants of concern to public health in the Netherlands.

The highest MPA level in drinking water found in this study was 1.26 ng/L. When a daily intake of 2 L of water per person is assumed, this results in a maximum daily intake of 2.52 ng/day. This is well

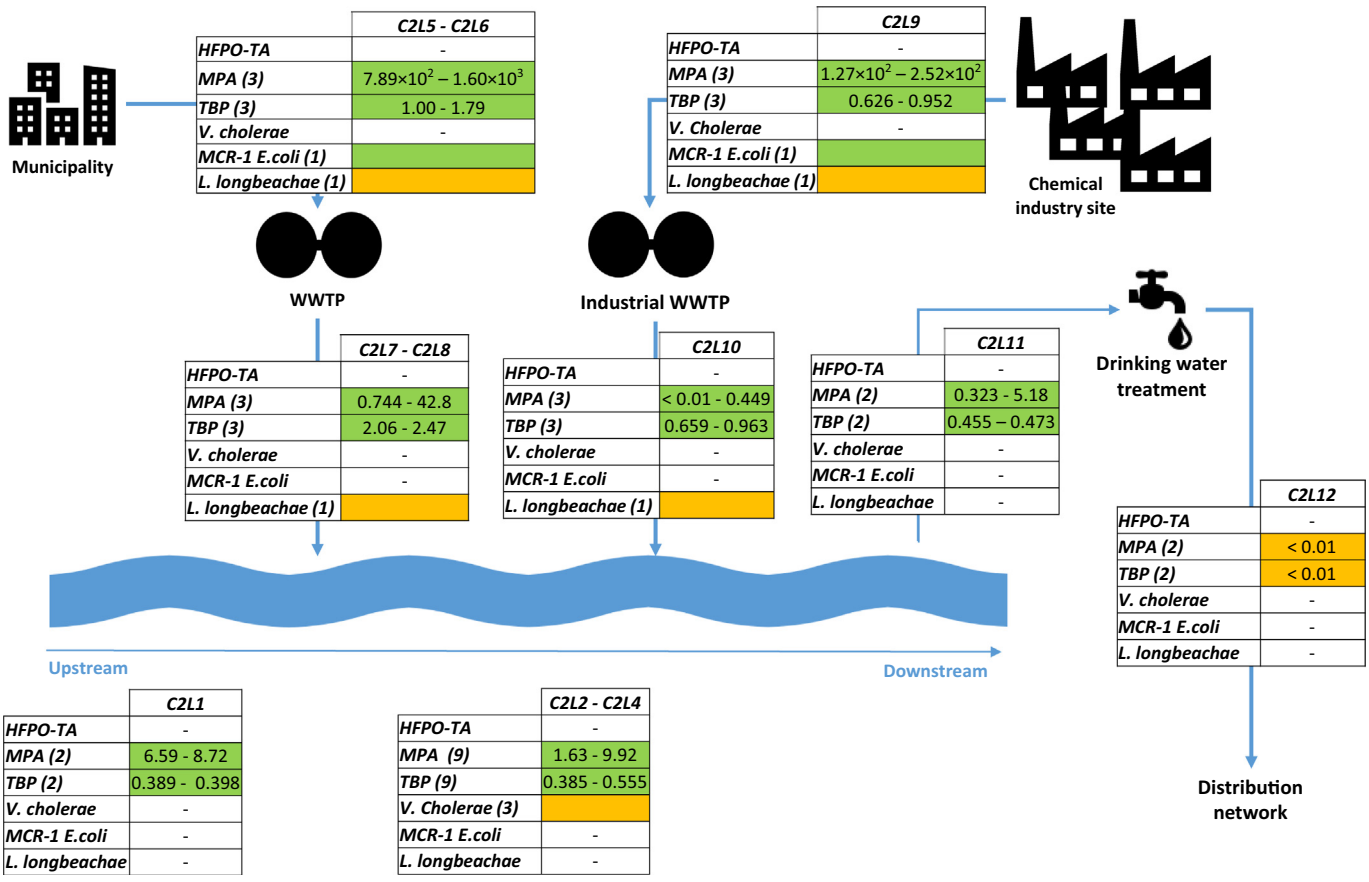

Fig. 3. Results of HFPO-TA, MPA, TBP, V. cholerae, MCR-1 *E. coli* and *Legionella longbeachae* analyses in surface water, wastewater and drinking water samples collected during Campaign 2. Green = detected, orange = not detected, - = not analysed. For chemical contaminants the detected concentration is shown in ng/L (minimum–maximum). Detection limits are, depending on the sample 1 or 10 ng/L for HFPO-TA and 0.01 ng/L for both MPA and TBP. In case of V. cholerae, MCR-1 *E. coli* and *L. longbeachae*, the concentration in the samples could not be determined based on the performed analyses. For details on sample locations see Fig. 1. The number between brackets behind each contaminant is the number of samples the contaminant is analysed in at the specific location(s). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

below the acceptable daily exposure of 75 μg per day (Straub et al., 2019).

Straub et al. (2019) provide an overview of measured environmental concentrations of MPA in surface waters in Europe and found a median measured concentration of 2 ng/L and a maximum measured concentration of 656 ng/L. The overall mean of all the studies was 22 ng/L. These data are restricted to studies conducted in Switzerland, Poland and Spain. Based on available toxicological data, a no-observed-effect concentration (NOEC) was derived of 132 ng/L (Straub et al., 2019).

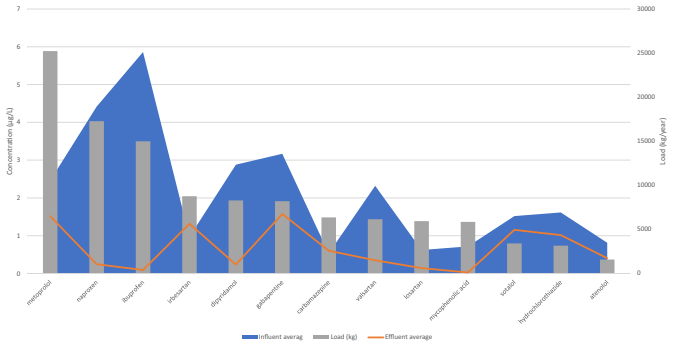

Fig. 4. Average detected concentrations of pharmaceuticals in influent and effluent of Dutch WWTPs in 1990–2019. The presented concentrations for mycophenolic acid are based on this study, whereas the concentrations shown for the other 12 pharmaceuticals are based on the Dutch Watson Database. The loads are calculated using number of DDDs prescribed in the Netherlands in 2018 multiplied by the DDD (https://www.gipdatabank.nl/databank#/g//B_01-basis/vg/L04AA06, 2019),

This study detected MPA levels in surface water between 0.24 and 8.72 ng/L, which were well below the NOEC. Therefore, based on this study, no risk to drinking water safety or the aquatic environment from MPA exposure in the Netherlands is expected.

The highest concentration of TBP was 5.47 ng/L and was detected in treated wastewater from the WWTP sampled in Campaign 1. This is comparable to the lowest concentrations detected in surface water by Brand et al. (2018). The maximum concentration of TBP detected in surface water in this study was 0.49 ng/L. Brand et al. (2018) found concentrations of up to 4700 ng/L. Based on these results, TBP is not expected to pose a risk to the production of safe drinking water in the Netherlands.

HFPO-TA was detected at 11.7 ng/L in one industrial wastewater sample, but was not detected in any of the surface water samples. Pan et al. (2018) reported trace levels of HFPO-TA upstream of the perfluorochemical company. However, these were based on a very low limit of detection (0.1 ng/L) and do not indicate any use of HFPO-

Table 4
Number of colonies suspected to be MCR-1 *E. coli* in different volumes tested of wastewater samples taken at locations C1L25, C2L9 and C2L6, - = no suspected colonies were isolated.

Type of sample tested	Location code		
	C1L25	*C2L9*	*C2L6*
1×10^{-2}	54	8	268
1×10^{-1}	-	36	>200
1 mL dilution	-	-	1
10 mL dilution	5	3	21

Table 5
Bacterial species isolated from surface water samples in the Netherlands. All species shown are *Vibrio* species, except for those indicated by *.

Volume tested (mL)	Location code					
	C1L5	C1L6	C1L10	C2L2	C2L3	C2L4
100	–	*cholerae*	*cholerae*	*plesiomonas**	–	*alginolyticus*
10	–	–	*cholerae*	–	–	–
1	*fluvialis*	–	*cholerae*	–	*aeromonas**	*alginolyticus*

TA by the fluorochemical company in the Netherlands. Also, no HFPO-TA was found in municipal wastewater. As HFPO-TA was not detected in any of the surface water samples (C1L1–C1L12), or drinking water sample (C1L28) above 1 ng/L, no other significant sources for HFPO-TA to enter the aquatic environment are expected. Based on these findings, HFPO-TA is not expected to pose a risk to the production of drinking water in the Netherlands.

Due to unforeseen circumstances, HFPO-TA was only analysed in one sample at locations C1L25 (=influent WWTP from municipality), C1L27 (=intake water for drinking water production) and C1L28 (= drinking water). However, the fact that HFPO-TA was not detected >10 ng/L in 37 surface water samples taken from eight different locations around the intake point for drinking water production, supports the result of HFPO-TA not being detected >1 ng/L in riverbank filtrated water and finished drinking water (C1L27 and C1L28). Also, since HFPO-TA was not detected >10 ng/L in five different WWTP effluent samples (C1L26), it could be concluded that the WWTP is not discharging HFPO-TA to the Beneden Merwede River. Colistin resistant bacteria were detected in all three untreated wastewater samples. To our knowledge this is the first study to report the presence of MCR-1 *E. coli* in Dutch wastewater. Jin et al. (2017) detected MCR-1 *E. coli* specifically in hospital wastewater. Here, MCR-1 *E. coli* was also detected in wastewater not influenced by hospital wastewater as well as industrial wastewater.

The presence of MCR-1 *E. coli* was confirmed by multiplex PCR. The positive control used in the PCR did not show a band at MCR-1 *E. coli*. This is probably due to the fact that the concentration used was too low. Colonies cultured from all three tested samples showed very clear bands at the MCR-1 location. Therefore, the presence of MCR-1 *E. coli* in these samples was considered conclusively shown despite the failing positive control.

The number of wastewater samples analysed for the presence of MCR-1 *E. coli* was limited (N = 3). Also, only untreated wastewater samples were tested for the presence of MCR-1 *E. coli* as no information was available on the level of MCR-1 *E. coli* present in wastewater in the Netherlands. In order to determine the magnitude of the prevalence of MCR-1 in the Dutch population, further quantification of MCR-1 *E. coli* samples, surface water and drinking water is needed.

The novel variant of *V. cholerae* O1 E1 Tor first reported by Bhattacharya et al. (2016) was not detected in the analysed samples. *V. cholerae non-O1/O139* was isolated from samples taken at locations C1L6 and C1L10. The salinity at these locations in July 2019 was estimated to be between 0.006 and 0.009% (van Winden, 2019). *Vibrio* species are rarely detected in freshwater. Schets et al. (2011) detected *V. cholerae non-O1/O139* at a location in the North-Western part of the Netherlands at the Lake Ijsselmeer, near Enkhuizen, with similar salinity ranges (0.007 to 0.015%).

L. longbeachae was not isolated from the collected industrial and municipal wastewater samples (both treated and untreated). However, for practical reasons, only a limited number of wastewater samples were analysed. Caicedo et al. (2019) reviewed the available literature on *Legionella* species in industrial and municipal wastewater and pointed out several disadvantages of the, although broadly applied, culture method. Reported disadvantages that might have influenced the results in this study are: (1) sample pre-treatment which can temper the cultivability of *Legionella* and (2) the optimisation of the method for *L. pneumophila* SG1 which might make it less suitable for *L. longbeachae*. A suggestion for future research would be to develop the optimal culturing conditions (nutrient composition and amount and culture temperature) for *Legionella longbeachae* in wastewater. Then the analysis of more Dutch industrial and municipal wastewater samples for presence of *Legionella longbeachae* would be valuable.

5. Recommendations and conclusions

In Hartmann et al. (2019), we suggested health and environmental agencies, water authorities or drinking water companies to run the literature mining methodology twice a year in order to keep the number of records manageable. This would enable drinking water companies and water authorities to use the resulting list of contaminants (such as Appendix A) when designing risk-based monitoring campaigns (van den Berg et al., 2019). A few suggestions can be made for effectively directing a sampling campaign based on early signals of new aquatic contaminants in scientific literature. First, several information sources are available to find out which contaminants reported in the scientific literature could be of potential concern in a specific river basin or drinking water production chain. These information sources include: REACH registrations, patents and discharge permits. Also, the paper reporting the contaminant for the first time might already give an indication of the circumstances in which the contaminant might be of concern (e.g. Thornley et al., 2017).

As information on potential sources of chemicals, in particular, is often scattered, the involvement of key stakeholders such as drinking water companies, water authorities and industry is crucial. Drinking water companies and water authorities can be contacted to find out whether (non-target) monitoring data is available or whether data needs to be collected. Also, the early inclusion of industry as a potential source of contamination would be useful to investigate whether they

Table 6
Results of *Legionella* analysis in four wastewater samples, both untreated (C2L6 and C2L9) and treated (C2L8 and C2L10).

Location code	Type of sample	Nr. of colonies tested	Nr. of colonies suspected			Nr. of colonies confirmed
			Day 3	Day 7	Day 10	
C2L6	Influent municipal WWTP	16	0	0	1	0
C2L8	Effluent municipal WWTP	13	0	0	0	0
C2L9	Influent industrial WWTP	9	0	0	0	0
C2L10	Effluent industrial WWTP	9	0	0	1	0

are aware of (the level of) potential emission of the contaminant. Including as many stakeholders as possible increases the impact of the signalling process as more stakeholders will have knowledge about the contaminant.

In this study, by screening scientific literature, six example contaminants were selected from screening the scientific literature as potential contaminants of concern to drinking water in the Netherlands. The chemical contaminants, mycophenolic acid, tetrabutylphosphonium compounds and HFPO-TA, were detected in low concentrations in wastewater and surface water and were thus not expected to pose a risk to Dutch drinking water. Colistin resistant *Escherichia coli* was detected for the first time in Dutch wastewater not influenced by hospital wastewater indicating the circulation of bacteria resistant to this last-resort antibiotic in the general Dutch population. Four out of six contaminants were thus detected in surface or wastewater samples, which showed that screening the scientific literature to direct sampling campaigns for both microbial and chemical contaminants is effective for early warning purposes.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.140546.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

First, we would like to give our special thanks to everyone who made the collection of samples for the purpose of this study possible: Soesila Ganeshi, Peter van As and colleagues from Rijkswaterstaat, Rosa Sjerps and colleagues from the drinking water company Oasen, Gerdien de Kloe and colleagues from Aqualab Zuid, Ralph Bröcheler, Pim Kruijen and colleagues from Waterschapsbedrijf Limburg, Peter van Diepenbeek from the drinking water company WML and Carlijn van der Sluis. Furthermore, we wish to recognise the invaluable assistance given by Paul Schwillens, Sharona de Rijk, Willemijn Lodder, Fabio Martins Gueth, Harold van den Berg and Hetty Blaak during the microbial and chemical analyses of the water samples. Finally, we would like to thank Marit de Vries and Martina Paulin for assisting in the development of Fig. 1 and Bastiaan Venhuis for his assistance in indicating mycophenolic acid as a yet unknown aquatic contaminant of concern in the Netherlands. This research was funded by the RIVM Strategic Research Project PS DRINK (S/121014).

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