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Drugs of abuse in tap water from eight European countries: Determination by use of supramolecular solvents and tentative evaluation of risks to human health

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ABSTRACT

Recent research findings have confirmed the presence of illicit drugs in tap water from some European Union (UE) member states. Contaminants in tap water come directly from drinking water sources such as rivers or lakes owing to inefficient removal at wastewater treatment and water purification plants. This work was aimed at setting a starting point for assessing the health risks of exposure to twelve drugs of abuse through consumption of tap water in the European population. For this purpose, a method using supramolecular solvents (SUPRAS) was developed to extract drugs in the opioid, amphetamine, cocaine and cannabinoid groups from tap water for their determination by liquid chromatography–tandem mass spectrometry (LC–MS/MS). A total of 119 tap water samples were collected from eight EU countries for analysis. Seven drugs were found at concentrations from 0.3 to 340 ng/L in 72 of the samples (60.5%). The mean exposure to the drugs through consumption of tap water was calculated to be 0.0064–3.531 ng/kg·day for adults and 0.0247–6.7580 ng/kg·day for children, whereas that resulting from dermal contact was estimated to be 4–7 orders of magnitude lower. Exposure values were compared with the minimum required performance levels (MRPL) for the drugs in urine set by the World Anti-Doping Agency (WADA). Based on the results, a need clearly exists for further research into the adverse effects on health of inadvertent, sustained exposure to low doses of drugs of abuse.

1. Introduction

Over the last decade, the drug market in the European Union (EU) has grown steadily by effect of globalization and new technologies promoting the emergence of online markets and alternative distribution routes (EMCDDA, 2021, 2019). Massive production and consumption, and inefficient disposal in water treatment plants, of drugs of abuse have led to their pseudo-persistent presence as environmental contaminants. In fact, drugs of abuse have been deemed a new class of emerging environmental pollutants in the water cycle, where they can be transformed through biological, chemical or photochemical processes, or adsorbed in the particulate fraction of water (Borova et al., 2014; Mendoza et al., 2014; Rodayan et al., 2016). Illicit drugs can have adverse impacts on human health, aquatic organisms and ecosystems, whether individually or synergistically with other pollutants (Pomati et al., 2006).

Drugs of abuse and their metabolites are reportedly present widely in river (Boleda et al., 2009; Huerta-Fontela et al., 2008a; Krizman-Matasic et al., 2018; Prosen et al., 2017; Zuccato et al., 2008), lake (Boix et al., 2015) and groundwater (Jurado et al., 2012) used to obtain drinking river. Illicit drugs can reach the water cycle through different routes. One is accidental or deliberate disposal of drugs by clandestine laboratories and trafficking networks (Borova et al., 2014; Pal et al., 2013). In this way, drugs can reach rivers, seas or sewage systems, whether directly or indirectly (e.g., as surface runoff from rainwater) (Pal et al., 2013). Aquifers can also be contaminated by leakage from sewage systems or seepage of surface water (Peng et al., 2019). Drugs are partially metabolized by the body and excreted, mainly as metabolites, in urine. As a result of wastewater being discharged into rivers, lakes and seas (Borova et al., 2014; Huerta-Fontela et al., 2008a, 2007; Pal et al., 2013; Zuccato et al., 2008), drugs of abuse enter drinking water treatment plants (DWTPs) and reach the supply network.

Drugs of abuse include structurally unrelated substances of widely variable polarity that can be present at very low concentrations in

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drinking water and thus require sensitive an analytical methods for their determination (Boleda et al., 2011a, 2011b, 2009; Borova et al., 2014; Huerta-Fontela et al., 2008b, 2007; Krizman-Matasic et al., 2018; Peng et al., 2019; Prosen et al., 2017; Valcárcel et al., 2012; Watanabe et al., 2020). Such methods typically involve solid-phase extraction (SPE), which enables mixed-mode interactions with drugs, followed by liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) for detection. Detecting the typically low levels of drugs in water usually requires using large volumes of sample (200–500 mL), and also large volumes of organic solvents and reagents such as methanol, hydrochloric acid, isopropyl alcohol, ethyl acetate, ammonium hydroxide, phosphoric acid or acetonitrile (2–13 mL). In addition, SPE cartridges are expensive and the process is time-consuming, which detracts from sample throughput.

This work was undertaken with a twofold aim, namely: (*a*) to assess the increasing presence of illicit drugs in drinking water and their distribution in the EU in order to confirm whether drinking water is an actual source of exposure to drugs of abuse in some EU territories; and (*b*) to develop a straightforward method for their determination in water with reduced costs and increased sample throughput. For this purpose, we examined the presence of the twelve most widely used illicit drugs of four types (viz., cocaine and its metabolites, amphetamines, opioids and cannabinoids) in 119 tap water samples from eight different EU countries. The results were used to estimate daily exposure through consumption and dermal contact with water in adults and children. Sample treatment was simplified by extracting the drugs with a supramolecular solvent (SUPRAS) that was synthesized *in situ*. The solvent consisted of inverted aggregates of hexanol with hydroxyl groups surrounding aqueous cavities and hydrocarbon chains dispersed in tetrahydrofuran (Salatti-Dorado et al., 2017).

SUPRAS are nanostructured liquids forming by spontaneous self-assembly and coacervation in colloidal solutions of amphiphiles (Rubio, 2020). The SUPRAS used here was a highly suitable replacement for typical SPE solvents to extract illicit drugs. Thus, it dissolves drugs via a mixed-mode mechanism thanks to its amphiphilic nanostructure providing differential polarity micro-environments. Also, the size of the aqueous cavities, and hence their exclusion ability, can be tailored by setting an appropriate environment in the form of, for example, an optimal THF/water ratio, for coacervation (Ballesteros-Gómez and Rubio, 2012). In this way, SUPRAS can extract low-molecular weight solutes while excluding macromolecules through chemical (e.g., protein precipitation) and physical mechanisms (size exclusion of carbohydrates, humic acids, etc.). Because a SUPRAS is not a continuous phase, but rather a collection of coacervate droplets, mass transfer during extraction is quite fast, and so is sample treatment as a result.

2. Materials and methods

2.1. Sampling

A total of 119 drinking water samples were obtained from public areas in eight EU member countries from winter 2020 to summer 2021. Samples were collected in 15 mL-polypropylene centrifuge tubes that were sealed with parafilm and stored tightly closed at –20 °C in the dark until analysis to avoid losses and degradation. Fig. 1 shows the geographical distribution of sampling points in the studied countries (France, Spain, Belgium, Germany, Portugal, Turkey, Luxembourg and Italy). Countries were selected on the grounds of their seizure figures (EMCDDA, 2021), and included those where the drugs analyzed were seized at the largest volume (e.g. cocaine in Belgium; cannabinoids in Spain, and opioids and amphetamines in Turkey) and those covering a wide range of seizures of drugs (Spain > Turkey > France > Belgium > Italy > Germany > Portugal > Luxembourg), being the seizures in Spain and Luxembourg of 429.835 kg and 439 kg, respectively (EMCDDA, 2021). Further details on sampling points are given in Table S1, Supplementary Material (SM).

2.2. Chemicals and reagents

All chemicals were analytical reagent-grade and used as supplied. The specific chemicals used and their suppliers are stated in Section 1 of Supplementary Material (SM). The target drugs were selected on the grounds of their use in Europe (EMCDDA, 2019), their seizure figures and their reported presence in wastewater (Boleda et al., 2011a, 2011b, 2009; Huerta-Fontela et al., 2008b). Table S2 in SM shows their main physico–chemical properties.

Stock solutions of the individual drugs and isotopically labelled standards at a concentration of 25 μg/mL were prepared in acetonitrile. Intermediate solutions containing a mixture of the twelve drugs and the five isotopic standards at a 1 μg/mL concentration were made biweekly by appropriate dilution with acetonitrile. All solutions were stored at –20 °C in the dark until use. Calibration standards were prepared on a daily basis by diluting the intermediate solutions in a (50:50, v:v) water–methanol mixture.

2.3. Optimization of sample treatment and validation of the method

The SUPRAS used was synthesised *in situ* by adding hexanol and THF

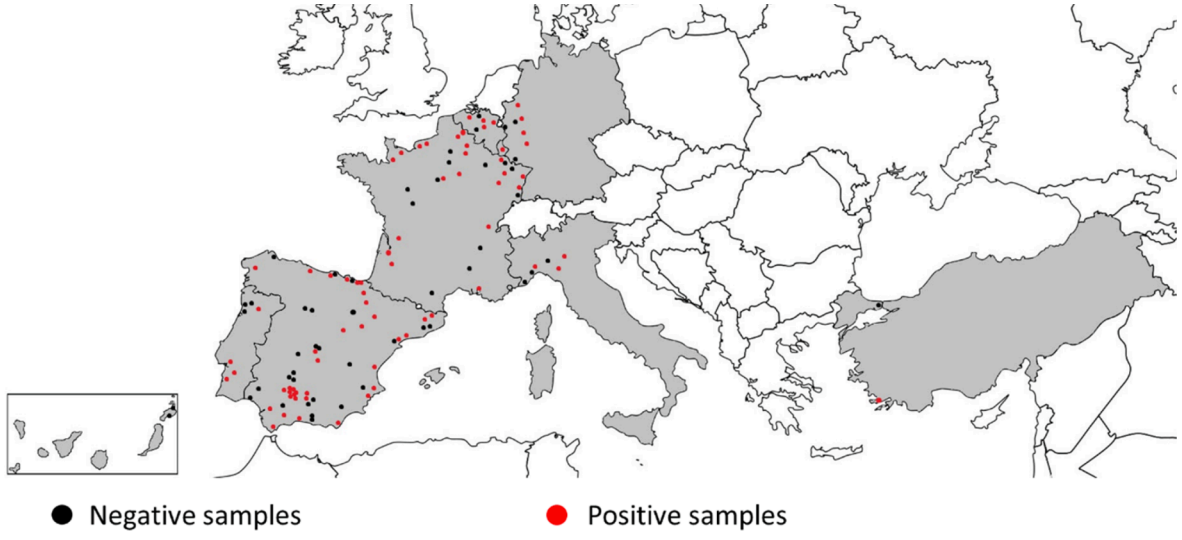

Fig. 1. Sampling locations.

to the samples. The main variables governing the drug extraction efficiency were optimized as described in Section 2 of SM. SUPRAS extracts were directly analysed by LC–MS/MS and the ensuing method was validated by following the European Commission guidelines (Directive 2002/657/EC) as described in Section 3 of SM.

2.4. Determination of drugs of abuse in drinking water

2.4.1. SUPRAS-based microextraction

A volume of 100 μL of hexanol was dissolved in 200 μL of THF in 2-mL Safe-Lock microtubes from Eppendorf Ibérica (Madrid, Spain). This was followed by addition of 1700 μL of sample previously adjusted to pH 10.5–11 with ammonia, the mixture being vortexed at 3000 rpm at room temperature on a REAX Top shaker from Heidolph (Schwabach, Germany) for 10 min and centrifuged at 11 290 × g on a MPW- 350R centrifuge with a 36 × 2.2/1.5 mL rotor (ref. 11462) from MPW Med-Instruments (Warsaw, Poland) for 30 min to expedite separation of the SUPRAS from the sample. Finally, a 75 μL aliquot of SUPRAS extract containing the drugs was withdrawn with a micropipette for analysis by LC–MS/MS. Fig. 2 depicts the overall analytical procedure for determining illicit drugs in drinking water alongside the SUPRAS nanostructures.

2.4.2. Quantification by LC–MS/MS

The target drugs were quantified by LC–MS/MS, using an 1200 Series liquid chromatograph from Agilent Technologies (Waldbronn, Germany) coupled to a 6420 triple quadrupole mass spectrometer from the same manufacturer. The spectrometer was equipped with an electrospray ionization source operating in both the positive and the negative ion mode (ESI ±). The analytical column was an ACE 3 C18-PFP model (150 mm long × 3.0 mm id) and the mobile phase consisted of (A) ammonium formate buffer (2 mM, pH 3.57) and (B) a (90:10, v:v) acetonitrile/solvent A mixture. The elution program started with 90% of A, which was reduced to 10% in 10 min, then kept constant for 3 min, subsequently increased to 65% in 2 min and finally restored (90%) in 0.5 min. The overall elution time was 20 min, the flow rate 250 μL/min and the injected volume 4 μL. Contamination of the ESI source was avoided by splitting each chromatographic run into segments and injecting only those containing some analyte into the MS instrument.

The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode. The MS/MS parameter values used, which were optimized by direct infusion of individual drug solutions, are shown in Table S2, SM. The operating conditions of the ESI source were as follows: source gas temperature 350 °C; capillary voltage 3500 V; and nebulizer gas pressure 35 psi. The analytes were quantified by using the isotopic dilution method.

2.5. Daily exposure to the drugs through drinking of tap water

Daily exposure to the target drugs through ingestion of drinking water ($D_{\text{ingestion}}$, mg/kg·day) was estimated from eq. (1) as recommended by the Public Health Assessment Guidance Manual from the Agency for Toxic Substance and Disease Registry (ATSDR, 2005).

$$D_{ingestion} = \frac{C \cdot IR \cdot EF}{BW} \quad (1)$$

where C (mg/L) denotes drug concentration, IR (L/day) water intake rate, EF a dimensionless exposure factor and BW (kg) body weight. An average water consumption of 1.4 L/day for adults and 0.74 L/day for children was assumed (ATSDR, 2005). Also, all water consumed by adults and children was assumed to come from a single source, and EF to be unity as the potential fraction of drugs in water was ingested from drinking water alone. Finally, an average weight of 70.8 kg for adults (Walpole et al., 2012) and 18.25 kg for children 5 years old or younger was adopted (WHO, 2021).

2.6. Daily dermal exposure through contact with water

Dermal exposure to organic compounds typically occurs through daily activities such as showers or cleaning. The degree of dermal exposure is influenced by a number of factors such as the permeability the chemical concerned, the body surface area that is exposed and the duration of the event. The permeability coefficient (K_p, cm/h) of a compound is a measure of its ability to cross dermal layers (USEPA, 2004). The K_p value for each target drug was calculated by using the empirical predictive correlation recommended by the United States Environmental Protection Agency (USEPA, 2004), namely:

$$\log K_p = b + a \cdot \log K_{ow} - c \cdot MW \quad (2)$$

where K_{ow} is the octanol/water partition coefficient and MW the molecular weight of the drug; and parameters a, b and c are correlation coefficients obtained from the experimental Flynn database of absorption of chemicals dissolved in water through human skin (USEPA, 2004), namely: 0.66, –2.80 and 0.0056.

The daily exposure dose from dermal contact with tap water for citizens in the studied countries, D_{dermal} (mg/kg·day), was calculated from the following equation:

$$D_{dermal} = \frac{C \cdot K_p \cdot SA \cdot ET \cdot CF}{BW} \quad (3)$$

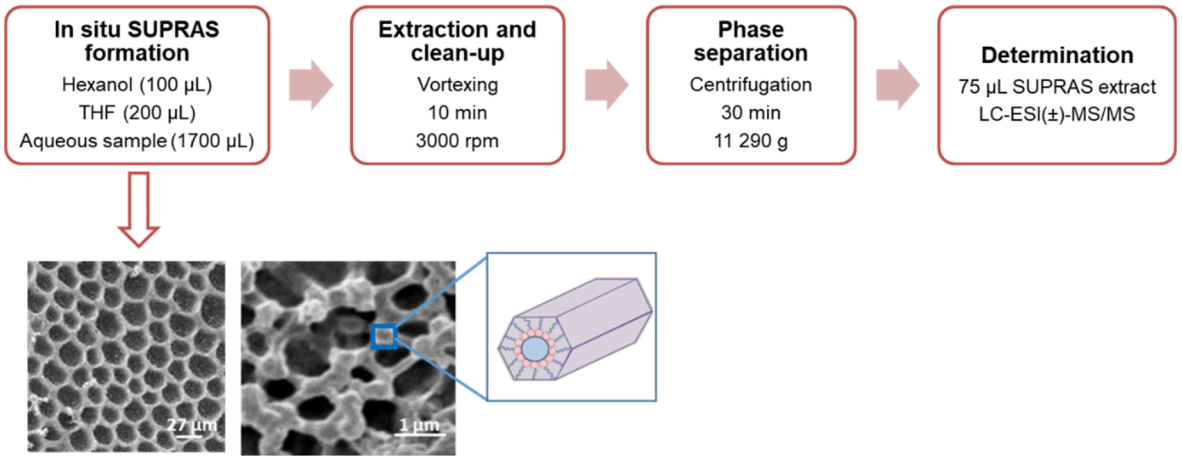

Fig. 2. Procedure for the LC–ESI(±)MS/MS quantification of the target drugs in drinking water following extraction with SUPRAS, and electron micrographs and schematic depiction of the nanostructures they formed.

where K_p (cm/h) is the permeability coefficient of the drug, SA (cm^2) the body surface area exposed, ET (h/day) the exposure time, CF a conversion factor (1 L = 1000 cm^3) and BW (kg) body weight. D_{dermal} was calculated under the assumption of an average exposed body surface are of 17 750 cm^2 for adults and 7400 cm^2 for children (Haycock et al., 1978; Mosteller, 1982), and an average weight of 70.8 kg for the former (Walpole et al., 2012) and 18.25 kg for children 5 years old or younger (WHO, 2021). Following the World Health Organization (WHO) recommendations for sustainable, appropriate use of shower water, the average exposure time was taken to be 5 min.

2.7. Quality control and quality assurance

The proposed method was validated in terms of linearity, sensitivity, matrix effects, recovery and precision by following the guidelines of the European Commission (Directive 2002/657/EC). For this purpose, fresh working solutions of the target analytes were prepared on a daily basis by dilution of the stocks solutions (see Section 3 of SM for greater details). The drugs were quantified by using the isotopic dilution method. Each batch of 15 drinking water samples was expanded with one of ultrapure water to detect potential carryover, and three of also ultrapure water that were spiked with a 10 ng/L concentration of the target analytes and subjected to the whole process. Analyte recovery was assessed by spiking the samples with a 10 ng/L concentration of the analytes and one of 15 ng/L of IS.

3. Results and discussion

3.1. Optimization of sample treatment and validation of the method

Hexanol dissolves in THF by forming reverse micellar aggregates. Adding water (a poor solvent for hexanol) to the mixture causes the aggregates to grow and eventually separate as a new liquid phase: a SUPRAS (Salatti-Dorado et al., 2017). The amphiphile molecules in a SUPRAS arrange as inverted hexagonal aggregates where polar groups surround aqueous cavities and hydrocarbon chains disperse in THF (Ballesteros-Gómez et al., 2010). The electron micrographs of Fig. 2 illustrate such nanostructures. The composition (viz., the hexanol, THF and water contents), volume and size of the aqueous cavities in a SUPRAS can be tailored by adjusting the water/THF ratio in the synthesis solution in order to maximize analyte extraction and facilitate interference removal.

Section 2 of SM describes the procedure followed to optimize extraction of the target drugs with hexanol-based SUPRAS. Six SUPRAS of variable composition and/or volume were directly synthesized in the samples by using variable proportions of hexanol (3–5%) and THF (10–20%). The volume of SUPRAS formed in each case was consistent with that predicted by Eq. (4):

$$V_{SUPRAS} = (10.7 \pm 0.3) \cdot \%hexanol \cdot e^{(0.0330 \pm 0.0007) \cdot \%THF} \quad (4)$$

The SUPRAS obtained with a proportion of 3% of hexanol were discarded because their volume was too low for a representative aliquot to be obtained. Absolute analyte recoveries increased with increasing proportion of hexanol but differed little with that of THF (Table S3). Since, based on Eq. (4), the SUPRAS volume was linearly dependent on the proportion of hexanol and exponentially dependent on that of THF (Eq. (4)), the optimum SUPRAS composition (viz., that leading to the highest possible concentration factors for the analytes) was taken to be 5% of hexanol and 10% of THF.

The selected SUPRAS were examined for matrix effects by using tap water spiked with five representative deuterated internal standards. Matrix effect values, in the form of signal suppression/enhancement ratios, ranged from 87 to 104.3% (Table S4). Since the size of aqueous cavities in inverted hexagonal aggregates (Fig. 2) increases with increasing proportion of THF (Salatti-Dorado et al., 2017), these results suggest that any macromolecules such as proteins, humic acids or carbohydrates present in the samples were efficiently removed by SUPRAS obtained with 10 or 20% of THF. Also, recoveries were greater at pH greater than 7, where most of the drugs should be uncharged (Table S5). An extraction time of 10 min was chosen as optimal as it led to the highest recoveries (Table S6).

Calibration curves were linear over a wide range of drug concentrations (LOQ was 5000 ng/L) and coefficients of determination ranged from 0.9920 to 0.9992 (Table S7). The limits of detection (LOD) and quantification (LOQ) spanned the range 0.12–0.73 and 0.25–1.30 ng/L, respectively (Table S7), and recoveries fell in the range 93–112% with a concentration of 2 ng/L and 94–108% with one of 10 ng/L. Also, repeatability was 4–14% with 2 ng/L and 2–6% with 10 ng/L, and reproducibility 6–15% with the former concentration and 2–6% with the latter (Table S8). Finally, signal suppression/enhancement (%SSE) ranged from 92 to 115% (Table S8).

Solid-phase extraction (SPE) with Oasis HLB cartridges is a widely used sample treatment for extracting drugs of abuse from drinking water. Conditioning and eluting SPE cartridges requires using 10–20 mL of methanol per sample. Also, evaporated extracts usually require redissolution in a water:methanol mixture. As a result, sample volumes easily amount to 200 mL. All this increases cost and analysis time per sample. By contrast, the SUPRAS-based method uses only 0.1 mL of hexanol, 0.2 mL of THF and 1.7 mL of sample; also, it requires no additional sample treatment to provide good recoveries and limits of quantification (LOQ). The proposed microextraction method has a low cost per sample, simplifies sample treatment, reduces analysis times and uses green chemistry.

3.2. Presence of drugs of abuse in tap water

The proposed method was used to determine the target drugs (Table S2) in tap water from eight EU countries (see sampling points in Table S1). A total of seven illicit drugs [viz., methadone (MET), cocaine (COC), benzoylecgonine (BZE), 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA), 3,4-methylenedioxy-methamphetamine (MDMA), methamphetamine (MA) and amphethamine (AM)] were detected in 72 of the 119 samples, with 64 containing the drugs at levels above the method quantification limit (MQL). Therefore, more than 60% of all samples tested positive for at least one of the target drugs. Fig. 1 shows the locations where the water samples testing positive for some drug were collected. The drug concentrations found, and their relative standard deviations, are shown in Table S9. Drug recoveries from samples spiked with a 10 ng/L concentration ranged from 70 to 120% (Table S10). Table 1 shows the mean concentration of each drug, and its detection frequency (%DF), as well as the number of samples with concentrations exceeding MQL.

Drugs from the cocaine group were the most frequently detected. Thus, 35 samples (29.4%) from Spain, France, Belgium, Germany, Portugal, Luxembourg, Turkey and Italy tested positive for them. Cocaine (COC) was detected in 34 samples (28.6%) but BZE (its main metabolite) only in 3 (2.5%) (Fig. 1). A number of samples contained COC concentrations exceeding those previously reported by Boleda et al. (2011b) (maximum 2.3 ng/L in Spain and 2.9 ng/L in Germany) and Mendoza et al. (2016) (0.11–85.67 ng/L in Spain). Such concentrations were 16–102 ng/L in Spain, < MQL–72 ng/L in France, 7.3 ng/L in Belgium, < MQL–18 ng/L in Germany, < MQL–340 ng/L in Portugal, 3–83 ng/L in Italy and 1.4 ng/L in Turkey (Table S9).. Spain, France, Italy, Portugal and Germany were the countries with the highest frequencies and average concentrations of COC (Table 1). These results are consistent with prevalence data of COC use among young adults (15–34 yr) (EMCDDA, 2019), which were similar in Spain (2.8%) and France (3.0%), and slightly lower in Italy and Germany (1.1–2.5%). The greatest amounts of residual COC in wastewater (2018) from these four countries were found in two Spanish cities, namely: Barcelona (1000 mg/1000 inhabitants/day) and Valencia (750 mg/1000 inhabitants/

Table 1
Detection frequency (%) and mean concentration (ng/L) of each drug in tap water.

Country	MET		COC		BZE		AM		MA		MDEA		MDMA	
	DF	Conc [a]	DF	Conc [a]	DF	Conc [a]	DF	Conc[a]	DF	Conc [a]	DF	Conc [a]	DF	Conc [a]
Spain	7	0.5 (3)	22	37.2 (13)	0	–	38	13.0 (19)	0	–	3	1.4 (2)	5	–
France	0	–	37	18.6 (10)	3	12.0 (1)	40	15.3 (11)	3	–	0	–	3	0.5 (1)
Belgium	50	0.4 (1)	17	7 (1)	0	–	0	–	17	1.0 (1)	0	–	0	–
Germany	14	0.3 (1)	57	11.7 (3)	0	–	14	6.4 (1)	0	–	0	–	0	–
Portugal	0	–	57	166.7 (3)	14	100.0 (1)	0	–	0	–	0	–	0	–
Italy	0	–	50	32.8 (3)	0	–	0	–	0	–	0	–	0	–
Turkey	0	–	50	1.4 (1)	0	–	50	7.1 (1)	0	–	0	–	50	–
Luxembourg	100	0.5 (1)	0	–	100	7.0 (1)	0	–	0	–	0	–	0	–

DF detection frequency. [a]mean concentration as calculated for the samples exceeding MQL (method quantification limit). The numbers of samples with analyte concentrations above MQL are shown in brackets.

day). The high concentrations of COC found in drinking water from Portugal are inconsistent with the fact that its COC prevalence (≤0.5%) and residual concentrations in wastewater were both lower than those in Spain, France and Italy (EMCDDA, 2019). This result may have been a consequence of Portuguese ports being among the major access points for COC reaching the EU from South and Central America (EMCDDA, 2019). By way of example, Figure S1 shows the chromatogram for the sample from Sines (Portugal).

The drugs in the amphetamine group were the second most detected. Thus, a total of 36 samples (30.2 %) contained amphetamines at levels above MQL. AM was the most widely detected drug in the group (26.9% of samples), with concentrations from 0.9 to 86.2 ng/L. The other amphetamines were encountered in 1.7% (MDEA) and 0.8% (MDMA and MA) of samples. These results depart from previously reported values. Thus, Boleda et al. (2011b) found AM in 4% of their samples and average concentrations below MQL. However, our results are in line with the latest European reports on drugs, based on which AM is the second most widely used stimulant (EMCDDA, 2021). The growing demand for amphetamines is leading to local production in uncontrolled home laboratories from which residual amounts enter the water cycle. The highest AM frequencies were observed in Spain and France, with similar mean concentrations (13 ng/L in the former country and 15 ng/L in the latter) consistent with prevalence data for young adults (15–34 yr): 0.6–1.0% (EMCDDA, 2019). The concentration of AM residues in wastewater from Valencia and Barcelona was 25 and 50 mg/1000 inhabitants/day, respectively; and below the limit of quantification in wastewater samples from France (EMCDDA, 2019). In any case, amphetamine consumption has grown in recent years, and so has its concentration in wastewater in most countries as a result (EMCDDA, 2021).

In the opiate group, MET was detected at levels above MQL in 6 (5.0%) samples from Spain, Belgium, Germany and Luxembourg, with concentrations of 0.3–0.70 ng/L and a mean of 0.46 ng/L in Spain. The opiate frequency was lower than those of previous reports (14–29%; Mendoza et al., 2016); by exception, that of methadone was similar to reported values. The presence of these compounds in drinking water can be ascribed to the widespread use of methadone in the EU, where it is also used therapeutically as a replacement for heroin on drug addicts (EMCDDA, 2019). Because conventional purification processes eliminate MET from water only in part, additional treatments such as reverse osmosis, ozonation or granulated activated carbon (GAC) filtration are required for its complete removal (Boleda et al., 2011b, 2009; Valcárcel et al., 2012).

None of the target cannabinoids was found in the samples despite their being the most widely used drugs of abuse in the EU. Possibly, their high hydrophobicity (log K_{ow} greater than 6) causes breakdown to a greater extent than in other illicit drugs, and its adsorption onto solid particles and biosolids as a result. In addition, perchlorination and sand filtration have proved very effective for their removal at drinking water purification plants (DWTP; Boleda et al., 2009; Valcárcel et al., 2012).

3.3. Tentative evaluation of the potential risk of human exposure to drugs of abuse through drinking water in the EU

Drugs of abuse overcome some barriers in wastewater treatment and water purification plants, eventually reaching the water cycle as a result. In fact, the efficiency with which drugs are removed depends on the particular treatment applied. In any case, a complete removal is usually impossible. Thus, drugs such as morphine are typically removed by more than 99%, whereas others such as MDMA, BZE, codeine and methadone are eliminated to a variable extent (25–99%) depending on the particular purification treatment. In previous work, COC was removed by 99% and MDA by 7% (Boleda et al., 2011a, 2009; Rodayan et al., 2016).

Because illicit drugs are increasingly present in tap water, assessing the health risks of the populations being exposed to them is more than warranted. In this work, we conducted a tentative assessment of health risks for the European population posed by exposure by direct ingestion and dermal contact.

3.3.1. Daily intake of drugs through drinking water

Table 2 shows the mean calculated exposure to the target drugs through drinking water in adults and children, and Table S11 those for each sample containing some drug. $D_{ingestion}$ decreased in the following sequence: COC > BZE > AM > MA > MDEA > MDMA > MET. Also, COC and its metabolite BZE had $D_{ingestion}$ values up to 300 times greater than those for the other drugs, and were the two main drugs present in adults and children in almost all countries. Although no COC was detected in the only sample from Luxembourg, its $D_{ingestion}$ value for BZE was quite high (0.15 ng/kg·day for adults and 0.58 ng/kg·day for children). Obviously, this result cannot be held representative of drinking water in the whole country since only one sample from it was analysed; however, the fact that BZE was indeed detected suggests that $D_{ingestion}$ for COC would have increased with increasing number of samples. The highest $D_{ingestion}$ value for AM was found in France, with a mean of 0.33 ng/kg·day for adults and 0.62 ng/kg·day for children, followed by Spain, with 0.27 ng/kg·day for adults and 0.53 ng/kg·day for children. The $D_{ingestion}$ values for MA, MDEA, MDMA and MET in the countries where they were detected in some sample were all lower than 0.1 ng/kg·day for both adults and children.

The degree of exposure to the target drugs in the European countries studied was assessed by comparing the calculated $D_{ingestion}$ values with the minimum required performance levels (MRPL) in urine set by the World Anti-Doping Agency (WADA, 2022), namely: 50 000 ng/L for drugs in the amphetamine group and BZE, 10 000 ng/L for COC and 25 000 ng/L for MET. The sample from Sines (Portugal) testing positive for COC and BZE was calculated to have a $D_{ingestion}$ value of 7.2 ng/kg·day for COC and 2.1 ng/kg·day for BZE in adults. Cocaine is rapidly metabolized in the body, usually by enzymatic hydrolysis to BZE mainly, only 1–5% being excreted as COC in urine. Multiplying the average weight of European adults (70.8 kg) by the calculated daily exposure dose (7.2 ng/kg·day) yielded the amount of cocaine inadvertently ingested in one day: 510.0 ng. If only 5% of all cocaine is excreted

Table 2
Average daily exposure ($D_{ingestion}$ and D_{dermal}, ng/kg·day) to the target drugs through consumption of drinking water and dermal contact in adults and children.

		MET		COC		BZE		AM		MA		MDEA		MDMA	
	Average exposure (ng/kg/day)	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children
Spain	$D_{ingestion}$	0.01	0.02	0.79	1.51	–	–	0.27	0.53	–	–	0.03	0.05	–	–
	D_{dermal}	6.8E-07	1.1E-06	4.3E-05	6.8E-05	–	–	1.1E-04	1.8E-04	–	–	5.4E-06	8.7E-06	–	–
France	$D_{ingestion}$	–	–	0.39	0.75	0.25	0.99	0.33	0.62	–	–	–	–	0.01	0.04
	D_{dermal}	–	–	2.1E-05	3.4E-05	6.7E-06	1.1E-05	1.3E-04	2.1E-04	–	–	–		2.1E-06	3.3E-06
Belgium	$D_{ingestion}$	0.01	0.04	0.15	0.30	–	–	–	–	0.02	0.08	–	–	–	–
	D_{dermal}	6.4E-07	1.0E-06	8.3E-06	1.4E-05	–	–	–	–	7.4E-06	1.2E-05	–	–	–	–
Germany	$D_{ingestion}$	0.01	0.02	0.20	0.38	–	–	0.14	0.53	–	–	–	–	–	–
	D_{dermal}	4.5E-07	7.3E-07	1.1E-05	1.7E-05	–	–	5.4E-05	8.7E-05	–	–	–	–	–	–
Portugal	$D_{ingestion}$	–	–	3.53	6.76	2.12	8.22	–	–	–	–	–	–	–	–
	D_{dermal}	–	–	1.9E-04	3.1E-04	5.6E-05	9.0E-05	–	–	–	–	–	–	–	–
Italy	$D_{ingestion}$	–	–	0.69	1.33	–	–	–	–	–	–	–	–	–	–
	D_{dermal}	–	–	3.7E-05	6.1E-05	–	–	–	–	–	–	–	–	–	–
Turkey	$D_{ingestion}$	–	–	0.03	0.11	–	–	0.15	0.58	–	–	–	–	–	–
	D_{dermal}	–	–	1.6E-06	2.6E-06	–	–	5.9E-05	9.6E-05	–	–	–	–	–	–
Luxembourg	$D_{ingestion}$	0.01	0.04	–	–	0.15	0.58	–	–	–	–	–	–	–	–
	D_{dermal}	7.2E-07	1.2E-06	–	–	3.9E-06	6.1E-06	–	–	–	–	–	–	–	–

unchanged, and the mean volume of urine excreted in one day is taken to be 1.4 L, then the excreted concentration of COC and BZE is 18.2 and 346.1 ng/L, respectively. This concentration in urine is equivalent to 0.2% and 0.7% of MRPL for cocaine and BZE, respectively. Because the concentration of BZE found in each sample should be added, the combined concentration of BZE in urine was 453.2 ng/L, which is 0.9% of its MRPL. However low these proportions may seem, they are not negligible because ingestion of BZE through tap water is involuntary and MRPL are used to check whether athletes have used doping substances voluntarily —and in greater amounts. Consequently, the amounts of drugs of abuse involuntarily ingested through tap water over a lifetime should be estimated as accurately as possible in order to anticipate potential adverse effects on health. In this work, we assumed a worst-case scenario. Thus, the whole population in the studied countries was assumed to drink tap water instead of bottled water, and to consume 1.4 L/day (adults) or 0.74 L/day (children). Also, the primary aim was not to obtain absolute data of exposure to drugs of abuse, but rather to show that tap water can be a new source of exposure to such drugs in humans.

3.3.2. *Daily exposure to drugs through dermal contact*

Whilst people are exposed to drugs of abuse mainly by direct ingestion of contaminated drinking water, alternative routes such as dermal contact should also be considered. As can be seen from Table 2, D_{dermal} followed the same pattern as $D_{ingestion}$ since the two were closely related to the drug concentrations found in the samples. As expected, D_{dermal} values were 4–7 orders of magnitude lower than $D_{ingestion}$ values; also, the former were much lower than WADA's MRPL, so dermal exposure to the target drugs should pose no serious health risk. However, one should consider that dermal exposure occurs every day over a lifetime.

There are additional sources of exposure that have not been considered here (e.g. food cooked in tap water, inhaled water aerosols or recreational baths in swimming pools) due to their intermittency over time and expected low ratios of exposure. Thus, not all the food consumed is cooked with water, the inhalation of water aerosols does not occur every day and recreational baths only occur on a certain date of the year and not for all the citizens.

4. Conclusions

A novel method for the extraction of twelve different drugs of abuse from tap water with supramolecular solvents and their determination by liquid chromatography–tandem mass spectrometry was developed and validated. The proposed method allows the drugs to be extracted and interferents removed in a single stage, which simplifies sample treatment and reduces analysis times. Also, it avoids the need for high volumes of solvents and is thus compliant with the principles of green chemistry. The method was used to quantify the 12 target drugs in 119 drinking water samples collected from 8 different EU countries. A total 72 samples tested positive for at least one drug, 64 containing drug concentrations above the method quantification limit (MQL). Cocaine (COC) and amphetamine (AM) were the two drugs detected in the greatest numbers of samples (31%) and also at the highest concentrations (0.48–340 ng/L). These results are consistent with the European Drug Report, and confirm that wastewater and water purification treatments are not entirely effective to remove these contaminants, about which no specific law has been passed. A tentative evaluation of health risks from exposure to the drugs through ingestion of tap water provided mean $D_{ingestion}$ values of 0.0064–3.531 ng/kg·day in adults, and 0.0247–6.7580 ng/kg·day in 5-year-old and younger children. All $D_{ingestion}$ values were lower than the MRPL set by the World Anti-Doping Agency (WADA), so there should be no risk to human health; however, they are still important since the drugs are involuntarily ingested through tap water. Exposure through dermal contact with tap water was also evaluated. Despite the extremely low levels found, dermal exposure illustrates the wide variety of potential sources of exposure to the target

drugs and suggests that their potential combined effect during a lifetime should be carefully considered. Therefore, future studies should address the actual risk of exposure of these drugs from multiple sources.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107281.

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