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Simultaneous ozonation of 90 organic micropollutants including illicit drugs and their metabolites in different water matrices†

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The ozonation of 90 chemically diverse organic micropollutants (OMPs) including four classes of illicit drugs and their metabolites was studied in pure buffered water, tap water and wastewater effluent at three specific ozone doses and three pH levels. The second order rate constants for the reaction of 40 OMPs with ozone were known and span across 8 orders of magnitude, from below 1 M^{-1} s^{-1} to above 10^7 M^{-1} s^{-1}. 47 of the tested OMPs were removed to at least 90% at the highest specific ozone dose of 0.3 mM O_3 per mM C at pH 7. However, most illicit drugs, including cocainics, amphetamines and ecstasy-group compounds, were ozone-resistant due to their lack of ozone-reactive functional groups. Exceptions included some opioids and the cocaine biomarker anhydroecgonine methylester which contain olefinic bonds and/or activated benzene rings. Different removal trends at different pH for OMPs were due to the combined effect of target compound speciation and ozone stability, leading to elimination of less than 70% for all OMPs at pH 11. In both tap water and wastewater effluent scavenging by matrix components led to lower ozone exposure compared to pure buffered water and consequently lower removal of OMPs. This multi-compound ozonation study utilised liquid chromatography-mass spectrometry to provide a large dataset on the removal of environmentally relevant OMPs, including those of interest for drinking water regulations. Besides including pharmaceutically active compounds that have not been studied with ozone before (*e.g.* gliclazide, anhydroecgonine methylester, quetiapine, 6-monoacetylmorphine), this study simultaneously shows ozonation data for a wide range of illicit drugs.

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Water impact

Ozonation is a promising technology for the removal of organic micropollutants from water. Here, ozonation results for 90 chemically diverse micropollutants including illicit drugs are reported and interpreted based on compound chemical structure. The study provides a valuable ozonation database for a large variety of micropollutants with specific focus on occurrence and ozonation of illicit drugs in drinking water.

1. Introduction

Many different organic micropollutants (OMPs) including pharmaceuticals, personal care products, hormones and their transformation products can be found at trace concentrations in surface water, groundwater and finished drinking water.[1–4] OMPs may reach drinking water resources through numerous routes, with their main sources being the discharge of wastewater effluent and diffuse pollution, such as agricultural and urban runoff.[5,6] OMPs have raised scientific and public concern regarding their impact on the environment and on human health, including short-term and long-term toxicity, endocrine disruption, antibiotic resistance of microorganisms and accumulation in soils, plants and animals.[7,8] A group of OMPs of particular interest are illicit drugs and their metabolites,[9–12] due to biological

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activity and largely unknown effects on the environment and on water quality.[13,14]

Ozonation is among the most effective methods for the abatement of OMPs in full-scale water treatment applications.[15] Ozone is a strong oxidant which reacts with organic compounds in water either directly, or indirectly through free radicals produced from ozone decomposition.[16] The ozonation of single compounds has been extensively studied in terms of degradation, reaction kinetics and identification of transformation products.[17–20] Analytical advancements have also enabled the investigation of the simultaneous ozonation of mixtures of OMPs. Multi-component ozonation studies have been performed at lab-, pilot- and full-scale and have included a wide range of compounds.[21–25] However, the ozonation of some classes of OMPs, including illicit drugs and their metabolites, remains less conclusively studied.[11,26–28]

The reactivity of organic compounds with ozone depends on their chemical structure, with second order rate constants reaching across several orders of magnitude.[29] Kinetic parameters of ozonation reactions can be determined experimentally or calculated through QSAR (quantitative structure–activity relationship) models.[30] In complex water matrices, such as surface water, the properties of the matrix affect the stability of dissolved ozone, while matrix components act as oxidant scavengers, increasing the required ozone dose for a desired extent of OMP abatement. Therefore, the abatement of OMPs by ozonation can be related to kinetic parameters, operational parameters (*e.g.* ozone dose, temperature) and water quality parameters (*e.g.* organic carbon concentration, pH, alkalinity).[31,32]

The aim of this study was to gain insights into the simultaneous ozonation of 90 chemically diverse OMPs. The selection of the compounds was based on existing and proposed EU legislation, UK prescription data, metabolism and excretion from the human body, known environmental occurrence, persistence during wastewater treatment and toxicity to aquatic organisms.[33] Ozonation experiments were conducted in three different water matrices (pure buffered water, tap water and wastewater effluent), at different ozone doses and pH levels. In contrast to the majority of previous ozonation studies, several illicit drugs and illicit drug metabolites were investigated. For some compounds, the reactivity with ozone in water is investigated for the first time, including the diabetes drug gliclazide, the cocaine biomarker anhydroecgonine methylester, the antipsychotic drug quetiapine and the heroin metabolite 6-monoacetylmorphine (O-6-MAM).

2. Materials and methods

Chemicals

OMPs were either purchased dissolved in 0.1 or 1.0 mg mL^{-1} solutions or as powder. Stock solutions from powders were prepared at 1 mg mL^{-1} in either acetonitrile or methanol and stored in the dark at −20 °C. All aqueous solutions were made in ultrapure water (Milli-Q, Millipore, USA). Chemicals and solvents (purity 95% or higher) were used as received from various commercial suppliers. Methanol, ammonium acetate (NH_4OAc), ammonium fluoride (NH_4F) and acetic acid (CH_3-$COOH$) for chromatographic analysis (all HPLC grade), phosphoric acid (H_3PO_4), disodium phosphate (Na_2HPO_4), monosodium phosphate (NaH_2PO_4) and sodium tetraborate ($Na_2B_4O_7$) were obtained from either Sigma-Aldrich or Fisher Scientific, sodium thiosulfate ($Na_2S_2O_3$) from Merck, sodium hydroxide (NaOH) from PanReac.

Table 1 provides a list of the 90 OMPs studied, including information about their estimated or known ozone reactivity. The referenced studies consist of both mechanistic single-compound studies and multi-compound studies. Table S1† provides CAS number, molecular weight, formula, structure, and instrument detection and quantification limit for each compound. Table S2† provides second order rate constants for the reactions of the compounds with OH radicals, when available.

Ozonation experiments

All reactions were conducted in 10 mL glass flasks. Freshly prepared methanol stock solution containing all 90 compounds at equal mass concentration was spiked into empty flasks. The solvent was evaporated under a gentle stream of nitrogen followed by re-dissolution with the aqueous phase, which consisted of either buffered ultrapure water at pH 3 (10 mM H_3PO_4/H_2NaPO_4), pH 7 (10 mM H_2NaPO_4/HNa_2PO_4) or pH 11 (10 mM H_3BO_3), tap water (total organic carbon (TOC) 1.5 mg C L^{-1}, pH 7.5) or secondary wastewater effluent (TOC 7.1 mg C L^{-1}, pH 7.8) from a wastewater treatment plant in the Southwest of England. The concentration of each OMP in the final reaction solution was approximately 100 μg L^{-1}, which translated into a TOC of 6 mg C L^{-1} added to the TOC of the matrix. A high initial concentration of each OMP was chosen to avoid an analyte concentration step prior to LC-MS (liquid chromatography coupled with tandem mass spectrometry) analysis.

Ozone was produced with a BMT 803 N ozone generator (BMT Messtechnik, Berlin, Germany). Stock solutions (1.3–1.5 mM, 62–72 mg L^{-1}) were made by sparging ozone gas through ultrapure water (≤4 °C) that was cooled in an ice bath. The dissolved ozone concentration of stock solutions was quantified directly spectrophotometrically using a molar absorption coefficient of ε = 3000 M^{-1} cm^{-1} at an absorption wavelength of λ = 258 nm.[69]

The ozone stock solution was added under vigorous stirring to each flask to achieve ozone doses on a carbon basis of 0.05 mM O_3 per mM C (0.2 g O_3 per g C), 0.15 mM O_3 per mM C (0.6 g O_3 per g C) and 0.3 mM O_3 per mM C (1.2 g O_3 per g C), to cover the range used for water treatment. Specific ozone doses on a molar basis are hereafter used. After 5 min reaction time, the samples were quenched with 0.1 M sodium thiosulfate ($Na_2S_2O_3$) and analysed within 24 h.

Analytical methods

A detailed description of the analytical method used for the OMPs can be found elsewhere.[33] Briefly, the target

Table 1 Studied organic micropollutants (in alphabetical order). k_{O_3} values are experimental or calculated by QSAR as indicated. Estimated ozone reactivity is based on compound structure. Literature column shows reference for k_{O3} or other relevant study. pK_a values were obtained from[33]

Chemical	Mode of action/use	pK_a (most acidic)	pK_a (most basic)	Ozone-(non) reactive functional groups	k_{O_3} (M^{-1} s^{-1}) at pH 7 or estimated ozone reactivity	Literature
1,7 Dimethylxanthine	Human indicator	8.5	0.2	Amide, imidazole	Medium	34
10,11 Dihydro 10 hydroxycarbamazepine	Anti-epileptic metabolite	13.8	−0.5	Amide, benzene ring	Low	
Acetaminophen	NSAID	9.9	1.7	Benzene ring	4.1×10^6	35
Amphetamine	Stimulant	—	9.9	(Protonated) amine, benzene ring	Low	27
Anhydroecgonine methylester	Stimulant metabolite	—	8.0	Olefin, (protonated) amine	High	
Atenolol	Beta-blocker	13.9	9.4	Amide, (protonated) amine, benzene ring	1.7×10^3	36
Atorvastatin	Lipid regulator	4.3	0.4	Benzene ring	Medium	
Azathioprine	Anti-cancer	—	7.5	(Deactivated) thioether, imidazole	Low	37
Azithromycin	Antibiotic	13.3	8.6	(Protonated) amine	1.1×10^5	38
Benzophenone-1	UV filter	7.7	—	Benzene ring	High	
Benzophenone-2	UV filter	7.0	—	Benzene ring	High	39
Benzophenone-3	UV filter	7.6	—	Benzene ring	6.9×10^5	40
Benzophenone-4	UV filter	−0.7	—	Benzene ring	Medium	41
Benzoylecgonine	Stimulant metabolite	3.4	10.8	(Protonated) amine, deactivated benzene ring	Low	11, 27
Bezafibrate	Lipid regulator	3.3	−2.1	Amide, benzene ring	590	18, 42
Bisphenol A	Plasticizer	10.3	—	Phenol	1.1×10^6	43
Butylparaben	Parabens	8.2	—	Phenol	7.9×10^7	44
Caffeine	Human indicator	—	0.5	Amide, imidazole	673	23, 45
Carbamazepine	Anti-epileptic	13.9	−0.5	Olefin, amide, benzene ring	3×10^5	18, 46
Carbamazepine 10,11 epoxide	Anti-epileptic metabolite	13.9	−0.5	Amide, benzene ring	Low	24
Cetirizine	Antihistamine	3.5	6.7	(Protonated) amine, benzene ring	1.7×10^5	47
Cimetidine	H2 receptor antagonists	14.1	7.1	Thioether, amidine, imidazole	High	
Citalopram	Anti-depressant	—	9.6	(Protonated) amine, deactivated benzene ring	Low	48, 49
Clarithromycin	Antibiotic	13.1	8.2	(Protonated) amine	7×10^4	50
Cocaethylene	Stimulant metabolite	—	9.0	(Protonated) amine, deactivated benzene ring	Low	
Cocaine	Stimulant	—	9.0	(Protonated) amine, deactivated benzene ring	Low	11, 27
Codeine	Analgesic	13.4	8.2	Olefin, (protonated) amine, benzene ring	High	24
Cotinine	Human indicator	—	4.7	Amide, pyridine	Low	11, 24
Creatinine	Human indicator	—	6.9	Amide, (protonated) amine	2	51
Desmethylcitalopram	Anti-depressant metabolite	—	10.5	(Protonated) amine, deactivated benzene ring	Low	48
Desmethylvenlafaxine	Anti-depressant metabolite	10.0	9.3	Phenol, (protonated) amine	High	49
Diclofenac	NSAID	4.9	−2.3	Aniline	1×10^6	18, 52
Dihydrocodeine	Analgesic	14.2	8.4	(Protonated) amine, benzene ring	Medium	
Dihydromorphine	Analgesic metabolite	9.6	8.4	(Protonated) amine, benzene ring	High	
Diltiazem	Calcium channel blocker	—	8.9	(Protonated) amine, benzene ring	High	
E1	Steroid estrogen	10.3	—	Phenol	9.4×10^5	43, 53
E2	Steroid estrogen	10.3	—	Phenol	2.2×10^6	43, 53
EDDP	Analgesic metabolite	—	7.7	Olefin, (protonated) amine, benzene ring	High	28
EE2	Steroid estrogen	10.2	—	Phenol	2.3×10^6	43
Ephedrine/pseudoephedrine	Drug precursor	14.0	9.4	(Protonated) amine, benzene ring	Low	
Ethylparaben	Parabens	8.3	—	Phenol	5.5×10^7	44

Table 1 *(continued)*

Chemical	Mode of action/use	pK_a (most acidic)	pK_a (most basic)	Ozone-(non) reactive functional groups	k_{O_3} (M^{-1} s^{-1}) at pH 7 or estimated ozone reactivity	Literature
Fexofenadine	Antihistamine	4.4	9.4	(Protonated) amine, benzene ring	9.0×10^3	47
Fluoxetine	Anti-depressant	—	10.1	(Protonated) amine, benzene ring	1.6×10^4	54
Gliclazide	Diabetes	6.1	3.9	Amide, (protonated) amine, deactivated benzene ring	High	
Heroin	Opioid	—	7.9	Olefin, (protonated) amine, benzene ring	High	
Ibuprofen	NSAID	4.4	—	Benzene ring	9.6	18
Ifosfamide	Anti-cancer	—	1.4	Phosphamide	<1 (QSAR)	55
Iopromide	X-ray contrast media	10.6	−2.6	Amide, deactivated benzene ring	<0.8	18
Irbesartan	Hypertension	4.2	2.6	Amide, (protonated) amine, benzene ring	24	25
Ketamine	Anaesthetic	—	6.5	(Protonated) amine, deactivated benzene ring	Medium	27
Ketoprofen	NSAID	4.2	—	Deactivated benzene ring	0.40	56
Lisinopril	Hypertension	2.2	10.5	(Protonated) amine, benzene ring	Low	
MDA	Stimulant	—	10.0	(Protonated) amine, anisole	High	
MDMA	Stimulant	—	10.3	(Protonated) amine, anisole	High	11, 27
MDPV	Stimulant	—	8.4	(Protonated) amine, anisole	Medium	
Mephedrone	Stimulant	—	7.4	(Protonated) amine, deactivated benzene ring	Medium	
Metformin	Diabetes	—	12.3	(Protonated) amine	1.2	19
Methadone	Analgesic	—	9.5	(Protonated) amine, benzene ring	Low	28
Methamphetamine	Stimulant	—	10.4	(Protonated) amine, benzene ring	Low	27
Methotrexate	Anti-cancer	3.5	5.6	Aniline, amide, (protonated) amine	High	57
Methylparaben	Parabens	8.3	—	Phenol	4.8×10^7	44
Metoprolol	Beta-blocker	13.9	9.4	(Protonated) amine, benzene ring	2.0×10^3	36
Mirtazapine	Anti-depressant	—	8.1	(Protonated) amine, benzene ring, pyridine	Medium	49
Morphine	Analgesic	9.5	8.3	Olefin, (protonated) amine, benzene ring	6.4×10^6 (QSAR)	55
Naproxen	NSAID	4.8	—	Naphthalene	2×10^5	58
N-Desmethyltramadol	Analgesic metabolite	14.5	10.6	(Protonated) amine, anisole	Medium	
Nicotine	Human indicator	—	8.0	(Protonated) amine, pyridine	Medium	11, 24
Norcodeine	Analgesic metabolite	13.3	9.3	Olefin, (protonated) amine, benzene ring	High	26
Norephedrine	Stimulant metabolite	12.1	8.5	(Protonated) amine, benzene ring	Low	
Norfluoxetine	Anti-depressant metabolite	—	9.1	(Protonated) amine, benzene ring	65	54
Norketamine	Anaesthetic metabolite	—	6.3	(Protonated) amine, deactivated benzene ring	Medium	
Normorphine	Analgesic metabolite	9.2	9.5	Olefin, (protonated) amine, benzene ring	High	
O-6-MAM	Opioid metabolite	9.4	8.0	Olefin, (protonated) amine, benzene ring	High	
O-Desmethyltramadol	Analgesic metabolite	10.0	9.6	(Protonated) amine, phenol	High	
Pholcodine	Cough suppressant	13.4	8.2	Olefin, (protonated) amine, benzene ring	High	
Propranolol	Beta-blocker	13.8	9.5	Naphthalene, (protonated) amine	1×10^5	36
Propylparaben	Parabens	8.2	—	Phenol	7.0×10^7	44
Quetiapine	Anti-psychotic	14.4	6.7	Amidine, benzene ring, thioether	High	
Ranitidine	H2 receptor antagonists	—	8.4	Amidine, furan, thioether	2.1×10^6	59

Table 1 *(continued)*

Chemical	Mode of action/use	pK_a (most acidic)	pK_a (most basic)	Ozone-(non) reactive functional groups	k_{O_3} (M^{-1} s^{-1}) at pH 7 or estimated ozone reactivity	Literature
Sertraline	Anti-depressant	—	9.5	(Protonated) amine, benzene ring	Medium	49
Sulfamethoxazole	Antibiotic	5.8	1.4	Aniline, sulfonamide	2.6×10^6	18, 60
Sulfasalazine	Antibacterial	2.7	0.9	Benzene ring, sulfonamide	High	
Tamoxifen	Anti-cancer	—	8.7	Olefin, benzene ring	High	61
Temazepam	Hypnotic	11.7	1.6	Amide, deactivated benzene ring	Low	62
Tramadol	Analgesic	14.5	9.6	(Protonated) amine, anisole	2.2×10^3	63
Triclosan	Antibacterial	7.8	—	Benzene ring	3.8×10^7	64, 65
Trimethoprim	Antibiotic	—	7.0	(Protonated) amine, pyrimidine, benzene ring	2.7×10^5	38, 66
Tylosin	Veterinary	13.1	7.4	Olefin, (protonated) amine	5.1×10^5	38
Valsartan	Hypertension	3.6	0.6	Amide, benzene ring	38 (QSAR)	55, 67
Venlafaxine	Anti-depressant	14.8	9.3	(Protonated) amine, anisole	1.3×10^3	49, 68

compounds were analysed by liquid chromatography-tandem mass spectrometry (LC-MS) using a Waters Acquity UPLC system (Waters, Manchester, UK) coupled to a Xevo TQD (Triple Quadrupole Mass Spectrometer, Waters, Manchester, UK) equipped with an electrospray ionisation source. The determination of acidic and basic compounds was performed

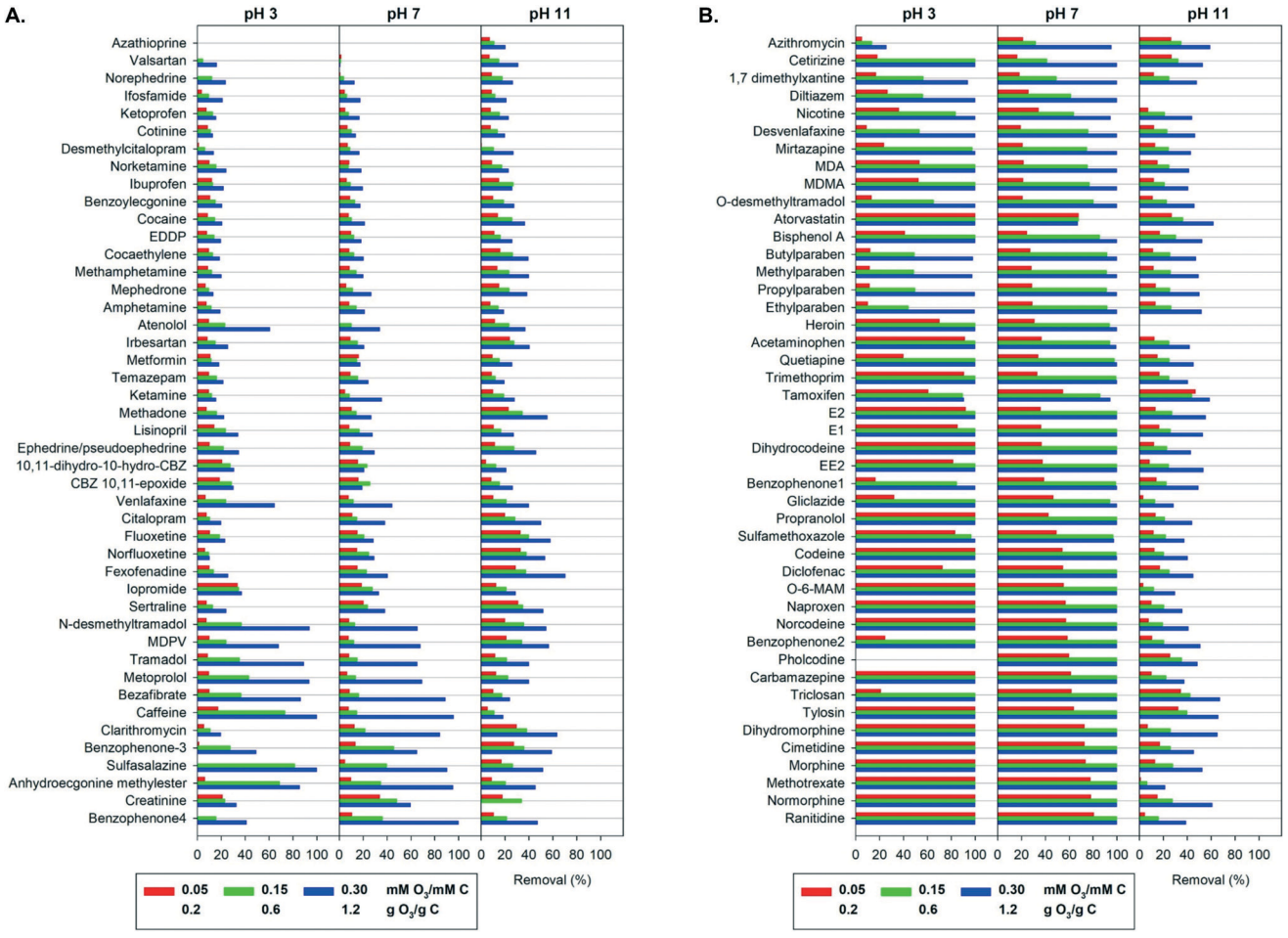

Fig. 1 A. Simultaneous removal of 90 organic micropollutants added to pure buffered water as a function of the specific ozone dose and the pH (arranged with increasing average removal at pH 7). Error bars from duplicate analysis of samples were omitted for figure overview and are provided in the ESI† xlsx-data file. B. Simultaneous removal of 90 organic micropollutants added to pure buffered water as a function of the specific ozone dose and the pH (arranged with increasing average removal at pH 7). Error bars from duplicate analysis of samples were omitted for figure overview and are provided in the ESI† xlsx-data file.

in negative and positive ionisation mode, respectively. Limits of quantification and detection for individual analytes are presented in Table S1.† Each sample was analysed in duplicate. Method performance is described in detail elsewhere.[33]

Total organic carbon was analysed with a Shimadzu TOC-VCPN Analyzer (Shimadzu, Kyoto, Japan). Spectroscopic measurements were conducted with a Cary 100 UV–Vis Spectrometer (Agilent Technologies, Santa Clara, California, USA).

Ozone and OH radical exposures

The exposure (time-integrated concentration) of OH radicals was estimated from the elimination percentage of ketoprofen (KET). Ketoprofen was selected because it is the compound with the lowest ozonation second order rate constant (0.4 M^{-1} s^{-1}) among the compounds included in this study (see Table 1). Additionally, ketoprofen has a known and high second order rate constant for its reaction with OH radicals (see Table S2). Therefore, its reaction with ozone can be considered negligible, while the OH radical exposure was calculated based on eqn (1):

$$k_{\mathrm{OH/KET}}\int [\mathrm{OH}]\,\mathrm{d}t = -\ln\left(\frac{[\mathrm{KET}]}{[\mathrm{KET}]_0}\right) \quad (1)$$

The ozone exposure was then estimated from the elimination percentage of carbamazepine (CBZ), or tramadol (TRA) in cases when carbamazepine was below the limit of quantification after ozonation. Carbamazepine has a high ozone reactivity that does not depend on the pH, while tramadol has a moderate ozone reactivity that does depend on the pH, which was considered (see Table 1). The ozone exposure was calculated from eqn (2):

$$k_{\mathrm{OH/CBZorTRA}}\int [\mathrm{OH}]\mathrm{d}t + k_{\mathrm{O_3/CBZorTRA}}\int [\mathrm{O_3}]\,\mathrm{d}t = -\ln\left(\frac{[\mathrm{CBZ\ or\ TRA}]}{[\mathrm{CBZ\ or\ TRA}]_0}\right) \quad (2)$$

3. Results and discussion

Abatement by ozonation of organic micropollutants including illicit drugs added to pure water at pH 7

An overview of the elimination of the 90 OMPs by ozonation in pure buffered water at three different pH values and at three specific ozone doses is shown in Fig. 1. As expected by the chemical diversity of the OMPs (see Table 1 and Table S1†), the results range from no removal to complete removal. At the highest ozone dose of 0.3 mM O_3 per mM C and at pH 7 almost half of all compounds were removed to below the limit of detection. The medium ozone dose of 0.15 mM O_3 per mM C at pH 7 led to 80% or higher removal for more than a third of compounds. At the lowest ozone dose of 0.05 mM O_3 per mM C at pH 7 partial removal occurred for most compounds.

The OMPs may be classified into three groups according to their attenuation at the highest specific ozone dose at pH 7: group I compounds were readily removed by more than 90%, group II compounds had a moderate removal of 50 to 90% and group III compounds were hard to remove with less than 50% removal. Group I consisted of 47 (52%) of the tested compounds, 10 compounds (11%) were in group II, while 33 (37%) were in group III. Similar classifications of OMPs have been used in previous studies, with comparable elimination observed in municipal and hospital wastewater effluent at the same specific ozone doses.[32,55] However, it should be noted that high concentrations of OMPs in waters with a low scavenger concentration (in this case pure buffered water) may affect the ozone and OH radical exposures,[70] and therefore the observed OMP elimination (see also below discussion on ozone and OH radicals exposures).

Group III included most illicit stimulants, antidepressants and their metabolites. These compounds exhibit no functional groups that are readily reactive with ozone. As an electrophile, ozone reacts selectively with electron-rich moieties, such as neutral amines, activated benzene rings and olefins.[16] Compounds in group III include deactivated benzene rings (*e.g.* ketoprofen, cocaine), amides (*e.g.* cotinine, ifosfamide) and protonated amines (*e.g.* citalopram, metformin), which have second order rate constants with ozone <10 M^{-1} s^{-1} (see Table 1). Their elimination can be attributed to reaction with less selective OH radicals. The OH radical second order rate constants (k_{OH}) of most OMPs vary by only one order of magnitude, between 10^9 M^{-1} s^{-1} and diffusion-controlled values of 10^{10} M^{-1} s^{-1} (see Table S2). Group III compounds can be more effectively attenuated with advanced oxidation processes (AOPs) that aim to increase the concentration of OH radicals, such as the peroxone process (O_3/H_2O_2) or ultraviolet (UV) light combined with hydrogen peroxide (UV/H_2O_2).[15]

Few compounds such as the carbamazepine metabolites carbamazepine-10,11-epoxide and 10,11-dihydro-10-hydroxycarbamazepine, exhibited unclear elimination trends with increasing ozone dose, which may be ascribed to simultaneous degradation and formation from the oxidation of structurally similar compounds. Azathioprine had the lowest removal of all compounds in this study, and there is only limited information about its ozone reactivity in the literature.[37]

Most antibacterial agents and antibiotics, analgesics and their metabolites, UV filters, parabens and steroid estrogens belong to Group I and exhibit high elimination with ozone. Group I compounds contain moieties known to react fast with ozone: activated benzene rings, such as phenols (*e.g.* methylparaben, estrone, bisphenol A) and anilines (*e.g.* methotrexate, diclofenac), amines (*e.g.* mirtazapine, gliclazide), olefins (*e.g.* morphine, pholcodine) and thioethers (*e.g.* ranitidine). Note that several compounds contain more than one ozone-reactive sites.

The illicit drugs and illicit drug metabolites included in this study fall into four categories: opioids (heroin, O-6-MAM,

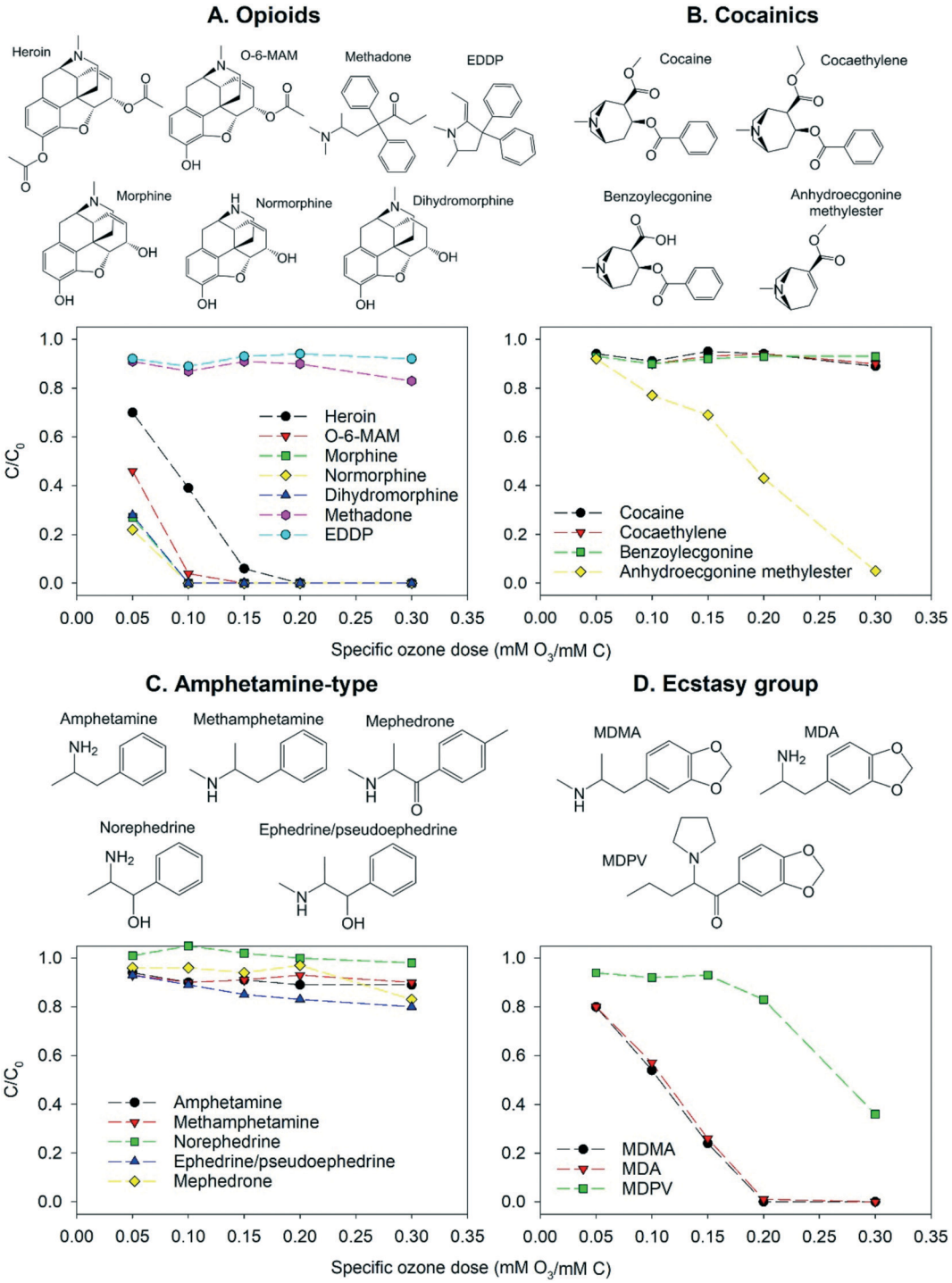

Fig. 2 Abatement of illicit drugs and their metabolites as a function of the specific ozone dose in pure buffered water at pH 7. All compounds were added as a mixture of 90 OMPs in total. Error bars from duplicate analysis of samples were omitted for figure overview and are provided in the ESI† xlsx-data file.

morphine, normorphine, dihydromorphine, methadone, EDDP), cocainics (cocaine, cocaethylene, benzoylecgonine, anhydroecgonine methylester), amphetamine-type (amphetamine, methamphetamine, mephedrone, norephedrine, ephedrine/pseudoephedrine [a precursor]) and ecstasy group (MDMA, MDA, MDPV). Fig. 2 provides an overview on the elimination of the four substance categories at five different specific ozone doses in pure buffered water at pH 7.

Five of the opioids (heroin, O-6-MAM, morphine, normorphine, dihydromorphine) have a similar molecular structure. They contain an activated benzene ring (phenol or

anisole), a tertiary or secondary amine (pK_a = 7.9–9.6) and, apart from dihydromorphine, a carbon double bond. These opioids are efficiently removed by ozonation at pH 7. Second order rate constants for reactions of opioids with ozone have not been determined experimentally, while for morphine the rate constant has been estimated with a QSAR approach as 6.4×10^6 M^{-1} s^{-1}.[55] Second order rate constants of other structurally similar opioids can be expected to be close to this value. Since dihydromorphine appears to have the same ozone reactivity as morphine, the primary site of ozone attack at pH 7 is likely the activated benzene ring rather than the olefinic bond. In contrast, methadone and its metabolite EDDP were both poorly removed by ozonation at pH 7, despite EDDP having a carbon double bond. Only partial removal of these two compounds has been observed in waterworks employing different treatment methods, while trace concentrations of both compounds have been detected in finished drinking water.[28,71]

Cocaine and two of its metabolites (cocaethylene and benzoylecgonine) have similar structures containing a deactivated benzene ring (carbonyl-substituted) and a protonated amine (pK_a = 9–10.8). As a result, their reactivity with ozone is low and minimal removal at pH 7 was observed. Cocaine has been shown to be more ozone reactive than benzoylecgonine,[27] which was not observed in this study, due to the very low removal of both compounds. These three cocainics have been found as traces in tap water of different countries.[71,72] In contrast, anhydroecgonine methylester (a biomarker for the use of crack cocaine) contains an olefinic bond and has a lower pK_a of 8. Accordingly, as shown in Fig. 2, this compound has a much higher ozonation removal than the other compounds in this category.

The amphetamine-type compounds contain a deactivated or slightly activated benzene ring and an amine (pK_a = 7.4–10.4). Fig. 2 shows that all amphetamine-type compounds were ozone-resistant at pH 7. Mephedrone and methamphetamine have been detected in drinking water samples from the UK, which had undergone treatment including ozonation.[12] Methamphetamine is reported to be more ozone-reactive than amphetamine due to the presence of a secondary rather than a primary amine.[27] This was not observed in this study due to the very low removal of both compounds under the employed conditions. However, this effect could be observed for ephedrine/pseudoephedrine which had a higher elimination than norephedrine.

Drugs of the ecstasy group contain a benzene ring activated by two anisole substituents, and an amine with pK_a of 8.4–10.3 (primary-MDA, secondary-MDMA, tertiary-MDPV). The main reactive site is expected to be the benzene ring leading to high removal. MDA and MDMA differ by only one methyl group attached to the amine and showed the same ozone reactivity, while MDPV contains an additional carbonyl substituent on the benzene ring, inducing partial deactivation and lower reactivity. MDMA has been detected in surface water and was only partly removed during the ozonation step of drinking water production.[11]

Effect of pH on micropollutant abatement by ozone in pure buffered water

Changes in pH strongly affect ozone chemistry in water. An elevated pH leads to faster ozone decay due to two phenomena: hydroxide ions initiate the chain reaction of ozone decomposition and at the same time electrophilic ozone reacts faster with deprotonated or dissociated species of the dissolved organic matter.[73,74] In the experimental system of this study the latter phenomenon is expected to be more important due to the increased concentrations of OMPs. Deprotonated alkylamines (typical pK_a = 9–11) have up to six orders of magnitude higher reactivity with ozone than the protonated species.[29] The second order rate constant for the reaction of ozone with dissociated phenolic compounds is five orders of magnitude higher compared to the corresponding non-dissociated species.[30] Despite lower ozone exposure at higher pH, the OH radical exposure remains roughly constant with pH in natural waters.[73]

The estimated ozone and OH radical exposures in pure buffered water under each set of conditions are shown in Table 2 (tap water and wastewater effluent are discussed in the next section). At a given specific ozone dose, the ozone exposure increased by two orders of magnitude as the pH decreased by 4 units. The OH radical exposure remained roughly constant within the uncertainty of the employed estimation method (approximately accurate within an order of magnitude). The ozone exposure values at pH 3 and 7 were of the same order of magnitude as those measured in natural waters,[73] while those at pH 11 were lower and accompanied by slightly higher OH radical exposures. It should be noted that samples were quenched of residual ozone after 5 minutes of reaction, which may have resulted in lower ozone

Table 2 Estimated ozone and OH radical exposures in each water matrix and specific ozone dose, calculated from the elimination of carbamazepine/tramadol and ketoprofen, respectively

Specific ozone dose ($mM O_3$ per mM C)	OH radical exposure (M s)			Ozone exposure (M s)		
	0.05	0.15	0.30	0.05	0.15	0.30
Buffered at pH 3	7×10^{-12}	9×10^{-12}	6×10^{-12}	3×10^{-4}	4×10^{-3}	3×10^{-2}
Buffered at pH 7	4×10^{-12}	3×10^{-12}	8×10^{-12}	3×10^{-6}	4×10^{-5}	4×10^{-4}
Buffered at pH 11	8×10^{-12}	1×10^{-11}	2×10^{-11}	6×10^{-8}	3×10^{-7}	7×10^{-7}
Tap water	1×10^{-13}	6×10^{-12}	1×10^{-11}	5×10^{-7}	1×10^{-6}	5×10^{-6}
Wastewater effluent	1×10^{-11}	7×10^{-12}	2×10^{-11}	3×10^{-7}	1×10^{-6}	3×10^{-6}

exposure than the maximum possible. The ratio of OH radical exposure to ozone exposure, *i.e.* the R_{ct} value,[75] was in the range of 10^{-4} to 10^{-10} across the three pH levels.

The combined effect of different ozone exposure and target compound speciation has led to different removal trends among the 90 OMPs (Fig. 1). The amines fluoxetine (pK_a = 10.1) and sertraline (pK_a = 9.5) were better removed at higher pH due to deprotonation. In contrast, the four parabens (phenols with pK_a of 8.2 to 8.3) followed a distinct trend: their removal increased with a change of pH from 3 to 7 (due to increased dissociation of the phenols which enhanced their ozone reactivity) and then decreased at pH 11 (due to lower ozone exposure). The four benzophenones followed the same trend. However, the removal of the phenolic hormones E1, E2 and EE2 and the plasticizer bisphenol A decreased with higher pH, indicating that the increased reactivity of the dissociated form was outweighed by the lower ozone exposure. For olefins, such as carbamazepine and tamoxifen, a sharp drop of removal was observed at pH 11. In these cases, the effect of the pH is only due to the different ozone and OH radical exposures.

The effect of the pH on the ozonation of illicit drugs and their metabolites was also examined. Four of the opioids with structure similar to morphine have a phenolic moiety with $pK_a > 9$. However, the effect of the pH change on their removal seems to be mainly due to the different ozone exposure rather than the dissociation of the phenolic moiety. Decreased elimination was observed with an increase of pH from 3 to 7 but only at the lowest ozone dose. At pH 11 removals were markedly lower than those at pH 3 and 7, with the highest one being 61% for dihydromorphine and the lowest being 21% for O-6-MAM. In contrast, methadone was better removed at higher pH due to deprotonation of its amine moiety (pK_a = 9.5) and reached 50% removal at pH 11 with the highest ozone dose. The removal of EDDP also slightly increased with pH but remained poor (<20%) under all conditions.

Cocaine, cocaethylene and benzoylecgonine showed enhanced removal at pH 11, since their main ozone-reactive moiety is an amine (pK_a = 9–10.8). Despite this increase, their removal was still below 35%. The fourth compound of the cocainics class, anhydroecgonine methylester, is an olefin and showed decreased elimination at pH 11 due to lower ozone exposure. The amphetamine-type compounds were ozone-resistant at all pH values (removal below 35%), but an increase of removal was observed at pH 11 due to deprotonation of the amine (pK_a = 7.4–10.4). The removal of MDA and MDMA decreased at higher pH due to the lower ozone exposure, as their main ozone-reactive site is an activated benzene ring. The less reactive MDPV showed a slight increase of removal at pH 11, indicating that the amine (pK_a = 8.4) plays a more important role in its reaction with ozone due to partial deactivation of its benzene ring.

An overview of the complete dataset is presented as box and whisker plots in Fig. 3. Since a similar broad range of compounds can be expected in real water matrices, such as river water,[33] the box and whisker plots provide a rough estimation on ozonation performance for multi-compound mixtures. Overall, the optimal pH for the elimination of the selected OMPs was 3 and 7. At pH 3 higher removal compared to pH 7 was observed at the lowest ozone dose, while the removal was similar at the other two applied ozone doses. Ozonation at pH 11 was ineffective and would require higher ozone doses to yield results like those of the lower pH values. The only compounds whose removal improved at pH 11 were Group II and III compounds, including amines with $pK_a > 7$. Typical pH for ozonation in treatment practice is 7 to 8.5.

Removal in tap water and wastewater effluent

Although the ozone dose was normalised to the TOC concentration, the dissolved organic carbon in each water matrix used has different characteristics. In pure buffered water, the organic matter consists of the added OMPs, while in tap water and wastewater effluent it also includes the bulk organic matter. The bulk organic matter was 20% of the total TOC in tap water and 54% in wastewater effluent (on a mass

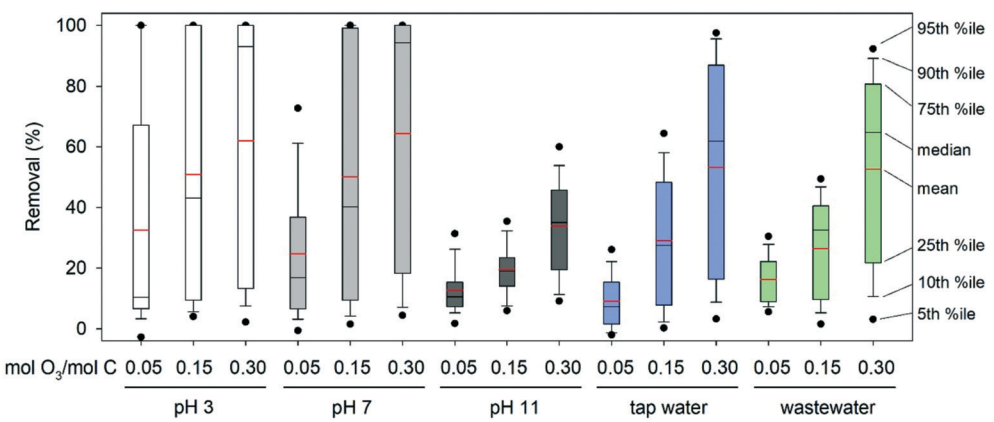

Fig. 3 Box and whisker plots of the removal of the 90 OMPs under the different conditions used in this study. %ile: percentile.

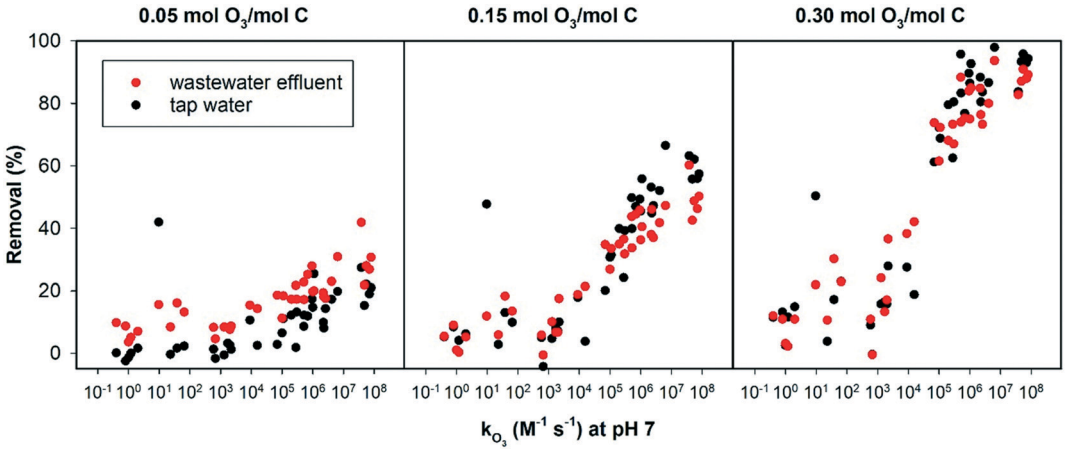

Fig. 4 Removal of 40 OMPs in wastewater effluent and tap water *versus* their known from the literature ozonation second order rate constants.

basis). The ozone reactivity of bulk organic matter varies depending on the origin and characteristics of the sample, and typically covers a range of several orders of magnitude.[76] Different fractions of dissolved organic matter promote or inhibit ozone decay and the production of OH radicals, leading to different ozone and OH radical exposures.[16,77] The characteristics of the organic matrix, such as aromaticity, protein and humic acid content, were not determined in this study.

As shown in Table 2, the ozone exposure in tap water (pH 7.5) and wastewater effluent (pH 7.8) was one to two orders of magnitude lower than the one in pure buffered water at pH 7, but higher than that at pH 11. For most of the compounds that react fast with ozone, the removal in tap water or wastewater effluent decreased compared to pure buffered water at pH 7 (see ESI† xlsx-data file). This matrix effect is also evident in Fig. 3, especially at the intermediate ozone dose (0.15 mM O_3 per mM C) and can be attributed to partial ozone consumption by the bulk organic matter. With 0.15 mM O_3 per mM C, no compound was removed by more than 90% in tap water or wastewater effluent. The maximum removal in tap water at this ozone dose was 79% (cimetidine), while in wastewater effluent it was 60% (triclosan). At the highest ozone dose (0.30 mM O_3 per mM C) removal of cimetidine and normorphine to below the limit of detection was achieved in tap water, but removal was partial for all compounds in wastewater effluent.

The water matrix had a smaller effect on the OH radical exposure and the elimination of ozone-resistant compounds (Table 2 and ESI† xlsx-data file). Due to their high concentrations, the OMPs already reacted very fast with OH radicals in pure buffered water. Therefore, no additional scavenging of OH radicals by the bulk organic matter in tap water and wastewater effluent was observed. For a few compounds, such as citalopram, ibuprofen and valsartan, even an enhanced elimination in tap water or wastewater effluent was noticed as a result of a slightly increased OH radical exposure. The average R_{ct} value was 2×10^{-5} in wastewater effluent and 2×10^{-6} in tap water, which was higher compared to previously reported values for wastewater effluent.[78,79]

Fig. 4 shows the elimination of 40 OMPs with known second order rate constants for their reaction with ozone, added in tap water and wastewater effluent. Data including compound names are provided in the ESI.† Overall, at the lowest specific ozone dose, ozone reactivity had a small effect on the removal of the OMPs in tap water or wastewater effluent, as all 40 compounds were poorly removed (<50% removal). The effect of ozone reactivity became obvious at the intermediate and the highest ozone dose.

4. Conclusions

We conducted the simultaneous ozonation of 90 OMPs including illicit drugs and their metabolites in different aqueous matrices. Target compounds were chosen based on their relevance for current and future legislation and their environmental occurrence, persistence and toxicity. Forty-seven of the tested compounds were readily removed by ozone, including most antibacterials, antibiotics, analgesics, UV filters, parabens and steroids since these compounds contained moieties that are highly reactive with ozone. Compounds that were hard to remove with ozone contained deactivated benzene rings, amide and protonated amine moieties that are unreactive with ozone and included most illicit stimulants, antidepressants and their metabolites. This study provides a valuable database of both literature and experimental results on a wide range of OMPs, including some compounds not studied with ozone before. We specifically focused on discussing results for illicit drugs, including their occurrence in drinking water because ozonation of illicit drugs and their metabolites is significantly less studied compared to the pharmaceuticals and other compounds investigated here. The results of this study are important to predict the performance of ozonation for the removal of trace organic contaminants during water treatment.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 29th April 2020, which contained errors in the units of ozone dose.

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