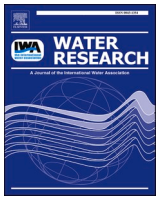
Water Research 238 (2023) 119903

Contents lists available at ScienceDirect

Water Research

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



Delivering on sustainable development goals in wastewater reuse for agriculture: Initial prioritization of emerging pollutants in the Tula Valley, Mexico

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A B S T R A C T

Wastewater reuse for agricultural irrigation is a widespread beneficial practice, in line with the sustainable development goals. However, contaminants of emerging concern (CECs) present in wastewater, such as pharmaceuticals, pose an environmental risk. The Tula Valley in Mexico is one of the world's largest agricultural areas reusing wastewater for agriculture. However, no untargeted CEC monitoring has been undertaken there, limiting the information available to prioritise local environmental risk assessment. Furthermore, CEC environmental presence in the Global South remains understudied, compared to the Global North. There is a risk that current research efforts focus on CECs predominantly found in the Global North, leading to strategies that may not be appropriate for the Global South where the pollution profile may be different. To address these knowledge gaps, a sampling campaign at five key sites in the Tula Valley was undertaken and samples analysed using multi-residue targeted and untargeted liquid chromatography mass spectrometry methods. Using the targeted data, ten CECs were found to be of environmental risk for at least one sampling site: 4-tert-octylphenol, acetaminophen, bezafibrate, diclofenac, erythromycin, levonorgestrel, simvastatin, sulfamethoxazole, trimethoprim and tramadol as well as total estrogenicity (combination of three steroid hormones). Six of these have not been previously quantified in the Tula Valley. Over one hundred pollutants never previously measured in the area were identified through untargeted analysis supported by library spectrum match. Examples include diclofenac and carbamazepine metabolites and area-specific pollutants such as the herbicide fomesafen. This research contributes to characterising the presence of CECs in the Global South, as well as providing site-specific data for the Tula Valley.

1. Introduction

Wastewater reuse for agricultural irrigation has multiple benefits (Drechsel et al., 2022), especially in the face of changing weather patterns (Holt-Giménez et al., 2012), increasing food demand (UN-WWAP, 2015) and water scarcity (World Economic Forum, 2017). Wastewater is available all year round (Jovanovic, 2008) and contains valuable nutrients (Jimenez-Cisneros, 2006; Helmecke et al., 2020). Adequate wastewater reuse closely aligns with several United Nations Sustainable Development Goals (SDGs), in particular: Zero Hunger, Clean Water and Sanitation, Sustainable Cities and Communities, Responsible Consumption and Production, Life Below Water and Life on Land. Despite the benefits and prominence of the practice (Thebo et al., 2017), environmental and health risks are posed by pathogens, heavy metals and contaminants of emerging concern (CECs) (Drechsel et al., 2022). These latter include pharmaceuticals, illegal drugs, pesticides, etc., and are known to possess environmental toxicity (Carter et al., 2019) as well as promote antimicrobial resistance (Feng et al., 2021). Recent global studies show that 80% of wastewater is not treated adequately and is used to irrigate 11% of croplands, with higher proportions used for irrigation in the Global South, particularly in China, India, Pakistan, Mexico and Iran (Thebo et al., 2017; Kookana et al., 2020; Jones et al., 2021). Despite higher wastewater reuse for irrigation in the Global South than North, research regarding chemical pollution from this practice remains more prominent in the Global North (Madikizela et al., 2017; Carter et al., 2019). To align to the United Nations SDG 17: Partnerships for the Goals, and to reflect the fact that pollution does not respect boarders, it is pivotal that the chemical pollution knowledge gap of the Global South is addressed. This geographical knowledge gap has been recognised for more than a decade (Boxall et al., 2012), and to this

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https://doi.org/10.1016/j.watres.2023.119903
Received 22 November 2022; Received in revised form 18 March 2023; Accepted 20 March 2023
Available online 24 March 2023

date global chemical pollution prioritizing efforts are carried out with datasets lacking crucial information from regions like Mexico, Central America and Sub-saharan Africa (Wang et al., 2022; Yang et al., 2022). Despite efforts to bridge the knowledge gap (Madikizela et al., 2017; Fekadu et al., 2019; Peña-Guzmán et al., 2019; Khan et al., 2020), the Global North / South discrepancy remains. It is a complex issue to address due to differences in economic resources available for scientific research in the Global North and South, as well as differing scientific priorities (Reidpath and Allotey, 2019). For instance, should analysing CECs to inform on risk for wastewater reuse take priority over delivering equitable sanitation? Are these two examples, which each contribute to several SDGs in conflict or complementary to one other?

The occurrence of CECs vary geographically in pollutant type and concentration, depending on factors such as usage, environmental conditions and wastewater treatment practices (Tran et al., 2018). Therefore, it is important to understand the presence and environmental fate of CEC in each area to develop practices and technologies that work locally. The Tula Valley, in Mexico, is one of the world's largest areas where untreated wastewater has been used for irrigation for over 100 years (Chávez-Mejía et al., 2019). In the past 10 years, the construction and commissioning of the Atotonilco wastewater treatment plant (WWTP) has taken place with the aim of reducing some of the risks associated with wastewater reuse while maintaining its benefits (e.g., high nutrient content). This has been achieved by only using biological treatment on half of the influent flowrate, which the farmers of the area value (Mexican Ministry of the Environment and Natural Resources, 2007). Some areas of the Tula Valley are now irrigated using treated water from the Atotonilco WWTP, however other areas are irrigated using untreated wastewater (Chávez-Mejía et al., 2019). A recent review highlighted the need for further environmental CEC monitoring in areas where wastewater enters the environment in Mexico (Vázquez-Tapia et al., 2022).

To date, only targeted analysis CEC monitoring has been undertaken in the Tula Valley (Gibson et al., 2010; Félix–Cañedo, Duran-Alvarez and Jiménez–Cisneros, 2013; Lesser et al., 2018; Chávez-Mejía et al., 2019; Duran-Alvarez et al., 2021; Rodríguez-varela et al., 2021; Vázquez-Tapia et al., 2022). Targeted studies permit accurate quantification of specific and known CECs, allowing for environmental risk quotient calculations (Gadd et al., 2010; Ma and Yates, 2017; Phonsiri et al., 2019). Some previous studies have reported risk quotients based on a reduced number of sampling events as an exercise for prioritising contaminants in the aquatic environment (Aznar-Alemany et al., 2018; Aminot et al., 2019). However, targeted studies often do not include metabolites and transformation products unless these have already been identified and thus subsequently included in the targeted analysis (Di Carro et al., 2018; Richardson and Ternes, 2018; Wielens Becker et al., 2020). Pharmaceuticals and natural hormones are often excreted as conjugated metabolites, such as glucuronides or sulphates, which can be deconjugated in wastewater treatment plants or in the environment (Gomes et al., 2009). Similarly, parent pollutants may be transformed to other compounds in the wastewater treatment process, come of them more bioactive than the parent compound (Rodriguez-Narvaez et al., 2017). Furthermore, data on toxicity from transformation products and metabolites is scarce, and these pollutants may be found at higher concentrations than the parent pollutant (Carter et al., 2019). Targeted analysis, especially in areas with limited knowledge on presence and transformation is likely to miss transformation products, metabolites, illegal drugs and other unknown pollutants either because they are not (yet) known or due to a lack of analytical reference standards (Di Carro et al., 2018; Richardson and Ternes, 2018; Alygizakis et al., 2019).

Untargeted analysis, using liquid chromatography coupled to high resolution tandem mass spectrometry (LC—HRMS/MS) allows the identification of a wide range of chemicals for which standards may not be available (Richardson and Ternes, 2018). There is a need for an untargeted study in the Tula Valley to identify, for the first time, what unknown CECs are present. This will better align the Global South to the North; and make possible the utilisation of site-specific knowledge to more appropriately inform environmental policy, develop wastewater treatment technologies, and implement practices to minimise chemical pollution risk, while still reaping the benefits of wastewater reuse. Therefore the objectives of this study were to analyse Tula Valley water samples using a multi-residue targeted and an untargeted method for initial prioritization based on risk quotients obtained from a single time point and identification of unknown pollutants which may be of concern in the area.

2. Experimental

2.1. Site description and sampling campaign

The Tula Valley (85, 000 ha) lies between latitudes 19°54′ and 20°30′ North and longitudes 99°22′ and 98°56′ West. The mean annual temperature is 16.7 °C. Rainfall ranges from 435 to 618 mm and falls between May and October. The 1663 million m^3 (Mm^3) per year of wastewater generated in the Metropolitan Zone of Mexico City is transported 80 km to the Tula Valley through the subterranean Central Emitter, carrying an average of 1255.8 $Mm^3\ yr^{-1}$ and the open-air Gran Canal transporting an average of 407.2 $Mm^3\ yr^{-1}$ (Chamizo-Checa et al., 2020). In 2015, the Atotonilco WWTP was commissioned to remove pathogens but to leave most of the nutrients, as well as maintain the flowrates used for irrigation (CONAGUA, 2007). This plant aims to treat 60% of the Central Emitter flow. As shown in Fig. 1, untreated wastewater joins the Tula River, in the west part of Tula Valey, while the influent of the WWTP is divided into two streams. One stream is treated by coagulation-flocculation-sedimentation, followed by chlorination. The other is biologically treated using conventional activated sludge, then disinfection. The combined effluent enters the Tula River, mixing with untreated wastewater. The effluents mixture and untreated wastewater is conducted to the irrigation area by gravity (Chávez-Mejía et al., 2019). On the other hand, the wastewater from the Grand Canal, to the east of Tula Valley, remains untreated and is directly re-utilised in croplands (Rodríguez-varela et al., 2021).

Sampling was undertaken during the dry season, therefore CEC presence is presumably at its highest due to minimal dilution (Lesser et al., 2018). The five sampling locations are marked in Fig. 1: untreated and treated (mixed effluent from both treatment streams) wastewater from Atotonilco WWTP, the Tlamaco canal, which transports untreated wastewater to croplands, a mixture of treated and untreated wastewater from the Endho Dam and the Cerro Colorado spring, which is water that over decades has percolated through the soil and recharged the local aquifer (Chávez-Mejía et al., 2019). Grab samples were collected in amber glass bottles on the 30th of March 2019. The sampling depth was 20 cm below surface, with sampling from as all points mid-way between the edges, taken via either bridges or from a boat. Throughout the sampling day, samples were kept at 4.0 ± 0.5 °C, then preserved in the fridge at 4.0 ± 0.5 °C (Vanderford et al., 2011; Shimko et al., 2023). As an additional precaution, 1 mL of methanol was added to each 1 L bottle on arrival to the laboratory. Samples were kept refrigerated at 4 °C until they were passed through solid-phase extraction cartridges, 48 h after sampling.

2.2. Solid phase extraction

All samples were centrifuged at 10,500 rpm for 8 min, except the Cerro Colorado spring water. Endho dam water was additionally filtered using 8 μm particle retention ashless filters (Whatman, UK). The solid phase extraction and liquid chromatography methods have been validated for a multi-residue HPLC-MS/MS targeted analysis and are reported elsewhere (Garduno-Jimenez et al., In review). Briefly, HLB solid phase extraction cartridges (500 mg, 6 cc) from Waters (Elstree, UK) were conditioned using 5 mL of methanol followed by 5 mL of tri-distilled water, 250 mL of the aqueous sample were loaded at 5 mL

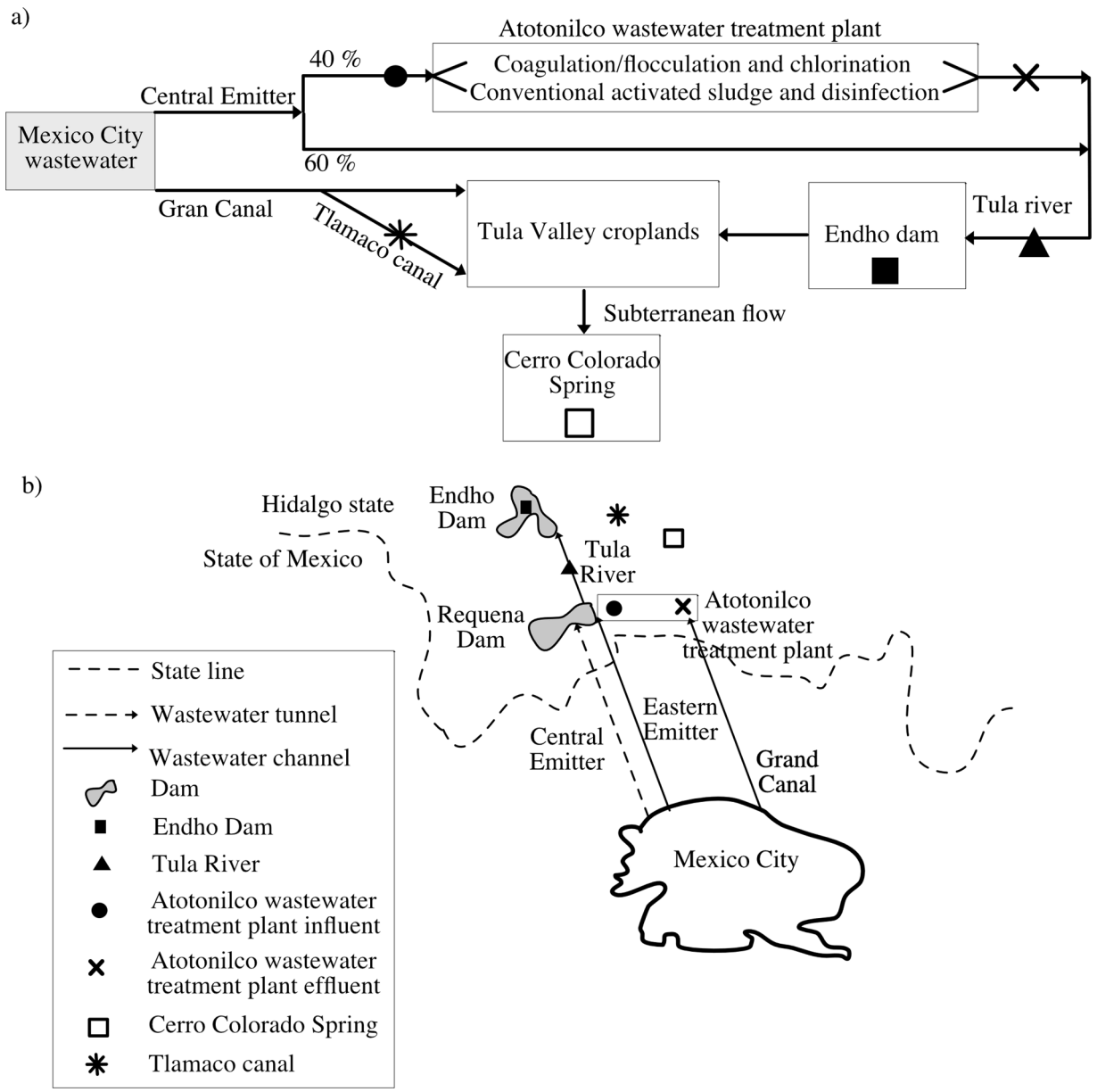

Fig. 1. a) Schematic Tula Valley map with sampling locations marked. b) Tula Valley map adapted from (Chávez-Mejía et al., 2019) Dot: Atotonilco wastewater treatment plant (WWTP) influent, Cross: Atotonilco WWTP effluent, Star: Tlamaco canal sampling point, Filled square: Endho dam sampling point, Triangle: Tula River sampling point, Empty square; Cerro Colorado spring sampling point.

min^{-1}. Cartridges were dried under vacuum. Methanol (8 mL) was used for elution with no vacuum and when dripping stopped vacuum was applied for a few seconds to collect all the eluate. Analytical duplicates from each sampling location were passed through separate SPE cartridges and analysed in both targeted and untargeted modes using liquid chromatography tandem mass spectrometry.

2.3. Chromatographic separation

Chromatographic separation was similar for both targeted and untargeted mass spectrometry analysis. Samples were analysed first in acidic and then in basic chromatography using a C18 Gemini Phenomenex (100 × 3 mm particle diameter 2 μm) column. The column was kept at 50 °C. For the acidic chromatography, mobile phase A was aqueous 0.1% formic acid and B was acetonitrile, with a starting composition of 95% A. The gradient ran from 95 to 5% A over 6 min, and was maintained for 1.6 min. Initial composition was re-established over 0.8 min and kept for 1.8 min for re-equilibration, with a total duration of 10 min. For the basic chromatography, mobile phase A was aqueous 10 mM ammonium bicarbonate in water and B was acetonitrile. The starting composition was 85% A and it was ramped to 5% A over 6 min; then, it was kept at 5% A for 1.4 min and ramped back to initial conditions over 1.6 min. Lastly, it was kept at initial (85% A) composition for 1.4 min, with a total run time of 10 min. The injection volume was 10 μL and the flow rate 0.3 mL min^{-1} for both chromatographic modes.

2.4. Targeted analysis

For targeted analysis 32 chemicals were selected (Table S2) based on previously measured concentrations which have been reported to be environmentally toxic, their inclusion in priority lists, such as the Second EU's Watch list (Loos et al., 2018) or the top 10 of most commonly reported pharmaceuticals in wastewaters (Wilkinson et al., 2017). However, this data is mainly from the Global North, which is why the

complementary untargeted analysis is so important. The analysis was carried out using a triple quadrupole (Agilent Scientific 1290 Series UPLC-MS/MS). For samples analysed using the acidic chromatography, positive ionisation mode was used with a capillary voltage of 5000 V, while for the basic chromatography ionisation was done in negative mode with a capillary voltage of 3000 V. The source temperature was 350 and 200 °C, and the nebuliser pressure was 50 and 45 psi for the positive and negative ionisation modes, respectively. The drying gas flow was 7 and 13 L min^{-1} for the positive and negative ionisation modes, respectively. Sheath gas flow was 12 L min^{-1} for both modes. All analytes were analysed in MRM mode, with a quantifier and qualifier product ion (details in Table S1). All runs were carried out with twelve-point calibration curves (0.5 – 300 ng mL^{-1}) at the start and end, and quality controls (QCs) consisting of the seventh and ninth calibration levels every five samples to ensure instrumental stability. SPE recoveries are reported in (Garduno-Jimenez et al., In review). Method limits of detection, and linearity can be found in Table S2.

2.5. Untargeted analysis

Untargeted analysis was carried out using a Q-Exactive Plus mass spectrometer (MS) equipped with Dionex U3000 UHPLC system (Thermo Fisher Scientific, Hemel Hempstead, UK). The untargeted mass spectrometry method as well as the computation workflow development and validation are reported elsewhere (Garduno-Jimenez et al., In review). Briefly, the mass spectrometry method was the same for both chromatographic methods and was operated in simultaneous ESI+ and ESI- acquisition modes. The spray voltage was 3.5 kV (ESI+) and 3.5 kV (ESI-), and the S lens RF level was 50 for both modes. The sheath, auxiliary and sweep gas flow rates were 45, 10 and 2.25 (arbitrary units), respectively, for both modes. Capillary and heater temperatures were maintained at 375 and 350 °C, respectively. Data was acquired for the LC—HRMS profiling with a resolution of 70,000 from *m/z* 70 to 1050. In addition, Top 10 data dependant MS/MS (ddMS/MS) was performed at a resolution of 17,500 and a stepped normalised collision energy (NCE) of 20, 30 and 40. A thirteen-point calibration curve (50–1000 ng mL^{-1}) was run at the start and end of samples, along with quality controls consisting of the seventh and ninth calibration levels every five samples to ensure signal stability.

Compound Discoverer 3.1SP1 (ThermoFisher Scientific, Hemel Hempstead, UK) was used for CEC identification with a workflow developed and validated previously (Garduno-Jimenez et al., In review). Briefly, spectra were selected in the range of 100 < Da < 5000, retention times were aligned across the sample sequence with ± 2 min tolerance. Compounds were identified allowing for methanol, potassium and sodium adducts with a mass tolerance of 5 ppm, a signal to noise ratio of 3 and a minimum peak intensity of 10,000 arbitrary units. Compounds identified were searched in the mzCloud based on the mass spectrum obtained. If it was not found in this database, the Mass List Search and Chem Spider were then searched. The unknown pollutants identified were screened with the following criteria, based on the method validated in (Garduno-Jimenez et al., In review): i) present in both analytical duplicates and not in blanks; ii) retention time ± 20 s across the sample sequence; and, iii) minimum 80% *mz*Cloud match score with matching parent ion and at least one matching product ion (± 5 ppm mass accuracy to the database).

Pollutants were identified with level 2 confidence, meaning their presence was confirmed by comparison of the mass spectrum obtained to that of the mzCloud database, which is considered the maximum confidence possible without a chemical reference standard (Sumner et al., 2007).

2.6. Risk quotient calculations

Risk quotients (RQs) indicate whether a pollutant concentration is above the minimum found to harm a representative species from a specific trophic level (Peake et al., 2016a). RQs were calculated as the ratio between the concentrations measured at each sampling point and the predicted no effect concentration (PNEC) (Phonsiri et al., 2019). PNECs were obtained from literature (Table S3), with the lowest being used. For the antibiotics, the minimum inhibitory concentration (MIC), the lowest concentration of an antibiotic preventing a specific organism growth under in vitro conditions, was also evaluated (AMR Industry Alliance, 2018) (Table S3). Oestrogenic activity risks to aquatic organisms were calculated using the total oestrogenic equivalent (EEQ_{total}) (Gadd et al., 2010; Ma et al., 2016) according to Eq. (1):

$$EEQ_{total} = \sum EEQ_i = \sum (C_i \times EEF_i) \quad (1)$$

Where EEQ_i = oestrogenic equivalent quotient of compound *i* (these are reported in the Supporting Information and are valued from the literature); C_i = concentration measured; EEF_i = oestrogenic equivalent factor which is defined as the ratio of the observed half-maximal (EC_{50}) oestrogenic activity of oestradiol for each pollutant (Gadd et al., 2010; Ma et al., 2016).

3. Results and discussion

3.1. Prioritising pollutants based on environmental risk or estrogenicity

Acetaminophen was found at the highest concentration, in a range of 2.1 to 3.0 μg L^{-1} (Table 1), within previously reported ranges in the Tula Valley and Latin America (Lesser et al., 2018; Peña-Guzmán et al., 2019). The high acetaminophen concentrations translated to RQs > 1, similar to previous reports in Mexico (Rivera-Jaimes et al., 2018), other Latin American countries (Valdez-Carrillo et al., 2020), and African countries (Fekadu et al., 2019). Therefore, existing data, such as disposal and consumption data may be used as a starting point for pollutant prioritisation. However, a high concentration does not necessarily translate to environmental risk, as this depends on pollutant bioactivity and local species sensitivity. Identifying pollutants with an RQ >1 facilitates prioritisation for further environmental attention from the vast number of pollutants present in natural waters. However, it is not possible to find PNECs for Mexican species so RQs were calculated using those mostly focusing on European species. One recommendation would be to develop PNECs for Mexican and other Global South aquatic species for the most toxic and prevalent pollutants. Estrogenicity of endocrine disruptive pollutants was also calculated, where oestrogenic pollutants have been shown to affect fish reproductive health (Arlos et al., 2018). Estrogenicity is a key pollution parameter which has driven environmental policy in Europe (Alina Dinu, 2019) though has yet to be translated to the Global South.

After acetaminophen, pollutants with the highest concentrations (in the range of thousands of ng L^{-1}) were erythromycin, naproxen, sulfamethoxazole, acetyl-sulfamethoxazole, bezafibrate, diclofenac, 4-tert-ocylphenol and carbamazepine. All these pollutants, except for carbamazepine, were found to have an RQ > 1 or to contribute to local estrogenicity. In total, ten pollutants presented RQs above 1 for at least one sampling site: 4-tert-octylphenol, acetaminophen, bezafibrate, diclofenac, erythromycin, levonorgestrel, simvastatin, sulfamethoxazole, trimethoprim and tramadol as well as total estrogenicity (combination of estrone-3-sulfate, estriol and estriol-3-sulfate) (Fig. 2).

Sulfamethoxazole concentrations (74.8 – 4954.2 ng L^{-1}) were within previous measurements in Tula Valley (Lesser et al., 2018). Sulfamethoxazole and trimethoprim have been found to have an RQ > 1 in surface water in central Mexico (Rivera-Jaimes et al., 2018), Latin America (Valdez-Carrillo et al., 2020), Africa (Fekadu et al., 2019) and South Asia (Khan et al., 2020), making sulfamethoxazole, acetaminophen and trimethoprim pollutants of concern in Global South.

Tramadol is an opioid not been previously detected in surface waters from Latin American (Peña-Guzmán et al., 2019; Valdez-Carrillo et al., 2020) or African countries (Fekadu et al., 2019) and was only reported

Table 1
Persistent organic pollutant measured in the Tula Valley, Mexico. BLD is below limit of detection, meaning a peak was found but the signal to noise ratio was below 3. ND is Not detected, meaning no peak was detected.

Pollutant	CAS	Concentrations measured at different locations in the Tula Valley (ng L^{-1})				
		Cerro Colorado spring	Atotonilco wastewater treatment plant effluent (treated wastewater)	Endho Dam	Tula River	Tlamaco Canal
4-tert-octylphenol	140–66–9	BLD	ND	954.0	1041.8	695.8
Acetaminophen	103–90–2	ND	25,808.4	22,934.8	20,960.9	29,912.6
Acetyl-sulfamethoxazole	21,312–10–7	ND	1282.1	703.6	2166.6	1860.2
Atenolol	29,122–68–7	ND	97.1	25.7	47.3	67.7
Bezafibrate	41,859–67–0	3.9	1610.1	933.1	1202.5	1419.2
Carbamazepine	298–46–4	36.5	407.1	2568.0	940.6	1279.7
Clofibric acid	882–09–7	ND	ND	ND	ND	ND
Codeine	76–57–3	ND	ND	ND	ND	ND
Diclofenac	15,307–86–5	BLD	4101.6	297.9	949.6	2387.9
Estrone (E1)	53–16–7	ND	ND	ND	ND	ND
Estrone-3-sulfate (E1–3S)	1240–04–6	ND	7.7	ND	5.0	4.5
Estriol (E3)	50–27–1	ND	453.3	170.7	427.8	454.9
Estriol-3-sulfate (E3–3S)	5150–64–1	ND	385.7	ND	ND	ND
Erythromycin	114–07–8	ND	206.6	9199.4	5506.9	9059.8
Gemfibrozil	25,812–30–0	ND	369.5	150.6	131.8	235.5
Ketoprofen	22,071–15–4	ND	202.8	239.9	124.8	232.0
Levonorgestrel	797–63–7	41.8	88.3	ND	61.2	56.4
Metoprolol	37,350–58–6	ND	739.3	285.8	333.8	625.9
Morphine	57–27–2	ND	ND	ND	ND	ND
Naproxen	22,204–53–1	ND	1548.9	2852.4	3544.5	7316.6
Oxytetracycline	2058–46–0	9.4	228.1	BLD	BLD	337.9
Paroxetine	61,869–08–7	ND	ND	ND	BLD	BLD
Phenazone	60–80–0	BLD	28.6	26.8	15.5	40.1
Propranolol	525–66–6	ND	13.4	13.4	16.7	26.0
Salicylic acid	69–72–7	BLD	BLD	BLD	6.5	264.4
Simvastatin	79,902–63–9	ND	14.2	ND	ND	ND
Sulfadiazine	68–35–9	ND	561.2	790.3	476.3	976.7
Sulfamethoxazole	723–46–6	74.8	3462.1	4321.7	3344.5	4954.2
Sulfapyridine	144–83–2	ND	163.5	78.5	99.7	260.0
Tramadol	27,203–92–5	BLD	278.6	548.2	292.2	772.1
Trimethoprim	738–70–5	ND	641.8	62.1	253.0	476.0

in the Global South to date in Sri Lanka surface waters at levels < 5 ng L^{-1} (Fekadu et al., 2019), resulting in an RQ < 1 for that case. Conversely, in this study a RQ > 1 was observed for all sampling sites, highlighting the importance of local assessments.

Diclofenac, also identified with RQ > 1 for all sampling points (Fig. 2), has been measured at concentrations above PNECs in surface waters of Pakistan and India (Khan et al., 2020), but not identified as of risk in African countries (Fekadu et al., 2019). Levonorgestrel is very toxic even at concentrations below 1 ng L^{-1} (Besse and Garric, 2009), concentrations measured in this study (Table 1) were on the lower end of the range reported in Latin American surface waters (Peña-Guzmán et al., 2019). Levonorgestrel has been found at concentrations above PNEC in surface waters in other Latin American countries (Peña-Guzmán et al., 2019) but was not identified as of risk in Africa (Fekadu et al., 2019), or measured in South Asian countries (Khan et al., 2020).

Estrogenicity is of concern for all sampling points, except for the Cerro Colorado spring, (Fig. 2). It would likely be higher if it has been possible to measure ethinyl oestradiol and estrone, but their concentrations were below the limit of detection. Ethinyl oestradiol and estrone have been previously quantified in Tula Valley waters from 32.3 to 166 ng L^{-1} (Lesser et al., 2018). Estriol, and its sulfate conjugate have not been previously measured in the Tula Valley and given their presence contributes to local estrogenicity, these pollutants merit further study. Furthermore, untargeted analysis results demonstrated that other pollutants may be adding to local estrogenicity, such as 6-methylquinoline and, 4,4′-dihydroxydiphenylsulfone (Table 2 and Table 3). Table 2 presents pollutants widely detected in the global aquatic environment, and also detected in Global South regions, but never detected in the Tula Valley. Table 3 presents pollutants not widely or never detected in Global South regions. The steroid hormones, estrone, oestradiol and estriol have all been identified of concern in African countries (Fekadu et al., 2019), but not in South Asian countries (Khan et al., 2020) and the sulfate conjugates have not been measured in these regions, meaning the risk from steroid hormones may be higher than previously estimated in the Global South.

Contaminants of emerging concern in the environment are drivers of antibiotic resistance development, a current global health emergency (Martin et al., 2018). Erythromycin MIC RQs were above one for all except treated wastewater effluent from the Atotonilco WWTP (Fig. 2). Erythromycin has not been found as a pollutant of concern in terms of environmental toxicity in other Latin American countries (Valdez-Carrillo et al., 2020), or in African countries (Fekadu et al., 2019).

Pollutants which are not of immediate concern for the Tula Valley are the opioids codeine and morphine. These were not detected in any of the samples and neither have been monitored in the Tula Valley previously. This is likely because these opioids are not produced in Mexico and it is difficult to obtain them as medicines (Knaul, 2021).

Naproxen carbamazepine, ibuprofen, ciprofloxacin and triclosan were identified to have RQs >1 in Africa (Fekadu et al., 2019), whereas they were not in the present study. Carbamazepine has also been reported to present RQs > 1 in Latin America (Valdez-Carrillo et al., 2020), the fact it was not found to be of concern in the present study may be due to a single time point sampling and emphasize the need for regular sampling campaigns. Similarities across the Global South highlight potential areas for collaboration to remediate the presence of pollutants such as acetaminophen, sulfamethoxazole, trimethoprim, and steroid hormones. However, it also highlights the importance of local environmental studies because even across regions in Mexico there are differences in the pollutants with RQs > 1, which should form the basis of immediate research for each area.

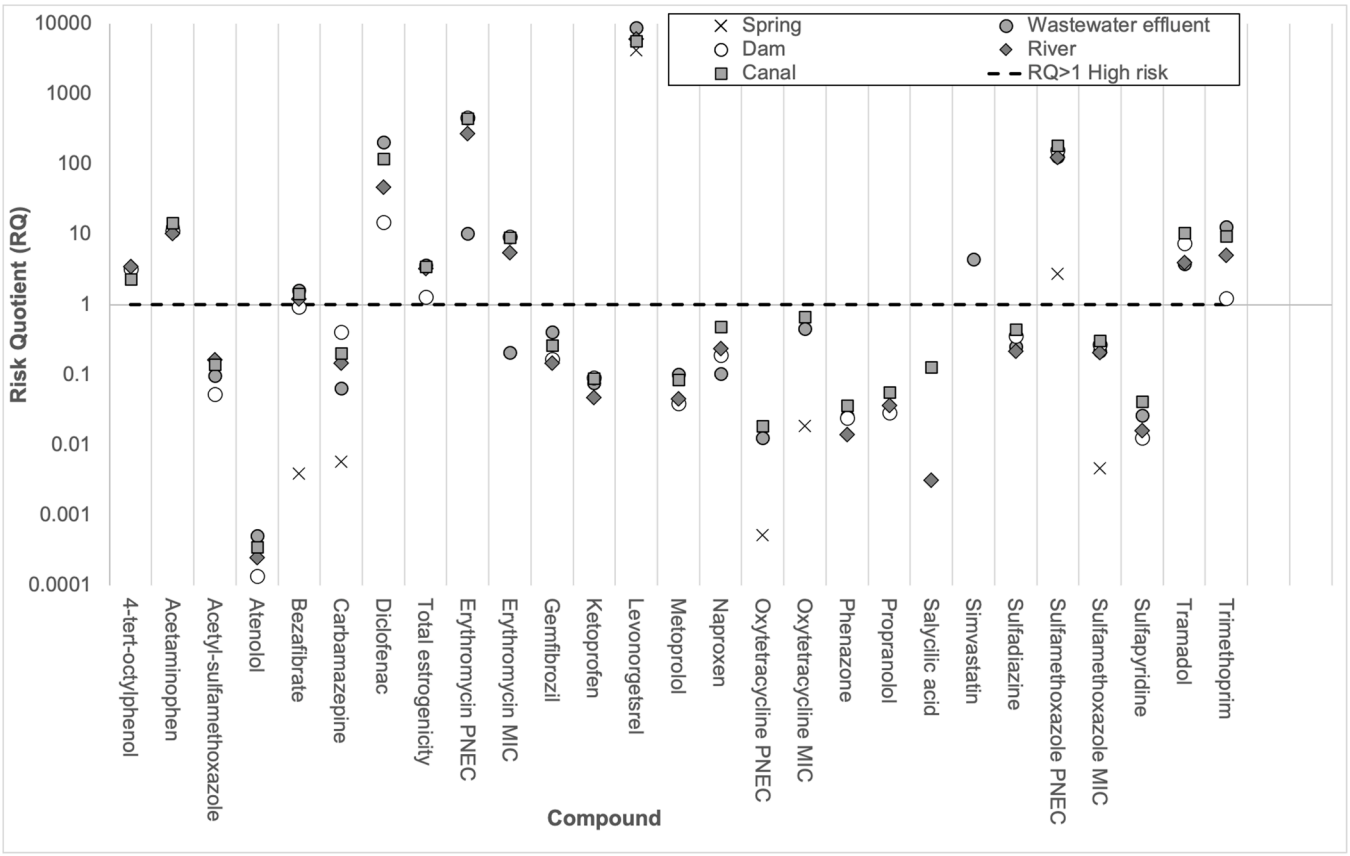

Fig. 2. Risk quotients (RQs) for pollutants measured in the Tula Valley, Mexico Total estrogenicity accounts for estrone-3-sulfate (E1–3S), estriol (E3) and estriol-3-sulfate (E3–3S). MIC stands for Minimum inhibitory concentration and PNEC stands for predicted no effect concentration.

3.2. Prioritising pollutants based on those found in Cerro Colorado spring water

Analysis of the Cerro Colorado spring water indicated persistent and widespread pollution presence in the Tula Valley. This is due to the water cycle, where for the pollutant to be present in the groundwater feeding the spring, it would be present in irrigation canals, surface runoff and/or groundwater percolation. Five pollutants were quantified in Cerro Colorado spring water, namely levonorgestrel, oxytetracycline, sulfamethoxazole, bezafibrate and carbamazepine (Table 1). The physical-chemical properties of CECs can be used to predict and understand their environmental distribution and prevalence. For example, levonorgestrel has demonstrated a weak adsorption onto soil particles and thus can be transport to the aquifer under rainfall or irrigation events (Yang et al., 2020), which is likely why it can be found in Cerro Colorado spring, after entering the groundwater. On the other hand, highly polar molecules, like benzafibrate and oxytetracycline, can readily be transported dissolved in water toward the aquifer, while less polar but persistent molecule carbamazepine can slowly migrate through the soil layers to achieve aquifer after several irrigation or rain events.

Conventional untargeted analysis provides no quantification, only detection, however recent efforts have made it possible to obtain semi-quantified results from this analysis (Aalizadeh et al., 2022). When semi-quantification is not used it is possible to compare detection signals across sampling sites. Therefore, for the untargeted data prioritising based on CECs found in Cerro Colorado spring water is particularly useful as it is not possible to calculate RQs. Twenty-nine pollutants were detected using untargeted analysis in Cerro Colorado spring (Tables 2 and 3), several of which are persistent and toxic, therefore further work is necessary to quantify environmental and human health risk. Such pollutants are the carbamazepine metabolite, carbamazepine-10, 11-epoxide (Table 2), which has been shown to be more toxic than carbamazepine under a standard OECD 233 test (Heye et al., 2016). On the other hand, the other carbamazepine metabolite detected, 10, 11-Dihydro-10,11-dihydroxycarbamazepine, is of lower priority as it has lower predicted toxicity than carbamazepine, and has been shown to have lower concentrations in groundwater due to (bio)transformations of sorption (Brezina et al., 2017). Cocaine has been demonstrated toxicity at environmentally relevant concentrations (Parolini et al., 2017), deserving further attention in future targeted studies in the Tula Valley. Desethylatrazine, is a transformation product of the widely used pesticide atrazine, the parent compound and transformation products have been found to present toxicity to zebra fish (Blahova et al., 2020) and other species (Singh et al., 2018) and should therefore be included in further evaluations of chemical pollution in the Tula Valley. 2-Hydroxybenzothiazole is a by-product of industrial activities and has been shown to be very persistent in the environment and accumulate in human fat tissue (Zhang et al., 2021), posing a potential long-term human health risk that should be further addressed. Similarly, 4-nitrophenol is an industrial pollutant used to manufacture dyes, pesticides, drugs, amongst others (Serrà et al., 2020). This pollutant is known to be prevalent in the environment (Serrà et al., 2020), but its environmental risk has not been assessed in the Tula Valley, and given it possesses toxic and mutagenic potential in humans and other living organisms (Serrà et al., 2020), this pollutant should be considered in future studies in the area. Galaxolidone is a transformation product of galaxolide (Ding et al., 2022), which has been reported to be prevalent in the environment and has predicted environmental toxicity (Wang et al., 2021). Therefore, both galaxolidone and galaxolide should be considered for future environmental toxicity assessments in the Tula Valley. Untargeted analysis also highlights the potential toxicity from substances that do not go

Table 2
Selected pollutants identified in the Tula Valley site, which have been widely detected/measured in the aquatic environment (full list can be seen in Table S4).

Pollutant Formula	CAS	Monoisotopic mass *Retention time* (min)	Peak area* ($n = 2$)						Literature
Atotonilco wastewater treatment plant influent (untreated wastewater)	*Tlamaco Canal*	*Tula River*	*Endho Dam*	*Atotonilco wastewater treatment plant effluent (treated wastewater)*	*Cerro Colorado spring*				
10,11-dihydro-10,11-dihydroxycarbamazepine $C_{15}H_{14}N_2O_3$	35,079–97–1	270.1002 *2.94*[a]	9.57 × 10^6	3.08 × 10^7	1.95 × 10^7	2.47 × 10^7	3.96 × 10^7	1.66 × 10^6	Carbamazepine metabolite detected and quantified in African environmental waters in the range 21 - 62 ng L^{-1} (Fekadu et al., 2019) .
2-hydroxybenzothiazole C_7H_5NOS	934–34–9	151.00926 *4.00*[a]	1.49 × 10^7	6.89 × 10^6	4.59 × 10^6	3.85 × 10^8	1.50 × 10^6	3.45 × 10^6	Benzotriazole by-product detected in wastewaters (Scott et al., 2018), not previously detected in Global South.
4′-hydroxydiclofenac $C_{14}H_{11}Cl_2NO_3$	64,118–84–9	311.01172 *3.56*[b]	6.59 × 10^7	6.20 × 10^7	8.28 × 10^6	2.04 × 10^6	8.13 × 10^7	–	Diclofenac human metabolite that accumulates in aquatic organisms (Peake et al., 2016). It has been detected in South Asian countries (Khan et al., 2020).
4-acetamidoantipyrine $C_6\ H_7\ NO$	83–15–8	245.11635 *2.36*[a]	3.38 × 10^8	3.94 × 10^8	2.33 × 10^8	2.51 × 10^8	5.25 × 10^8	–	Metamizole metabolite (Kim et al., 2019), measured in several Global North regions (including Germany, Hungary, amongst others) (Gyenge-Szabó et al., 2014; Habekost, 2018); not previously detected in Global South.
4-formylaminoantipyrine $C_{12}H_{13}N_3O_2$	1672–58–8	231.1007 *2.35*	1.20 × 10^8	1.36 × 10^8	7.80 × 10^7	7.61 × 10^7	1.70 × 10^8	–	Aminophenazone metabolite, detected in Hungary (Gyenge-Szabó et al., 2014), not previously detected in Global South.
4-nitrophenol $C_6H_5NO_3$	100–02–7	139.02709 *2.35*[b]	6.07 × 10^6	4.98 × 10^6	6.08 × 10^6	3.69 × 10^7	8.27 × 10^6	6.07 × 10^6	Limit set by the United States Environmental Agency in natural water is 10 ng L^{-1} due to its high toxicity (Huang et al., 2018); not previously detected in Global South.
6-methylquinoline $C_{10}H_9N$	91–62–3	143.07338 *4.66*[b]	3.95 × 10^7	8.16 × 10^7	3.48 × 10^7	3.07 × 10^7	9.72 × 10^7	–	Quinolone antibiotic (Kim et al., 2019). It has oestrogenic activity (Brinkmann et al., 2014); not previously detected in Global South.
ADBICA $C_{20}H_{29}N_3O_2$	1,445,583–48–1	343.22049 *2.28*[a]	5.68 × 10^8	2.45 × 10^8	6.26 × 10^8	3.69 × 10^8	7.92 × 10^7	2.12 × 10^6	Designer drug (Banister et al., 2015), not previously detected in Global South.
Benzotriazole $C_6H_5N_3$	95–14–7	119.0484 *2.54*[b]	2.98 × 10^7	2.34 × 10^7	1.85 × 10^7	8.24 × 10^7	1.98 × 10^7	–	Corrosion inhibitor, measured in tap water (227 ng L^{-1}) and groundwater (1032 ng L^{-1}). It has anti-oestrogenic effects and suspected human carcinogen (Rhodes-Dicker and Passeport, 2019).
Carbamazepine 10,11-epoxide $C_{15}H_{12}N_2O_2$	36,507–30–9	252.08957 *2.94*[a]	7.49 × 10^6	2.81 × 10^7	2.14 × 10^7	2.74 × 10^7	4.03 × 10^7	1.42 × 10^6	Carbamazepine metabolite measured in South Asian countries (Khan et al., 2020) and in African aquatic environments, ranging from 6.76 - 430 ng L^{-1} (Fekadu et al., 2019).
Caprolactam $C_6H_{11}NO$	105–60–2	113.08405 *2.08*[a]	2.82 × 10^9	1.96 × 10^9	3.48 × 10^9	8.16 × 10^9	1.30 × 10^9	1.31 × 10^9	Molecule used to manufacture nylon 6 filament and more (Kim et al., 2019). It has caused widespread environmental pollution (Rajoo et al., 2013), but not widely measured in the Global South.
Dextrorphan $C_{17}H_{23}NO$	125–73–5	257.17783 *3.87*[b]	1.45 × 10^7	7.06 × 10^7	4.94 × 10^7	8.65 × 10^7	7.49 × 10^7	–	Dextromethorphan metabolite, frequently detected in surface water and wastewater in Minnesota (Campos-Manas

(*continued on next page*)

Table 2 (*continued*)

Pollutant Formula	CAS	Monoisotopic mass *Retention time* (min)	Peak area* ($n = 2$)						Literature
Atotonilco wastewater treatment plant influent (untreated wastewater)	*Tlamaco Canal*	*Tula River*	*Endho Dam*	*Atotonilco wastewater treatment plant effluent (treated wastewater)*	*Cerro Colorado spring*				
									et al., 2017), it has not been previously detected in the Global South aquatic environment.
Desethyl atrazine $C_6H_{10}ClN_5$	6190–65–4	187.06227 *3.51*[a]	2.05 × 10^6	1.85 × 10^6	6.76 × 10^6	3.55 × 10^6	1.80 × 10^6	9.13 × 10^7	Degradation product of the pesticide atrazine found in Latin American wastewater effluent. It has been detected at 35 ng L^{-1} (Peña-Guzmán et al., 2019); not measured in other Global South countries aquatic environment.
Diuron $C_9H_{10}Cl_2N_2O$	330–54–1	232.0168 *5.21*[b]	7.24 × 10^6	5.32 × 10^7	6.41 × 10^7	1.09 × 10^8	1.04 × 10^8	–	Herbicide and environmental pollutant (Kim et al., 2019) found in Latin American surface waters 95.80- 75,000 ng L^{-1} (Peña-Guzmán et al., 2019); not measured in aquatic environment of other Global South countries.
Galaxolidone $C_{18}H_{24}O_2$	1222–05–5	272.17736 *5.84*[a]	4.40 × 10^8	5.32 × 10^8	3.27 × 10^8	9.47 × 10^8	6.68 × 10^8	1.51 × 10^7	Synthetic fragrance, often found in Global North aquatic environment (Vallecillos et al., 2017).
Laurolactam $C_{12}H_{23}NO$	947–04–6	197.17775 *5.28*[b]	–	–	–	6.62 × 10^9	–	1.40 × 10^{10}	Used in engineering plastics, such as nylon-12 and copolyamides (Oenbrink and Schiffer, 2009). Not previously detected in the Global South aquatic environment.
Methocarbamol $C_{11}H_{15}NO_5$	532–03–6	241.09477 *3.34*[b]	7.60 × 10^7	1.08 × 10^8	6.73 × 10^7	6.49 × 10^7	1.43 × 10^8	7.60 × 10^7	Muscle relaxant (Beckers et al., 2020), measured in USA wastewater in the range 10–1560 ng L^{-1} (Scott et al., 2018). Not previously detected in the Global South aquatic environment.
Methyl salicylate $C_8H_8O_3$	119–36–8	152.04747 *3.77*[b]	4.60 × 10^7	–	4.64 × 10^6	4.91 × 10^7	1.98 × 10^6	3.72 × 10^6	Naturally and commercially produced rubefacient, classified as an emerging contaminant (Real et al., 2012). Not previously detected in the Global South aquatic environment.
Nefopam $C_{17}H_{19}NO$	13,669–70–0	253.14644 *5.25*[a]	2.56 × 10^7	3.81 × 10^7	4.32 × 10^7	3.13 × 10^7	3.83 × 10^7	5.33 × 10^7	Non-opioid analgesic drug (Aymard et al., 2003). Part of the Contaminant Candidate List 4 (Richardson and Ternes, 2018). Not previously detected in the Global South aquatic environment.
Palmitoylethanolamide $C_{18}H_{37}NO_2$	544–31–0	299.28221 *7.94*[b]	3.37 × 10^8	7.64 × 10^6	3.56 × 10^6	2.65 × 10^6	9.27 × 10^6	–	Preventive for viral infections, available for human use as supplements (Wishart et al., 2018). Identified in sewage sludge (Black et al., 2019), and not widely detected in the Global South.
Tributyl phosphate $C_{12}H_{27}O_4P$	126–73–8	266.16457 *5.47*[a]	4.69 × 10^8	4.09 × 10^8	6.41 × 10^8	8.04 × 10^8	1.04 × 10^9	3.78 × 10^7	Identified as an emerging pollutant and in Arctic circle water samples (Choi et al., 2020). Not widely detected in the Global South.

* Peak area does not equate to concentration.

through any regulatory process, such as ADBICA, which is a designer drug with intended biological effects on humans (Uchiyama et al., 2013; Banister et al., 2015a), and has unknown environmental toxicity. Nicotine, has reported aquatic environmental toxicity (Oropesa et al., 2017; Venugopal et al., 2021) and as such should be considered in further assessments in the Tula Valley. These pollutants are not identified in recent global CEC prioritisation efforts (Wang et al., 2022; Yang et al., 2022), highlighting the need for local assessments.

Table 3
Selected pollutants identified in the Tula Valley which have not been widely detected in the aquatic environment worldwide and first time detecting in the Global South (full list can be seen in Table S5).

Pollutant Formula	CAS	Monoisotopic mass *Retention time* (min)	Peak area ($n = 2$)						Literature
			Atotonilco wastewater treatment plant influent (untreated wastewater)	*Tlamaco Canal*	*Tula River*	*Endho Dam*	*Atotonilco wastewater treatment plant effluent (treated wastewater)*	*Cerro Colorado spring*	
2,6-di-tert-butyl-4-methoxyphenol $C_{15}H_{24}O_2$	489–01–0	236.17768 *6.75*[b]	9.32×10^7	1.13×10^8	5.11×10^7	1.16×10^8	1.16×10^8	1.10×10^7	Inert pesticide ingredient (Kim et al., 2019), not previously detected in wastewater or surface water.
4,4′-dihydroxydiphenylsulfone $C_{12}H_{10}O_4S$	80–09–1	250.02999 *3.18*[b]	2.66×10^7	1.74×10^7	5.58×10^7	1.53×10^7	1.02×10^7	–	Endocrine disruptor used as a textile dye and in food packaging (Kim et al., 2019).
4-coumaric acid $C_9\ H_8\ O_3$	501–98–4	164.04764 *2.32*[a]	2.49×10^7	1.13×10^7	8.91×10^6	2.89×10^6	8.56×10^6	–	Used in flavours, perfumes, synthetic indigo and pharmaceuticals (Kim et al., 2019).
4′-methoxyacetophenone $C_9H_{10}O_2$	100–06–1	150.06548 *1.10*[a]	1.33×10^8	4.94×10^7	2.58×10^7	3.67×10^6	2.99×10^7	–	Found in alcoholic beverages and some fruits. It is used as flavouring agent (Wishart et al., 2018).
10-hydroxy carbazepine $C_{15}H_{14}N_2O_2$	29,331–92–8	254.10526 *3.60*[b]	2.93×10^7	3.92×10^7	2.61×10^7	3.81×10^7	6.46×10^7	–	Major active oxcarbazepine metabolite (Chen et al., 2019). Oxcarbazepine found at 300 ng L^{-1} in surface waters (Scott et al., 2018).
Acetophenone C_8H_8O	98–86–2	120.05743 *6.02*[a]	1.07×10^8	7.53×10^7	5.44×10^7	3.61×10^7	1.11×10^8	2.57×10^6	Flavouring agent, solvent, and catalyst (Kim et al., 2019).
Boldenone $C_{19}H_{26}O_2$	846–48–0	286.19303 *5.13*[b]	1.17×10^7	4.53×10^6	5.67×10^7	6.85×10^6	5.19×10^6	–	Banned in the EU as animal growth promoter (Destrez et al., 2009), used by human bodybuilders and illegal racing horse use (Oda and El-Ashmawy, 2012).
Fomesafen $C_{15}H_{10}ClF_3\ N_2O_6S$	72,178–02–0	437.98958 *4.72*[b]	3.29 x10^5	1.20×10^6	2.79×10^6	–	4.07×10^5	1.79×10^7	Herbicide (Kim et al., 2019) sold in Mexico (Syngenta Mexico, no date).
Lauric acid $C_{12}H_{24}O_2$	143–07–7	200.1776 *4.89*[b]	1.39×10^{10}	1.50×10^9	5.58×10^7	2.69×10^8	2.58×10^8	4.69×10^7	Fatty acid in coconut and palm oil (Kim et al., 2019). Antibacterial used to treat acne (Kozan et al., 2020).
Sodium [*dodecanoyl*(*methyl*) *amino*] acetate $C_{15}H_{29}NO_3$	137–16–6	271.21456 *4.79*[b]	2.56×10^8	1.01×10^8	9.65×10^7	1.02×10^7	2.89×10^6	1.80×10^6	Anionic surfactant not extensively studied (Das et al., 2013).

Furthermore, environmentally toxic caprolactam had the same order of magnitude peak in the Cerro Colorado spring as in the other sampling points (Table 2), indicating prevalence in the Tula Valley. Laurolactam, a macrocyclic lactam, was detected for the first time in the Global South (not having been included in other studies) and with the highest peak area in the Cerro Colorado spring out of all the sampling points, indicating persistence and potential accumulation, making it a priority pollutant in further targeted studies in this region and the Global South (Table 2). Similarly, nefopam, methyl salicylate and methocarbamol were all detected in Cerro Colorado spring water and have not been previously detected in the Global South (Table 2). Other pollutants that are likely of particular concern for the Tula Valley and meriting further study, are two agriculturally related pollutants; the pesticide 2,6-di-tert-butyl-4-methoxyphenol, and the herbicide fomesafen (Table 3).

3.3. Influence of Atotonilco WWTP on CEC occurrence in the Tula Valley

The Atotonilco WWTP influent flowrate is split between two treatment streams, one biological and one physico-chemical (Fig. 1). Whilst, this process maintains the nutrient levels that farmers rely on, a consequence is the likely lower CEC removal compared to WWTPs using only biological treatment, as primary treatment is not as effective at reducing CEC concentration (Rodriguez-Narvaez et al., 2017).

Acetaminophen, sulfamethoxazole and bezafibrate had inadequate removal in the WWTP due to relatively high (>25,000 ng L^{-1}) wastewater effluent concentrations, compared to concentrations measured at other sampling points. Further investigation would be required to determine whether this is due to inadequate removal in the WWTP, or due to very high influent concentrations. Either way, these pollutants remain of concern. In the literature, these pollutants have been reported to present high (> 80%) removal in biological treatment systems (Peake et al., 2016a; Rodriguez-Narvaez et al., 2017; Wang et al., 2019). Acetaminophen has been reported to have very low (< 3%) removal using coagulation alone (Teh et al., 2016). Similarly, sulfamethoxazole removal is higher in advanced biological nutrient removal unit technologies (versus conventional activated sludge, where there is 100% aeration) due to the denitrification stage (Wang et al., 2019). Atotonilco WWTP comprises conventional activated sludge biological treatment to keep the level of nutrients the farmers value (CONAGUA, 2007). This highlights the complexity of maintaining water with the nutrient levels that farmers rely on against protecting the environment for those CECs that pose environmental risk.

3.4. Influence of natural attenuation in CEC degradation

For a site of the magnitude and sun irradiation of the Tula Valley, it is important to consider that natural attenuation and dilution will play an important role in the environmental fate of CECs (Vázquez-Tapia et al., 2022). The concentration of the target pollutants was the lowest in Cerro Colorado spring water, which is the product of wastewater infiltration and further upwelling (Table 1). Previous studies in the area have demonstrated that the agricultural soil acts as a highly effective filter of CECs. The organic pollutants are first adsorbed on the organic domain of soil and then readily biodegraded by a soil biome that is highly specialized in using CECs as a carbon source or through co-metabolism (Chávez-Mejía et al., 2019). Other abiotic processes in soil, like oxidation–reduction processes and hydrolysis can also take place, though to a lower extent. Once in surface water, direct and indirect photolysis can further reduce the concentration of CECs; considering the high sunlight irradiation in the area along with the high concentration of dissolved salts in surface water, photodegradation can play an important role in the environmental fate of organic pollutants in the Cerro Colorado spring. On the other hand, wastewater irrigation canals are open and thus gas exchange occurs to some extent, which promotes aerobic biodegradation processes; also, important the sewage from the towns nearby is discharged in the main irrigation canals (including the Tlamaco and Tula river). Biodegradation, dilution, and photolysis to a lower extent, result in the lowering of the CEC concentration in locations further from Mexico City (Table 1) in what could be classified as an unplanned natural attenuation system that includes wastewater canals and dam along with agricultural soil (Table 1). Examples of natural attenuation are erythromycin, acetaminophen and naproxen, with concentrations decreasing from untreated wastewater to points further from Mexico City, which can be explained by biodegradation and dilution processes. On the other hand, trimethoprim concentration in the dam was lower than the rest of the sampling points (Table 1), this could be due to the long hydraulic retention time which favours the occurrence of nitrifying processes and/or adsorption on suspended solids to further precipitate (Radjenović et al., 2009). Considering the potential importance of natural attenuation processes in the removal of CECs in wastewater, assessing whether natural processes may degrade pollutants to an acceptable level and thus avoid over-engineering, reducing resource use and carbon footprint, is a priority matter of study.

3.5. Untargeted analysis to support equitable delivery of SDGs

Over one hundred pollutants not previously identified in the Tula Valley were identified using untargeted analysis. Approximately half of these pollutants have been widely studied in the Global North, although some, like carbamazepine and diclofenac metabolites have also been measured in African and South Asian countries (Table 2). The remaining half of the pollutants identified have not been previously measured in surface or groundwater (Table 3). Six pollutants identified have been previously quantified using targeted analysis in the Tula Valley, namely, benzoic acid, bisphenol A, caffeine, cotinine, paraxanthine and perfluorooctanoic acid (PFOA) (Table S4).

Two herbicides (fomesafen and diuron), one pesticide (desethyl atrazine) and one pesticide ingredient (2,6-di-tert-butyl-4-methoxyphenol) were identified for the first time in the Tula Valley (Tables 2 and 3), which is expected given that it is an agricultural zone. Fomesafen, desethyl atrazine and 2,6-di-tert-butyl-4-methoxyphenol were detected in Cerro Colorado spring water. Fomesafen, diuron and 2,6-di-tert-butyl-4-methoxyphenol presented higher signals in the Tlamaco canal than in the untreated wastewater. This indicates these pollutants are likely being used in the area for agriculture rather than being brought in through Mexico City wastewater. This is another example of the importance of local practices to prioritise pollutants of concern. 4-acetamidoantipyrine, metabolite of metamizole, was detected in this study (Table 2). Metamizole is prohibited in the USA but used in Mexico and other countries (Bonkowsky et al., 2002), demonstrating that untargeted CEC studies in the Global South are urgently needed to ensure pollutant prioritisation is adequate in the region.

Wastewater-based epidemiology allows us to obtain information on the health of a population in near-real time. Compared to other techniques such as questionaries or surveys, mortality and morbidity rates, prescription rates, amongst others, it presents several advantages. It is unbiased and it can focus on a broad range of diseases and biomarkers (Sims and Kasprzyk-Hordern, 2020). Compared to prescription data, it reveals what the population has actually consumed, including over-the-counter drugs and illicit drugs (Archer et al., 2018). However some challenges remain, such as uncertainties related to the contribution population and wastewater flows (Sims and Kasprzyk-Hordern, 2020). These challenges can be addressed with the use of biomarkers that are constantly excreted and total excretion should correlate to census population (Chen et al., 2014). Biomarkers can be used by allowing for the determination of an illegal drug consumption per capita without the need of an accurate estimate of the population as follows (Chen et al., 2014)

$$Drug\ consumption\ per\ capita = \frac{Drug\ concentration}{Biomarker\ concentration} \times \frac{Biomarker\ excretion\ rate}{Drug\ excretion\ rate}$$

Some of the pollutants identified in this study, such as caffeine, paraxanthine, nicotine and cotinine are of interest because even though the analysis was not designed specifically for them, they were detected, and they have been previously identified as suitable biomarkers for wastewater based epidemiology (Sims and Kasprzyk-Hordern, 2020).

Metabolites and transformation products are often missed during targeted monitoring campaigns, and this can underestimate the environmental risk present from these pollutants in the environment. For example, 10,11-epoxy carbamazepine is the main carbamazepine metabolite and is therapeutically active (Paz et al., 2016). Carbamazepine had an RQ < 1, however the identification of its metabolites reveals unaccounted for toxicity related to this pollutant. Identification of 4′-hydroxy diclofenac, a diclofenac human phase I metabolite, is of concern as diclofenac and its metabolites have been found to accumulate in aquatic organisms (Peake et al., 2016a). Another example is 4-acetamido antipyrine, a metabolite of the painkiller metamizole (Kim et al., 2019), not previously detected in Global South (Table 2). Similarly, dextrorphan, a dextromethorphan metabolite, has not been previously detected in the Global South aquatic environment (Table 2).

The sulfamethoxazole metabolite, acetyl-sulfamethoxazole concentrations presented an RQ > 1 (Fig. 2). However, this pollutant can undergo deacetylation in the environment, reforming sulfamethoxazole by the action of enzymes able to deconjugate an acetylated compound and turn it back to the parent compound (Gomes et al., 2009). Assuming 100% deacetylation in the environment, 86% of the acetyl-sulfamethoxazole concentration would be added to the sulfamethoxazole concentration. This means that at its maximum (in the Tula River), approximately 1863 ng L^{-1} would be added to the 3345 ng L^{-1} of sulfamethoxazole present in the river. Most risk assessment do not consider the production of pharmaceuticals from the hydrolysis of conjugates, therefore knowing the proportion of these metabolites can contribute to more accurate risk assessment. It is crucially important to know the occurrence of metabolites as they can not only transform into the parent pharmaceutical compound, but elicit some harmful effects to aquatic organisms.

4. Conclusion

As the first untargeted study of contaminants of emerging concern (CEC) in the Mexican aquatic environment this work puts forward pollutants which have not been previously considered in the region and more broadly, in the Global South. To ensure equitable SDG delivery, the benefits of wastewater reuse for agriculture in the Global South must be considered alongside the risks presented by CECs. Over 100 pollutants were detected for the first time using untargeted analysis in the Tula Valley, for example, 4-acetamidoantipyrine, a drug prohibited in several countries but used in Mexico. Other pollutants meriting further study, given they were detected for the first time in the Global South and due to their persistence are androsterone, ADBICA, 4-nitrophenol, galaxolidone, fumaric acid, cocaine, desethylatrazine, nicotine, caprolactam, laurolactam, nefopam and methyl salicylate methocarbamol. Pollutants that are likely of particular concern for the Tula Valley as they are agriculturally related (pesticide/ herbicide) are 2,6-di-tert-butyl-4-methoxyphenol and fomesafen. Untargeted analysis also unveils potential toxicity of parent drugs by identification of their metabolites and transformation products. In this study carbamazepine, diclofenac and metamizole metabolites were detected. The targeted study carried out allowed for the prioritisation of 10 pollutants due to their environmental toxicity, namely, 4-tert-octylphenol, acetaminophen, bezafibrate, diclofenac, erythromycin, levonorgestrel, simvastatin, sulfamethoxazole, trimethoprim and tramadol. As well as oxytetracycline and carbamazepine due to their persistence. Comparison with other Global South studies highlighted the risk from acetaminophen, carbamazepine, sulfamethoxazole and trimethoprim across the region, which could be a potential opportunity for collaborative work to address this issue. Next steps should include carrying out toxicological studies on Global South aquatic species, as environmental risk assessment is based on European species. Local estrogenicity was found to be of higher concern than previous estimates due to the measurement of two steroid sulfate conjugates never measured in the Tula Valley, as well as oestrogenic pollutants 6-methylquinoline and 4,4′-dihydroxydiphenylsulfone identified for the first time in the region, using untargeted analysis. This study also highlights the delicate balance between maintaining the nutrient levels farmers depend on from wastewater reuse and improving WWTP CEC removal. On the other hand, local climate and soil conditions can also aid in CEC removal, for example the photodegradation of salicylic acid. Further monitoring using targeted and untargeted studies for quantification and further identification as well as studying pollutants of concern in soils and crops should also be carried out to gain a comprehensive understating of the risk of CECs present in wastewater irrigation.

Funding

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) [grant number EP/M022234], BIOTRANSFOROMICS: Bioanalysis to engineer understanding in wastewater treatment.

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.

Data availability

Data will be made available on request.

Acknowledgements

The author (RLG) would like to acknowledge the support of Engineering and Physical Sciences Research Council (EPSRC) [grant number EP/M022234], BIOTRANSFOROMICS: Bioanalysis to engineer understanding in wastewater treatment. The author (AGJ, CVU: 748280) gratefully acknowledges the Mexican National Science and Technology Council (CONACyT) for her PhD scholarship and the University of Nottingham for the International Research Collaboration Award which funded her visit to Mexico in 2019. All authors would like to thank CONAGUA for the permission to sample wastewaters from the Atotonilco wastewater treatment plant. All authors thank Mario Rodriguez Varela for his help sampling.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2023.119903.

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