Chapter 12
Analysis, Occurrence, and Fate of Cyclophosphamide and Ifosfamide in Aqueous Environment

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Abstract Among numerous active pharmaceutical ingredients registered for chemotherapy, two of the oldest, cyclophosphamide (CP) and ifosfamide (IF), are still widely prescribed. Their administration can result in side effects such as cytotoxicity, genotoxicity, mutagenicity, and teratogenicity, which might affect aqueous biota once introduced into the environment. These compounds, which are excreted from the human body as parent compounds and metabolites, find their way into the environment via the sewerage system from hospitals and from homes, where cancer outpatients live. Concentrations of CP and IF in hospital wastewaters (WW), wastewater treatment plant (WWTP) influents and effluents, and surface waters (SW) range from ng L^{-1} to μg L^{-1}. To reduce the burden of CP and IF residues in wastewater and consequently surface and drinking water (DW), the development and optimization of biological and abiotic water treatment technologies is essential, especially since both compounds are recalcitrant. Studies report complete removal of CP and IF during certain advanced oxidation processes; however, these treatments are still not available due to the high costs involved. In addition, understanding the degradation pathways of these compounds is important, since their transformation products (TPs) could exhibit higher toxicity toward aquatic ecosystems than the parent compounds. Finally, several studies describing the analysis, occurrence, and formation of CP and IF transformation products during various water treatments are discussed in this chapter.

Keywords Cyclophosphamide · Ifosfamide · Occurrence · Analysis · Removal · Transformation products

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12.1 Methodology for Determining CP and IF in Water Samples

Cyclophosphamide (CP) and ifosfamide (IF) are two cytostatic agents used to treat cancer patients. In particular, CP is used to treat different types of leukemia, malignant lymphoma, some malignant solid tumors with or without metastases, Ewings' sarcoma, for various progressive autoimmune diseases (e.g., rheumatoid arthritis, erythematosus lupus, and myasthenia gravis) and as immunosuppressive therapy after organ transplantations. Ifosfamide is used to treat bronchial carcinoma, ovarian cancer, some testicular cancer tumors, soft tissue sarcomas, breast cancer, pancreatic carcinoma, renal cell cancer, carcinoma of the endometrium, and malignant lymphomas. Once excreted from our bodies, CP and IF residues reach SW and ground waters via treated WW. For quantitative analysis of cytostatic residues in aqueous samples, analytical methods typically employ solid-phase extraction (SPE) as sample preparation step followed by either gas chromatography (GC) or liquid chromatography (LC) coupled to mass spectrometry (MS). In the case of GC-MS, derivatization step is also applied, which was in the case of CP and IF successfully achieved by acylation with trifluoroacetic anhydride (Momerency et al. 1994; Steger-Hartmann et al. 1996; Česen et al. 2015).

Sample preconcentration for trace analysis of CP and IF is typically performed with N-vinylpyrrolidone and divinylbenzene (Oasis HLB™) copolymers (Ferrando-Climent et al. 2013, 2015; Gómez-Canela et al. 2012; Kovalova et al. 2012; Köhler et al. 2012; Martín et al. 2011; Moldovan 2006; Valcárcel et al. 2011) or surface-modified styrene-divinyl benzene (Strata X™) cartridges (Buerge et al. 2006; Busetti et al. 2009; Delgado et al. 2010; Garcia-Ac et al. 2010; Llewellyn et al. 2011). Several studies have extracted CP and IF using "on-line" SPE also with N-vinylpyrrolidone and divinylbenzene copolymer sorbent, proving that this technique is highly applicable for routine analysis of water samples (Garcia-Ac et al. 2009; Kovalova et al. 2012; Negreira et al. 2013). In these studies, multianalyte analysis was performed and the optimal conditions were determined for all investigated compounds.

Several studies report the use of GC or LC coupled to MS for determining the occurrence of CP and IF in aqueous environment. Among them, only two studies use GC-MS technique for their quantification (Table 12.1). Despite different instrumentation, the limits of detection (LODs) and quantification (LOQs) are comparable (all in low ng L^{-1} range), suggesting the adequate sensitivity of these methods for trace analysis, with the only exception being a study by Kiffmeyer et al. (1998), who used an UV detector (Table 12.1). In the case of GC-MS analysis, HP-5MS (5% diphenyl/95% dimethylpolysiloxane) and Permabond SE-52-DF (5% phenyl/95% methylpolysiloxan) columns were used for separation (Moldovan 2006; Steger-Hartmann et al. 1996). In both cases, ionization and mass analysis were based on EI and single quadrupole (Q; Table 12.1). Studies based on LC-MS used mainly reversed phase (RP) C18 columns and water in combination with either methanol (MeOH) or acetonitrile (ACN) as mobile phases (MPs). In addition, acidification of

Table 12.1 Studies reporting quantitative analysis of CP and IF in aqueous samples

Comp.	Matrix	Quantitative analysis		LOQ/LOD	References
		Separation	Detection		
CP, IF	WW	GC: on-column injection (Permabond SE-52-DF); carrier gas: helium	Single Q; electron ionization (EI) at 70eV; detection mode: selected ion monitoring (SIM)	LODs: 6 ng L^{-1} (CP) 7 ng L^{-1} (IF)	Steger-Hartmann et al. (1996)
CP, IF	River water, WW	RP HPLC: C18 column; MP: water/ACN with addition of 10 mM ammonium acetate (pH = 5.7)	QqQ-MS; ESI(+); detection mode: multiple reaction monitoring (MRM)	LODs: 10 ng L^{-1} (CP and IF)	Ternes (1998)
CP	SW	RP HPLC: C18 column; MP: phosphate buffer (pH = 3)/MeOH	UV detector (200 nm)	LOD: 200 µg L^{-1}	Kiffmeyer et al. (1998)
CP	WW	RP HPLC: C8 column. MP: 0.1% formic acid (pH = 2)/ACN	QqQ MS; ESI(+); detection mode: multiple reaction monitoring (MRM)	LOQ: 1.9 ng L^{-1}	Castiglioni et al. (2005)
CP	WW, SW	RP HPLC: C8 column MP: 0.1% formic acid (pH = 2)/ACN	QqQ MS; ESI(+) detection mode: MRM	n.a.	Zuccato et al. (2005)
CP, IF	WW, SW	RP HPLC: C18 column. MP: 0.1% formic acid/0.1% formic acid in MeOH	QqQ MS; ESI(+); detection mode: MRM	LODs: 0.02 ng L^{-1} (SW; CP and IF) 0.3 ng L^{-1} (WW; CP and IF)	Buerge et al. (2006)
CP	SW	GC: HP-5MS column; carrier gas: n.a.	Single Q; EI mode at 70 eV; detection mode: SIM	LOQ: 30 ng L^{-1}	Moldovan (2006)
CP, IF	WW	RP UPLC: C18 column; MP: 0.1% formic acid/ACN	QqQ MS; ESI(+); detection mode: MRM	LODs: 2 ng L^{-1} (CP and IF)	Yin et al. (2010b)
CP, IF	WW	RP HPLC: C18 column; MP: 0.1% formic acid/0.1% formic acid in MeOH	QqQ MS; ESI(+) and APCI; detection mode: selected reaction monitoring (SRM)	LOQs: 0.11–0.4 ng L^{-1} (CP) 0.16–0.24 ng L^{-1} (IF)	Llewellyn et al. (2011)
CP, IF	WW	RP UPLC: C18 column; MP: 0.1% formic acid/ACN	QqQ-LIT; ESI(+); detection mode: 2 SRMs for each compound	LOQs: 3.6 ng L^{-1} (CP) 5.8 ng L^{-1} (IF)	Ferrando-Climent et al. (2013)

(continued)

Table 12.1 (continued)

Comp.	Matrix	Quantitative analysis		LOQ/LOD	References
		Separation	Detection		
CP, IF	WW	RP UPLC: C18 column; MP: 0.1% formic acid/ACN	QqQ-LIT; ESI(+); detection mode: MRM	LOQs: 1.3 ng L^{-1} (CP) 1.7 ng L^{-1} (IF)	Ferrando-Climent et al. (2015)
CP	WW	RP HPLC: C18 column; MP: 0.1% formic acid/0.1% (v/v) formic acid in MeOH	Orbitrap ESI(+); detection mode: full scan and HRMS (resolving power = 50,000)	LOQ: 0.35 ng L^{-1}	Gómez-Canela et al. (2012)
CP, IF	WW	On-line solid-phase extraction (SPE)-RP HPLC: C18 column; MP: MeOH, ACN, 0.1% formic acid	QqQ ESI(+); detection mode: SRM	LOQs: 10–84 ng L^{-1} (CP) 2–17 ng L^{-1} (IF)	Kovalova et al. (2012)
CP, IF	SW, WW	RP HPLC: C18 column; MP: 0.1% formic acid in ACN/15 mM ammonium formate containing 0.1% formic acid	QqQ; ESI(+); detection mode: 2 MRMs	LOQs: 1.7–2.3 ng L^{-1} (CP) 1.1–1.7 ng L^{-1} (IF)	Martín et al. (2011)
CP, IF	SW, tap water	RP HPLC: C18 column; MP: ACN/0.1% formic acid	QqQ-LIT; ESI(+); detection mode: two SRMs	LOQs: 4 ng L^{-1} (CP) 1 ng L^{-1} (IF)	Valcárcel et al. (2011)
CP, IF	WW	RP HPLC: C18 column; MP: 0.4% formic acid/1% formic acid in MeOH	QqQ; ESI(+); detection mode: MRM	LOQs: 310 pg on column (CP) 454 pg on column (IF)	Busetti et al. (2009)
CP	Drinking water	On-line SPE-RP HPLC: C18 column; MP: 0.2% acetic acid/ACN	QqQ; ESI(+); detection mode: SRM	LOQ: 3.2 ng L^{-1}	Garcia-Ac et al. (2010)

MP with formic acid was often applied and the ionization was operated in electrospray ionization (ESI) positive mode with triple quadrupole (QqQ) being the most commonly used mass analyzer, followed by either QqQ-LIT (triple quadrupole Linear Ion-Trap) or Orbitrap (Table 12.1).

There are only few published studies concerning the formation of CP and IF TPs (Table 12.2). Separation of TPs was achieved in all cases using an RP C18 column. For ionization, ESI was used, while the applied mass analyzers differed (Table 12.2).

Table 12.2 Qualitative analysis for identification of CP and/or IF TPs

Comp.	Qualitative analysis		Reference
	Separation	Detection	
CP	RP LC: C18 column MP: water/ACN	Q-TOF; ESI(+)	Fernández et al. (2010) and Venta et al. (2005)
CP	RP LC: C18 column MP: 0.1% formic acid/ACN	IT; ESI(+)	Lutterbeck et al. (2015)
CP, IF	RP LC: C18 column MP: 0.1% formic acid for positive mode and 5 mM ammonium acetate for negative mode(A); 0.1% formic acid in MeOH for positive mode and 5 mM ammonium acetate in MeOH for negative mode (B)	QqQ; ESI (+/−)	Lai et al. (2015)
CP, IF	RP LC: C18 column MP: water/ACN	HCT Ultra IT (+/−)	Ofiarska et al. (2016)
CP, IF	RP LC: C18 column MP: 0.1% formic acid/0.1% formic acid in ACN	LTQ Orbitrap-XL	Česen et al. (2016)
CP	RP LC: C18 column MP: 0.1% formic acid/0.1% formic acid in MeOH	QqQ; ESI (+)	Zhang et al. (2017)

The suitability of these analyzers (QTOF, IT, QqQ, and Orbitrap) for the identification of unknown TPs is discussed in a review paper by Kosjek et al. (2007). Interestingly, only Česen et al. (2016), Fernández et al. (2010), and Venta et al. (2005) used hyphenated techniques enabling both, MSn experiments and HRMS.

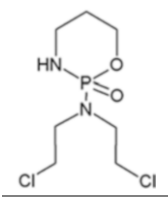
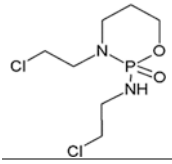
12.2 Environmental Occurrence and Transformations

12.2.1 Sources and Physicochemical Parameters of Cyclophosphamide and Ifosfamide

The current trend in chemotherapy is toward outpatient treatment, that is, patients go home once they have received their therapy at the hospital. This reduces the cost of cancer therapy and increases patient comfort. These patients may excrete cytostatic residues including CP and IF in the hospital, since intravenous treatment can last several hours or at home due to their long half-lives in the body (Kosjek and Heath 2011). In addition, there is still a number of hospitalized patients receiving chemotherapy with CP and IF, which makes hospitals an important source of anticancer drug residues that end up in WW (Kümmerer 2001). There have been several attempts to reduce pollution from hospitals by separating urine, but the emergence of outpatient therapies has meant that this strategy has not been implemented to any significant degree (Janssens et al. 2017).

Once in the environment, physicochemical properties, namely, solubility, dissociation constant (pK_a), bioconcentration factor (BCF), sorption constant (K_d), octanol–water (K_{ow}) and organic carbon–water (K_{oc}) partition coefficients, and Henry's law constant (HLC), will dictate distribution and fate of a certain compound. The solubility of CP and IF is significantly higher than their environmental concentrations; hence, it does not limit their occurrence in the aquatic compartment (Table 12.3). Based on their pK_a values, both compounds act as weak acids and are partially dissociated in neutral environment suggesting low sorption to organic matter. This agrees with their K_{oc} values that also indicate only partial adsorption onto organic matter in the soil and sediment compartments, for example, humus (Table 12.3). Moreover, the log K_{ow} value determines the distribution of a compound between water and organic matter, in particular, lipids and fats. In the case of CP and IF, their log K_{ow} values are <1, indicating their high polarity and, consequently, a tendency to distribute into the water phase (Table 12.3). In addition, the bioconcentration factor (BCF) predicts the potential of a compound to accumulate in aquatic organisms. For CP and IF, their BCF values (Table 12.3) indicate low potential for bioaccumulation. The data for sorption of CP and IF on solids like sludge, sediment, and soil are very scarce. Mioduszewska et al. (2016) report the low sorption potential of CP and IF onto soil and rapid leaching from soils once exposed to aqueous environment. However, the authors do not give the K_d values of CP and IF. It is known that CP and IF do not sorb onto activated sludge at wastewater treatment plants (WWTPs), suggesting limited elimination from WW by this mechanism (Kümmerer et al. 1997). Finally, reported HLC values (Table 12.3) suggest CP and IF have low volatility.

Table 12.3 Physicochemical characteristics of the investigated compounds

Structure	Solubility ($g\ L^{-1}$)	pKa	log K_{ow} and K_{oc}	BCF	K_d	HLC ($atm \times m^3\ mole^{-1}$)	References
CP 	40	6.00	0.63 52	3	n.a.[a]	1.4×10^{-11}	Mahoney et al. (2003) and Kosjek and Heath (2011)
IF 	38	3.75	0.86 70	3	n.a.	1.36×10^{-11}	Mahoney et al. (2003) andKosjek and Heath (2011)

[a]*n.a. not available*

12.2.2 Occurrence of Cyclophosphamide and Ifosfamide in Wastewaters and Surface Waters

Physicochemical properties of CP and IF suggest that they will occur mainly in the aqueous environment; however, a number of additional factors are also important for quantifying their presence in the environment. They include their consumption, disposal, pharmacokinetics, and fate during WW treatment. Table 12.4 gives the detected concentrations of CP and IF in various WWs (hospital WW and WWTP influents and effluents) and SWs as determined concentration ranges or, where these data was not available, as the mean value ± SD (standard deviation). The first studies, reporting the levels of CP and IF in SW and WW, were published 20 years ago (Ternes 1998; Steger-Hartmann et al. 1996, 1997). The presence of CP and IF in either ground water or tap water remains to be evaluated.

The highest concentrations of CP and IF are in hospital WWs, followed by WWTP influents and effluents (< LODs or LOQs to μg L^{-1}) and the lowest in SWs (Table 12.4). The low concentrations in SWs (< LODs or LOQs to ng L^{-1}) can be attributed to effluent dilution once it is introduced into the receiving SW. Except for Gómez-Canela et al. (2012) and Ternes (1998), who reported levels of CP $\leq$ 13,100 ng L^{-1} and of IF $\leq$2900 ng L^{-1} in WWTP effluent, respectively, the reported concentrations in influents and effluents ranged from below the LOD to ng L^{-1} (Table 12.4). In addition, several studies report comparable concentrations of CP and IF in pairs of WWTP influents and effluents, suggesting only limited biodegradation of these compounds (Buerge et al. 2006; Česen et al. 2015; Negreira et al. 2014; Franquet-Griell et al. 2017b). Recently, Franquet-Griell et al. (2017b) reported the occurrence of CP in WW effluent using novel macroporous ceramic passive samplers. The authors report comparable concentrations of CP in effluent using either passive or grab sampling approach, confirming the former as a useful tool for monitoring time-weighted average concentrations of CP in WWs (Table 12.4).

12.2.3 Environmental Transformations

The rate at which chemical (hydrolysis, oxidation), microbiological, and/or physicochemical (photodegradation) degradation occurs depends on many factors, including ambient temperature, the amount of solar irradiation, pH, the presence of other species, and the nature of the compound of interest. For example, Khetan (2007) found that seasonal variations in temperature and light intensity affect the fate of pharmaceutical residues in SW.

The environmental fate of CP and IF has been rarely reported. Haddad et al. (2015) reviewed all the available data on transformation products (TPs) of cytostatics, but no CP and IF TPs, formed under environmental conditions, are

Table 12.4 The occurrence of CP and IF in WW and SW

	Type of water	Sampling (flow-proportional, time-proportional or grab and number of samplings)	Concentration (ng L^{-1})	References
CP	Hospital WW	24 h time-proportional	19–4500	Steger-Hartmann et al. (1997)
		$n = 7$		
		24 h time-proportional	146	Steger-Hartmann et al. (1996)
		$n = 1$		
		Grab	< LOD (2) – 21	Thomas et al. (2007)
		$n = 12$		
		Grab	6–2000	Yin et al. (2010a)
		$n = 65$ (21 hospitals)		
		24 h time-proportional	5730	Gómez-Canela et al. (2012)
		$n = 1$		
		Grab	< LOQ (3.6) – 200.7	Ferrando-Climent et al. (2013)
		n = 1 (4 hospitals)		
		24 h time-proportional	< LOQ (3.0) – 100.0	Negreira et al. (2014)
		$n = 7$		
		Grab	< LOD (0.78) – 22,000	Česen et al. (2015)
		$n = 1$ (5 hospitals)		
		Grab	76–2680	Česen et al. (2016)
		$n = 7$		
		3 grab samples/day – mixed together	Effluent 1: 114–1187	Olalla et al. (2018)
		$n = 1$ (2 effluents from one hospital, 5 days in a row)	Effluent 2: 46–3000	
CP	WWTP influent	8 h time-proportional	< LOD (6) – 143	Steger-Hartmann et al. (1997)
		$n = 2$	< LOD (6) – 8	
		Flow-proportional (24 h)	2–11	Buerge et al. (2006)
		$n = 5$ (3 WWTPs)		
		24 h time-proportional	< LOD (2)	Thomas et al. (2007)
		$n = 2$		
		24 h time-proportional	< LOQ (7.1)	Martín et al. (2011)
		$n = 1$		
		24 h time-proportional	< LOD (0.35) – 13,100	Gómez-Canela et al. (2012)
		$n = 2$ (3 WWTPs)		
		Grab	< LOQ (3.6)– 25.5	Ferrando-Climent et al. (2013)
		$n = 2$ (3 WWTPs)		

(continued)

Table 12.4 (continued)

	Type of water	Sampling (flow-proportional, time-proportional or grab and number of samplings)	Concentration (ng L^{-1})	References
		24 h time-proportional	< LOQ (3.0) – 43.8	Negreira et al. (2014)
		$n = 1$ (12 WWTPs)		
		24 h time-proportional	< LOD (0.55) – 27	Česen et al. (2015)
		$n = 1$ (3 WWTPs)		
		24 h time-proportional	< LOD (2.3)	Česen et al. (2016)
		$n = 1$		
		Grab	15 ± 9	Franquet-Griell et al. (2017b)
		$n = 4$		
	WWTP effluent	8 h time-proportional	6–17	Steger-Hartmann et al. (1997)
		$n = 2$	8–15	
		Grab	< LOD (10) – 20	Ternes (1998)
		$n = 1$		
		24 h time-proportional	< LOQ (1.9) – 9	Castiglioni et al. (2005)
		$n = 9$ (different WWTPs)		
		Flow-proportional (24 h)	2–10	Buerge et al. (2006)
		$n = 5$ (3 WWTPs)		
		24 h time-proportional	Median: 0.6	Zuccato et al. (2005)
		$n = 1$ (8 WWTPs)		
		24 h time-proportional	< LOD (2)	Thomas et al. (2007)
		$n = 2$		
		24 h time-proportional and grab	< LOQ (5)	Busetti et al. (2009)
		$n = 3$ (2 WWTPs)		
		24 h time-proportional	< LOQ (7.7)	Martín et al. (2011)
		$n = 1$		
		Grab	0.19–3.7	Llewellyn et al. (2011)
		$n = 3$ (2 WWTPs)		
		24 h time-proportional	< LOD (0.35)	Gómez-Canela et al. (2012)
		$n = 2$ (3 WWTPs)		
		24 h time-proportional	< LOQ (SM) – 25.0	Negreira et al. (2014)
		$n = 1$ (12 WWTPs)		
		24 h time-proportional	< LOD (0.55) – 17	Česen et al. (2015)
		$n = 1$ (3 WWTPs)		
		24 h time-proportional	< LOD (2.3)	Česen et al. (2016)
		$n = 1$		
		Grab	17 ± 4	Franquet-Griell et al. (2017b)
		$n = 4$		
		Passive sampling with macroporous ceramic passive sampler	19 ± 3	
		$n = 3$		

(continued)

Table 12.4 (continued)

	Type of water	Sampling (flow-proportional, time-proportional or grab and number of samplings)	Concentration (ng L^{-1})	References
	SW	Grab	< LOD (10)	Ternes (1998)
		$n = 1$		
		Grab	0.05–0.17	Buerge et al. (2006)
		$n = 5$ (3 SWs)		
		2.5 h time-proportional	< LOD (not available)	Zuccato et al. (2005)
		$n = 1$ (2 SWs)		
		Grab	< LOQ (30) – 65	Moldovan (2006)
		$n = 2$ (4 SWs)		
		Grab	< LOQ (5.5)	Martín et al. (2011)
		$n = 1$		
		Grab	< LOD (3)	Valcárcel et al. (2011)
		$n = 5$ (5 rivers)		
		Grab	< LOQ (10)	de Jongh et al. (2012)
		$n = 7$ (7 rivers)		
IF	Hospital WW	Grab	< LOD (6) – 1914	Kümmerer et al. (1997)
		24 h time-proportional	24	Steger-Hartmann et al. (1996)
		$n = 1$		
		Grab	< LOD (2) – 338	Thomas et al. (2007)
		$n = 12$		
		Grab	4–10,647	Yin et al. (2010a)
		$n = 65$ (21 hospitals)		
		Grab	< LOQ (5.8) – 227.9	Ferrando-Climent et al. (2013)
		$n = 1$ (4 hospitals)		
		24 h time-proportional	< LOQ (2.0) – 19.4	Negreira et al. (2014)
		$n = 7$		
		Grab	< LOD (2.8) – 6800	Česen et al. (2015)
		$n = 1$ (5 hospitals)		
		Grab	26–47	Česen et al. (2016)
		$n = 7$		
		3 grab samples/day – mixed together	Effluent 1: < LOD (0.2) – 31	Olalla et al. (2018)
		$n = 1$ (2 effluents from one hospital, 5 days in a row)	Effluent 2: 58–4761	
	WWTP influent	6 h time-proportional	7–29	Kümmerer et al. (1997)
		$n = 2$	< LOD (6) – 29	
		Flow-proportional (24 h)	< LOD (0.3) – 15	Buerge et al. (2006)
		$n = 5$ (3 WWTPs)		
		24 h time-proportional	< LOD (2)	Thomas et al. (2007)
		$n = 2$		

(continued)

Table 12.4 (continued)

	Type of water	Sampling (flow-proportional, time-proportional or grab and number of samplings)	Concentration (ng L^{-1})	References
		24 h time-proportional	3.5 ± 0.1	Martín et al. (2011)
		$n = 1$	(mean ± SD)	
		Grab	< LOQ (5.8) – 130.1	Ferrando-Climent et al. (2013)
		$n = 2$ (3 WWTPs)		
		24 h time-proportional	< LOQ (2.0) – 27.9	Negreira et al. (2014)
		$n = 1$ (12 WWTPs)		
		24 h time-proportional	< LOD (0.36)	Česen et al. (2015)
		$n = 1$ (3 WWTPs)		
		24 h time-proportional	< LOD (4.8)	Česen et al. (2016)
		$n = 1$		
		Grab	< IDL[a] (0.009 ng)	Franquet-Griell et al. (2017b)
		$n = 4$		
	WWTP effluent	6 h time-proportional	10–40	Kümmerer et al. (1997)
		$n = 2$	< LOD (6) – 43	
		Grab	< LOD (10) – 2900	Ternes (1998)
		$n = 1$		
		Flow-proportional (24 h)	1.7–6	Buerge et al. (2006)
		$n = 5$ (3 WWTPs)		
		24 h time-proportional	< LOD (2) – 71	Thomas et al. (2007)
		$n = 2$		
		24 h time-proportional and grab	< LOQ (25)	Busetti et al. (2009)
		$n = 3$ (2 WWTPs)		
		24 h time-proportional	1.2 ± 0.1	Martín et al. (2011)
		$n = 1$	(mean ± SD)	
		Grab	< LOQ (0.24)	Llewellyn et al. (2011)
		$n = 3$ (2 WWTPs)		
		24 h time-proportional	< LOQ (2.0) – 15.9	Negreira et al. (2014)
		$n = 1$ (12 WWTPs)		
		24 h time-proportional	< LOD (0.36)	Česen et al. (2015)
		$n = 1$ (3 WWTPs)		
		24 h time-proportional	< LOD (4.8)	Česen et al. (2016)
		$n = 1$		
		Grab	< IDL (0.009 ng)	Franquet-Griell et al. (2017b)
		$n = 4$		
		Passive sampling with macroporous ceramic passive sampler	< IDL (0.009 ng)	
		$n = 3$		
	SW	Grab	< LOD (10)	Ternes (1998)
		$n = 1$		

(continued)

Table 12.4 (continued)

	Type of water	Sampling (flow-proportional, time-proportional or grab and number of samplings)	Concentration (ng L^{-1})	References
		Grab	0.05–0.14	Buerge et al. (2006)
		$n = 5$ (3 SWs)		
		Grab	< LOQ (4.4)	Martín et al. (2011)
		$n = 1$		
		Grab	< LOD (1) – 41	Valcárcel et al. (2011)
		$n = 5$ (5 rivers)		
		Grab	< LOQ (10)	de Jongh et al. (2012)
		$n = 7$ (7 rivers)		

[a]*IDL* instrumental detection limit

reported. To the author's knowledge, only two studies address the environmental degradation of CP and/or IF in Switzerland and Taiwan, both in synthetic and natural SWs (Buerge et al. 2006; Lin et al. 2013). Lin et al. (2013) investigated the degradation of CP, while Buerge et al. (2006) investigated the fate of both compounds. Both studies suggest limited environmental biodegradation and that direct photodegradation plays only a minor (if any) role in the degradation of CP and/or IF in the environment. This agrees with the findings from a recent study by Franquet-Griell et al. (2017a), who also report low degradation (< 20%) during artificial solar irradiation experiments for both compounds. However, the authors report an increase in photochemical degradation, which correlates to an increase in •OH formation in the presence of NO_3-N, a naturally present photosensitizer. They conclude that the highest degradation of CP and/or IF occurs in shallow, clear, NO_3-N-rich natural waters (Buerge et al. 2006; Lin et al. 2013).

12.3 Removal and Transformation During Various Water Treatments

Various WW treatment technologies exist, which are designed to remove compounds, particles, dissolved gasses, and pathogens from WW (Jjemba 2008). Certain compounds that are resistant to biodegradation, including CP and IF, can pass through the WWTPs either partially or completely unchanged (Eggen et al. 2015). The research toward upgrading existing conventional biological treatment has led to the development of new treatment technologies. The efficiency of conventional and advanced treatment techniques in terms of removal of CP and IF is discussed in the following paragraphs.

12.3.1 Biological Treatment

The results of published studies concerning the removal of CP and IF during biological treatment are given in Table 12.5. In general, both compounds show limited removal under experimental conditions with either suspended biomass or fungi. Despite different concentrations of CP and IF applied in the studies (ng L^{-1} to mg L^{-1} range), their highest removal efficiency was reported for conventional treatment, that is, 17% and 15%, respectively. In addition, these tests, lasting days to months, revealed no improvement in removal efficiency with prolonged time (Table 12.5). Four studies report the removal efficiency for CP using the MBR with inconsistent results (Delgado et al. 2011; Kovalova et al. 2012; Köhler et al. 2012; Seira et al. 2016). Delgado et al. (2011) and Seira et al. (2016) reported significant removal ($\leq$ 80% and 60%, respectively), while Kovalova et al. (2012) and Köhler et al. (2012) reported lower removals (< 20%). One reason for this discrepancy could be the use of different matrices, that is, hospital WW with varying amounts of contaminants that could affect biomass activity (real situation) versus artificial/semiartificial WW, that is less contaminated and has a constant composition to which biomass adapts. On the contrary, Česen et al. (2015) reports higher removal using attached growth biomass in the case of hospital WW compared to an artificial WW matrix (Table 12.5). However, the duration of experiments described by Česen et al. (2015) differs significantly (artificial WW: 120 days and hospital WW: 2 days). Higher removal (35%) in this study was observed also for IF, when hospital WW was introduced into bioreactors. To the author's knowledge, this the highest reported IF removal during biological WW treatment.

12.3.2 Abiotic Treatment

Various abiotic treatment technologies like UV irradiation, ozonation, advanced oxidation processes (AOPs), and physical treatment can be used to disinfect and/or remove not readily biodegradable compounds like CP and IF from water (Glaze et al. 1987; Huber et al. 2005; Legrini et al. 1993). A review of such treatments is given in the following paragraphs.

12.3.2.1 UV Irradiation

UV irradiation can be used for disinfection and removal (complete or partial degradation) of organic compounds in water. The latter can be achieved by direct and indirect photolysis (Klavarioti et al. 2009; Legrini et al. 1993). A review of the literature reveals four studies on the removal of CP and IF by UV irradiation. All four studies report similar results (Table 12.6). These compounds do not absorb

Table 12.5 The removal efficiency for CP and IF during various biological treatments

	Treatment type	Type of water	Conc.	Duration	Removal	References
CP	Modified Zahn-Wellens test (OECD 302 B)	OECD medium + activated sludge (AS) from WWTP	160 mg L^{-1}	28 days	None	Steger-Hartmann et al. (1997)
	Simulated WWTP	Synthetic WW + AS from WWTP	10 μg L^{-1}	42 days	Poor (≈ 17%)	Steger-Hartmann et al. (1997)
	OECD Confirmatory test (Degradation and Accumulation, 1992)	Synthetic WW + AS from WWTP	375 mg L^{-1} 750 mg L^{-1}	10 days	None (0 ± 5%)	Kiffmeyer et al. (1998)
			150 mg L^{-1}	14 days		
	Simulated WWTP	Influent + AS from WWTP	90 ng L^{-1} 900 ng L^{-1}	24 h	None	Buerge et al. (2006)
	Membrane bioreactor (MBR)	Synthetic WW + AS from WWTP	5 μg L^{-1}	139 days 115 days	≤ 80%	Delgado et al. (2011)
	MBR	Hospital WW	161 ng L^{-1}	1 year	< 20%	Kovalova et al. (2012)
	MBR	Hospital WW	Data not provided	5 days	≈ 12%	Köhler et al. (2012)
	Biological treatment with fungi *Trametes versicolor*	Hospital WW	10 mg L^{-1} 100 μg L^{-1}	8 days	None	Ferrando-Climent et al. (2015)
	Bioreactors with attached biomass on Mutag™ carriers	Artificial WW + AS from WWTP	10 μg L^{-1}	120 days	42 ± 12%	Česen et al. (2015)
		Hospital WW + AS from WWTP	5.3 μg L^{-1}	2 days	59 ± 15%	Česen et al. (2015)
	MBR	Semi-synthetic WW	5 μg L^{-1}	77 days	60%	Seira et al. (2016)
	Sequential batch reactors	WW effluent + AS from WWTP	50 μg L^{-1}	2 days	≈ 15%	Franquet-Griell et al. (2017a)
IF	Modified Zahn-Wellens test (OECD 302 B)	DW + AS from WWTP	160 mg L^{-1}	42 days	None	Kümmerer et al. (1997)
		Hospital WW + AS from WWTP	4.3 mg L^{-1}			

(continued)

Table 12.5 (continued)

	Treatment type	Type of water	Conc.	Duration	Removal	References
	Simulated WWTP	Effluent + AS from WWTP	11.4 μg L^{-1}	56 days	< 3%	Kümmerer et al. (1997)
	Simulated WWTP	Influent + AS from WWTP	120 ng L^{-1} 1200 ng L^{-1}	24 h	None	Buerge et al. (2006)
	Biological treatment with fungi *Trametes versicolor*	Hospital WW	10 mg L^{-1} 100 μg L^{-1}	8 days	None	Ferrando-Climent et al. (2015)
	Bioreactors with attached biomass on Mutag™ carriers	Artificial WW + AS from WWTP	10 μg L^{-1}	120 days	18 ± 11%	Česen et al. (2015)
		Hospital WW + AS from WWTP	6.8 μg L^{-1}	2 days	35 ± 9.3%	Česen et al. (2015)
	Sequential batch reactors	WW effluent + AS from WWTP	50 μg L^{-1}	2 days	≈ 15%	Franquet-Griell et al. (2017a)

photons under UV irradiation (due to the lack of aromatic rings or C = C bonds), which means that removal is poor regardless of the experimental conditions applied (Russo et al. 2017).

12.3.2.2 Ozonation

Ozonation is a treatment process, where ozone (O_3) is introduced into water. Similar to UV irradiation, it can be used for disinfecting and/or removing compounds from water via direct or indirect degradation processes.

Seven studies report the removal efficiency of CP and IF by ozonation using varying O_3 concentrations (Table 12.7). In general, removal efficiencies >60% can be achieved in up to 30 min regardless of the matrix type (deionized water or hospital WW) and initial CP or IF concentration. Only Česen et al. (2015) and Li et al. (2016) report lower removal, which can be related to the lower O_3 concentration used in their experiments (10 mg L^{-1} and 0.25–5 mg L^{-1}, respectively) compared to other studies. Table 12.7 also shows how pH plays an important role in removal. For example, Venta et al. (2005) report 20% removal of CP at pH 7 and 60% at pH 9. The crucial role played by pH in the removal is described also by Fernandez et al. (2010) and Lin et al. (2015) for both compounds (Table 12.7). These outcomes suggest that ozonation is a promising technique, especially for highly contaminated hospital WWs; however, installation and maintenance costs are high and further detailed operational costs of this treatment are needed (Ferre-Aracil et al. 2016).

Table 12.6 The removal efficiency for CP and IF during sole UV irradiation

	Type of water	UV lamp	Conc.	Duration	Removal	References
CP	Pure water	Low pressure (UV_{dose} = 230.4 mJ cm^{-2})	10 μg L^{-1}	60 min	< 20%	Kim and Tanaka (2009)
	Artificial WW	Low pressure (UV_{dose} = 44 mJ cm^{-2})	10 μg L^{-1}	120 min	21%	Česen et al. (2015)
	Pure water	Low pressure (UV_{dose} = 14,472 mJ cm^{-2})	50 μg L^{-1}	90 min	Negligible	Franquet-Griell et al. (2017a)
	Pure water	Low pressure (UV_{dose} = 400 mJ cm^{-2})	261 μg L^{-1}	3 min	Negligible	Zhang et al. (2017)
IF	Artificial WW	Low pressure (UV_{dose} = 44 mJ cm^{-2})	10 μg L^{-1}	120 min	16%	Česen et al. (2015)
	Pure water	Low pressure (UV_{dose} = 14,472 mJ cm^{-2})	50 μg L^{-1}	90 min	Negligible	Franquet-Griell et al. (2017a)

Table 12.7 The removal efficiency for CP and IF during ozonation treatment experiments

	O_3 concentration	Type of water	pH	Conc.	Removal	References
CP	45 mg L^{-1}	Pure water	7 9	261 mg L^{-1}	≈ 20% (pH = 7, after 12 min); ≈ 60% (pH = 9, after 12 min)	Venta et al. (2005)
	32 mg L^{-1}	Pure water	5.6 9 11	5 mg L^{-1} 20 mg L^{-1}	61% (pH = 5.6; after 30 min)–100% (pH = 11; after 5 min) not concentration dependent	Lin et al. (2015)
		Hospital WW	7.8	20 mg L^{-1}	100% after 20 min	
	6–15 mg L^{-1}	Pure water	8.1	100 ng L^{-1}	87% after 2 min 100% after 30 min	Garcia-Ac et al. (2010)
		DW	Ambient		96% after ≈ 5 min	
	30 mg L^{-1} 45 mg L^{-1}	Buffered water	7 9 11	130.5 mg L^{-1} 261 mg L^{-1}	75% (pH = 7) and 90% (pH = 9 or 11) after 40 min not concentration dependent	Fernández et al. (2010)
	10 mg L^{-1}	Artificial WW	7	10 μg L^{-1}	42% after 120 min	Česen et al. (2015)
	0.25–5 mg L^{-1}	Diluted treated WW with ultrapure water	7.2	5 μg L^{-1}	≈ 10–70% after 30 min (O_3 dose dependent)	Li et al. (2016)
	60 mg L^{-1}	Hospital WW	8.9	0.14–1187 μg L^{-1} (native concentrations)	97–100% after 10 min (O_3 dose dependent)	Ferre-Aracil et al. (2016)
IF	3 g O_3 h^{-1}	Deionized water	5.6 9 11	5 mg L^{-1} 20 mg L^{-1}	79% (pH = 5.6; after 30 min) – 100% (pH = 11; after 5 min) not concentration dependent	Lin et al. (2015)
		Hospital WW	7.8	20 mg L^{-1}	100% after 20 min	
	10 mg L^{-1}	Artificial WW	7	10 μg L^{-1}	36% after 120 min	Česen et al. (2015)

(continued)

Table 12.7 (continued)

	O_3 concentration	Type of water	pH	Conc.	Removal	References
	0.25–5 mg L^{-1}	Diluted treated WW with ultrapure water	7.2	5 μg L^{-1}	≈ 10–70% after 30 min (O_3 dose dependent)	Li et al. (2016)
	60 mg L^{-1}	Hospital WW	8.9	0.016–0.031 μg L^{-1} (native concentrations)	100% after 10 min (regardless of the O_3 dose)	Ferre-Aracil et al. (2016)

12.3.2.3 Advanced Oxidation Processes

Glaze et al. (1987) defined advanced oxidation processes as "those which involve the generation of hydroxyl radicals (•OH) in sufficient quantity to affect water purification." They described only O_3/H_2O_2, UV/O_3, and UV/H_2O_2 as AOPs. Nowadays, also other AOPs such as UV/TiO_2, Fe^{2+}/H_2O_2 (Fenton), $UV/Fe^{2+}/H_2O_2$ (photoassisted Fenton), and $UV/O_3/H_2O_2$ represent efficient DW and WW treatment technologies (Linden and Mohseni 2014; Saharan et al. 2014; Fabiańska et al. 2015). During AOP, the formation of •OH is followed by their reaction with the organic compounds present. These interactions lead to a series of complex oxidation reactions, which results in either their partial or complete degradation (Saharan et al. 2014). The high costs involved means that AOPs as WW treatment technologies can be applied as a tertiary treatment for WW containing high amounts of proteins or sugars, which are degraded during biological treatment, while the remaining biorecalcitrant organic matter can be degraded by an AOP (Oller et al. 2011).

The formation of •OH is common to all AOPs; however, the mechanism of their "synthesis" differs. For example, in the case of the Fenton process, •OH are formed due to the oxidation of Fe^{2+} to Fe^{3+}. This is a metal-catalyzed oxidation, in which iron acts as a catalyst (Saharan et al. 2014). A number of photoassisted AOP treatments also exist, such as UV/TiO_2, UV/H_2O_2, UV/O_3, $UV/O_3/H_2O_2$, and $UV/Fe^{2+}/H_2O_2$ (photoassisted Fenton AOP), which is an advanced version of Fe^{2+}/H_2O_2 with a higher •OH formation rate (Legrini et al. 1993; Saharan et al. 2014; Glaze et al. 1987; Andreozzi et al. 1999). Except for UV/TiO_2, which is a photocatalytic process, others can be described as photoactivated chemical reactions, where interactions between photons with sufficient energy levels and H_2O_2 or O_3 result in the formation of free radicals (mostly •OH), which react with the compounds present in water (Saharan et al. 2014). To achieve homolytic cleavage of H_2O_2, an UV irradiation (254 nm) is usually applied. When UV is used in combination with O_3, it is also recommended to use UV light with a wavelength of 254 nm (Andreozzi et al. 1999). An alternative way to produce •OH is by photo-catalytic oxidation with UV/TiO_2, where •OH are formed on the surface of a semiconductor catalyst, for example, titanium dioxide (TiO_2). The absorption of UV irradiation and consequent formation of electron–hole pairs on the catalyst's surface reduces the dissolved O_2 to the superoxide radical (O_2^-) ion and H_2O and OH^- to •OH (Saharan et al. 2014).

Besides UV/O_3, there are also other O_3-based AOPs: O_3/H_2O_2 and UV/O_3/H_2O_2. It is known that decomposition of O_3 in an aqueous solution is accompanied by the formation of both H_2O_2 and •OH (Legrini et al. 1993). The rate of •OH formation can be increased by adding H_2O_2 and by applying UV irradiation (Legrini et al. 1993).

To the author's knowledge, there are 15 AOP-based studies (Table 12.8), within which four report low removal efficiency of CP and/or IF (Wols et al. 2013; Lai et al. 2015; Zhang et al. 2017; Česen et al. 2015). Wols et al. (2013) report 10–15% (CP) and 10–30% (IF) removal efficiency during UV/H_2O_2 treatment in tap water and WWTP effluent (Table 12.8). This contradicts Kim et al. (2009a), who used similar experimental conditions, that is, WWTP effluent as a matrix, similar initial H_2O_2 concentration and UV dose, and reported $\leq$90% CP removal (Table 12.8). However, the initial CP concentration reported by Kim et al. (2009a), 3 ng L^{-1}, is far less than what is reported in the other cases. In addition, this value was below the LOD, which was determined using standard solutions, directly analyzed by LC-MS/MS without taking into account the concentration factor of SPE. This represents an additional ambiguity in their determination of CP removal. The two studies that report high CP removal efficiency ($\approx$ 90%) from WWTP effluent with similar initial CP concentrations used considerably higher UV and H_2O_2 doses (Kim et al. 2009b; Köhler et al. 2012).

Another study reporting low IF removal was described by Lai et al. (2015), who investigated the removal efficiency of IF during UV/TiO_2 treatment in one hospital WW, whereas higher removal was achieved in another hospital WW, deionized water and two WWs coming from pharmaceutical industry. The authors report a DOC-dependent removal efficiency, resulting from 10% for hospital WW with highest DOC value (29 mg L^{-1}) to 100% removal efficiency in deionized water with the lowest DOC value (data not provided) within 120 min of treatment (Lai et al. 2015). Although significantly shorter UV/H_2O_2 treatment (3 min) was performed by Zhang et al. (2017), the authors also report matrix-dependent removal efficiency with the lowest CP removal from treated WW ($\approx$ 45%). Interestingly, in Lai et al. (2015)'s study, who addressed IF, removal can be compared to that of Hui-Hsiang et al., (2013), who investigated CP removal using UV/TiO_2. Similar matrices (purified water) and initial CP/IF concentrations were applied in both cases (Table 12.8). The only difference was the TiO_2 concentration (20 and 100 mg L^{-1}), which accounts for the decrease in the time needed to remove 100% of either CP (2 h) or IF (10 min; Table 12.8).

Česen et al. (2015) also report low CP and IF removal during O_3/H_2O_2 treatment, that is, 30–40% and 26–39% after 120 min of treatment, respectively (Table 12.8). The authors report comparable or even decreased removal with an increased amount of H_2O_2. On the contrary, Ferre-Aracil et al. (2016) achieved complete CP removal using the same treatment of hospital WW in only 20 min for similar CP concentrations, but with higher O_3 and a significantly lower H_2O_2 concentration (Table 12.8). It can be assumed that in the first study, the high amount of H_2O_2 acted as scavenger of •OH produced by ozonation, which resulted in low CP and IF removal.

Table 12.8 The removal efficiency of CP and IF under various AOPs

	AOP	Conc.	$Fe^{2+}/TiO_2/H_2O_2/O_3$ conc.	Conditions	Matrix	Removal	References
CP	O_3/H_2O_2	261 mg L^{-1}	45 mg L^{-1} O_3 4.7–12.5 mg L^{-1} H_2O_2	pH = 7	Pure water	100% (15 min, all conditions)	Venta et al. (2005)
				pH = 9			
				pH = 11			
	UV/H_2O_2	μg L^{-1} (not reported)	6 mg L^{-1}	8 W lamp	Pure water	≈ 90% (75 min; UV dose = 1695 mJ cm^{-2})	Kim et al. (2009b)
			8.2 mg L^{-1}		Effluent		
	UV/H_2O_2	≈ 3 ng L^{-1}	7.8 mg L^{-1}	65 W lamp	Effluent	≈ 90% (5 min; UV dose = 923 mJ cm^{-2})	Kim et al. (2009a)
	O_3/H_2O_2	100 ng L^{-1}	10 mg L^{-1} O_3 2.5 mg L^{-1} H_2O_2	pH = 8	DW	100% (2 min)	Garcia-Ac et al. (2010)
	O_3/H_2O_2	261 mg L^{-1}	30–45 mg L^{-1} O_3 34 mg L^{-1} H_2O_2	pH = 7	Pure water	70–95% (15 min)	Fernández et al. (2010)
				pH = 9		60–80% (15 min)	
	UV/H_2O_2	1 μg L^{-1}	0.83–1.1 g L^{-1}	2–10 W lamp 250 W lamp	Effluent	≤ 90% (16 h with 4 kWh m^{-3} energy input)	Köhler et al. (2012)
	UV/H_2O_2	1 μg L^{-1}	5–20 mg L^{-1}	60 W lamp 2000 W lamp	Pure water	80–100% (500 mJ cm^{-2}; 5–20 mg L^{-1} H_2O_2	Wols et al. (2013)
					DW	10–15% (1000 mJ cm^{-2}; 10 mg L^{-1} H_2O_2)	
					Effluent		
	UV/TiO_2	100 μg L^{-1}	5–3000 mg L^{-1}	8 W; pH = 3–10	Pure water	100% (2 h, pH = 5.8, 20 mg L^{-1} TiO_2)	Hui-Hsiang Lin and Yu-Chen Lin (2013)
		27.6 mg L^{-1}	20 mg L^{-1} 300 mg L^{-1}	8 W; pH not reported		100% (4 h with 300 and 5 h with 20 mg L^{-1} TiO_2)	
	UV/H_2O_2	20 mg L^{-1}	333 mg L^{-1} 500 mg L^{-1} 666 mg L^{-1}	150 W	Pure water	100% (8 min, 333 mg L^{-1})	Lutterbeck et al. (2015)
	UV/Fe^{2+}/H_2O_2		434 mg L^{-1} Fe^{2+} 333 mg L^{-1} H_2O_2			100% (< 2 min)	
	UV/TiO_2		100–1000 mg L^{-1}			100% (32 min, 500 mg L^{-1})	

	UV/H_2O_2	10 μg L^{-1}	2.5–5 g L^{-1}	12 W	Artificial WW	65% (120 min or 44 mJ cm^{-2}; 5 g L^{-1})	Česen et al. (2015)
	UV/O_3		10 mg L^{-1}			59% (120 min or 44 mJ cm^{-2})	
	O_3/H_2O_2		10 mg L^{-1} O_3 2.5–5 g L^{-1} H_2O_2			30–40% (120 min)	
	UV/O_3/H_2O_2		10 mg L^{-1} O_3 2.5–5 g L^{-1} H_2O_2			99% (120 min or 44 mJ cm^{-2}; 5 g L^{-1} H_2O_2)	
	O_3/H_2O_2	0.14–1187 μg L^{-1}	60 mg L^{-1} O_3 21–128 mg L^{-1} H_2O_2	pH = 8.1–8.5	Hospital WW	100% (20 min; 21 mg L^{-1} H_2O_2)	Ferre-Aracil et al. (2016)
	UV/TiO_2	50 mg L^{-1}	5 g L^{-1}	Solar simulator (550 W m^{-2}); pH = 5.5	Pure water	≈ 100% (240 min)	Ofiarska et al. (2016)
	UV/Pt/TiO_2		5 g L^{-1}			≈ 100% (60 min)	
	UV/H_2O_2	261 μg L^{-1}	0.34–170 mg L^{-1}	5 W; pH = 7	Pure water	64% (3 min or 510 mJ cm^{-2}; 3.4 mg L^{-1}) ≈ 83% (3 min, 6.8 mg L^{-1})	Zhang et al. (2017)
			6.8 mg L^{-1}		DW	≈ 79% (3 min)	
			6.8 mg L^{-1}		Treated WW	≈ 45% (3 min)	
	UV/H_2O_2	50 μg L^{-1}	15 mg L^{-1}	Solar simulator; pH = 7.6	Pure water	100% (4 min or 643 mJ cm^{-2})	Franquet-Griell et al. (2017a)
IF	UV/H_2O_2	1 μg L^{-1}	5–20 mg L^{-1}	60 W lamp 2000 W lamp	Pure water	90–100% (500 mJ cm^{-2}; 5–20 mg L^{-1} H_2O_2)	Wols et al. (2013)
					DW	10–30% (1000 mJ cm^{-2}; 10 mg L^{-1} H_2O_2)	
					Effluent		
	UV/TiO_2			8 W	Pure water	100% after 10 min (100 mg L^{-1} TiO_2)	Lai et al. (2015)

(continued)

Table 12.8 (continued)

	AOP	Conc.	$Fe^{2+}/TiO_2/H_2O_2/O_3$ conc.	Conditions	Matrix	Removal	References
		100–20 mg L^{-1} (optimal: 100 µg L^{-1})	2–1000 mg L^{-1} (optimal: 100 mg L^{-1})		Hospital WW 1 and 2	1: 100% after 60 min 2: 10% after 120 min (DOC dependent)	
					Pharmaceutical industry WW 1 and 2	1 and 2: 40% after 120 min	
	UV/H_2O_2	10 µg L^{-1}	2.5–5 g L^{-1}	12 W	Artificial WW	70% (120 min or 44 mJ cm^{-2}; 5 g L^{-1})	Česen et al. (2015)
	UV/O_3		10 mg L^{-1}			49% (120 min or 44 mJ cm^{-2})	
	O_3/H_2O_2		10 mg L^{-1} O_3 2.5–5 g L^{-1} H_2O_2			26–39% (120 min)	
	UV/O_3/H_2O_2		10 mg L^{-1} O_3 2.5–5 g L^{-1} H_2O_2			94% (120 min or 44 mJ cm^{-2}; 5 g L^{-1})	
	UV/TiO_2	50 mg L^{-1}	5 g L^{-1}	Solar simulator (550 W m^{-2}); pH = 5.5	Pure water	≈ 100% (240 min)	Ofiarska et al. (2016)
	UV/Pt/TiO_2	5 mg L^{-1}	0.05–0.5 g L^{-1}	Solar simulator (550 W m^{-2}); pH = 5.5–9.5		≈ 100% (60 min)	
		50 mg L^{-1}	1.25–5 g L^{-1}	Solar simulator (550 W m^{-2}); pH = 5.5		≈ 100% (60 min; 5 g L^{-1})	
	UV/H_2O_2	50 µg L^{-1}	15 mg L^{-1}	Solar simulator; pH = 7.6	Pure water	100% (4 min or 643 mJ cm^{-2})	Franquet-Griell et al. (2017a)

Fernandez et al. (2010), who also investigated CP removal during O_3/H_2O_2, observed a decrease in removal efficiency at elevated pH values. This differs from ozonation treatment, where higher pH values result in more •OH being produced and consequently enhanced degradation (von Gunten and von Sonntag 2012). The authors explain the reverse phenomenon observed within the experiments, where the added H_2O_2 acts as a scavenger of the •OH produced at higher pH values. The same observation was reported by Venta et al. (2005), who reports complete CP removal within 15 min, but with a lower amount of H_2O_2 compared to Fernandez et al. (2010).

Within the UV-based AOPs (Table 12.8), the most efficient is photo-Fenton ($UV/Fe^{2+}/H_2O_2$), where CP was completely degraded in less than 2 min (Lutterbeck et al. 2015). This is comparable to O_3-based AOP, that is, O_3/H_2O_2, conducted at an environmentally relevant initial CP concentration, 100 ng L^{-1} (Garcia-Ac et al. 2010). In the latter study, the amount of H_2O_2 used is relatively small (2.5 mg L^{-1} compared to 333 mg L^{-1}); however, O_3-based treatment technologies are more costly compared to UV-based AOPs (von Gunten and von Sonntag 2012; Saharan et al. 2014). Wols et al. (2013), Zhang et al. (2017), and Franquet-Griell et al. (2017a) also achieved 100% CP and IF removal within only few min of UV/H_2O_2 treatment (comparable UV doses; Table 12.8), where low amounts of H_2O_2 (20, 6.8, and 15 mg L^{-1}, respectively) were applied. In all studies, environmentally relevant concentrations of CP and IF in pure water were used. In addition, the authors report a drop in removal efficiency with increased matrix complexity (Table 12.8). This can be explained by CP/IF competition with other species present in WW for reaction with •OH (Zhang et al. 2017; Wols et al. 2013).

A direct comparison among the different studies (Table 12.8) in terms of cost-efficiency for real-world applications is not possible at this point since the described experimental conditions vary significantly. For example, studies were performed in different matrices and volumes of samples (laboratory to pilot-scale experiments) using varying instrumentation and were conducted at different initial concentrations of CP and IF.

12.3.3 Physical Treatment

Adsorption on activated carbon (AC), nanofiltration (NF), and reverse osmosis (RO) are common physical treatment technologies, which can improve the quality of WW (Jjemba 2008). The main disadvantage of these techniques is that retained compounds are not degraded and require further treatment (Rakić et al. 2015).

The data on CP and IF removal using physical treatment are scarce (Table 12.9). A study by Chen et al. (2008) reports a carbon dose–dependent removal efficiency of CP (AC dose of 100 mg L^{-1} resulted in ≈ 90% removal). In addition, a correlation

Table 12.9 Removal efficiency of CP during various physical treatments (data for IF is unavailable)

Treatment	CP conc.	Matrix type	Removal	References
AC (0.1–100 mg L^{-1})	10 μg L^{-1}	Pure water	≈ 1–90%	Chen et al. (2008)
AC (22 mg L^{-1})	2 μg L^{-1}	Pure water	70%	de Ridder et al. (2009)
		SW	55%	
		Effluent	28%	
NF	1–10 μg L^{-1}	Pure water	20–40%	Wang et al. (2009)
		Effluent	60%	
RO	1–10 μg L^{-1}	Pure water	> 90%	
		Effluent	> 90%	

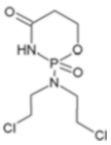
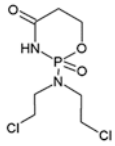
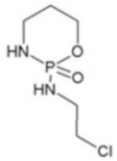
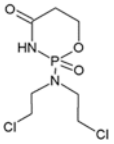
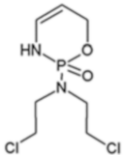
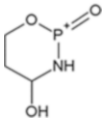
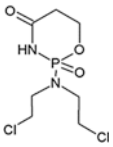
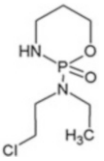
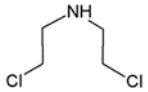
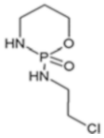
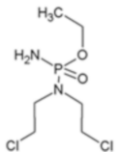
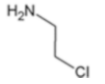
between matrix complexity and removal efficiency was also reported, with CP removal between 28% and 70% depending on tested matrix (de Ridder et al. 2009).

Nanofiltration and RO can be also used to treat WW by physically removing the dissolved compounds. In case of NF, particles with a diameter > 1 nm are retained, whereas in RO, only particles <0.1 nm in diameter can pass through the membrane. Pretreatment is also necessary to remove any solid particles that could affect the rejection efficiency of NF and RO (Ravikumar et al. 2014; Radjenović et al. 2008; von Gunten et al. 2006). Wang et al. (2009) studied the rejection efficiency of CP in pure water and treated WW by NF and RO. For NF, the rejection efficiency was matrix dependent (Table 12.9), where the lower rejection efficiency for untreated WW was correlated to membrane fouling by the organic matter present. The authors report over 90% rejection efficiency of CP by RO regardless of the matrix type (Table 12.9).

12.3.4 Transformations

Compounds undergo similar transformation reactions during water treatment as in the environment, that is, chemical, physicochemical, and/or microbiological transformations. However, these processes are typically more intense during treatment, where degradation and formation of TPs strongly depend on the applied conditions (Mompelat et al. 2009; Saharan et al. 2014). The transformations of CP and IF during biological treatment have not been studied yet, most likely due to their poor biodegradability, whereas TPs formed during abiotic treatments have been extensively investigated (Table 12.10). Seven studies have looked at CP degradation and identified 16 different TPs, whereas three studies report 17 different IF TPs (Tables 12.10 and 12.11). O_3-based treatments of CP produced one TP, a keto-CP. Ketonization was the most common reaction also during UV treatment and UV-based AOPs. Apart from keto-CP, there are several other reports of TPs that share the same molecular structure as known CP and IF human metabolites,

Table 12.10 Reported TPs of CP during various AOPs

AOP	Identified TPs			Reference
O_3/H_2O_2	Keto-CP 			Venta et al. (2005)
O_3, pH = 9	Keto-CP 			Fernández et al. (2010)
UV/H_2O_2 UV/TiO_2	3-dechloroethyl-CP (only UV/H_2O_2) 	Keto-CP 	Imino-phosphamide 	Lutterbeck et al. (2015)
	CP-TP1 			
UV/TiO_2	Keto-CP 	CP-TP2 (loss of Cl) 	bis(2-chloroethyl)amine 	Lai et al. (2015)
	3-dechloroethyl-CP 	CP-TP3 (loss CH_2) 	2-chloroethylamine 	

(continued)

Table 12.10 (continued)

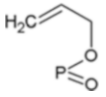
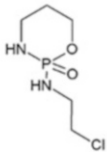
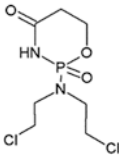
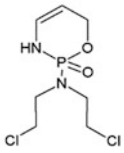
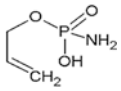
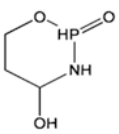
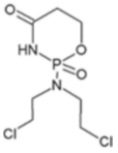
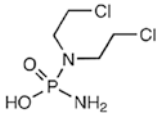
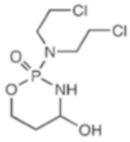
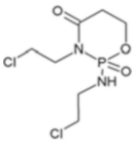
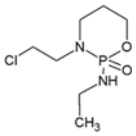
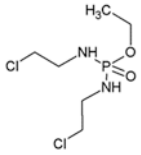
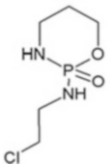
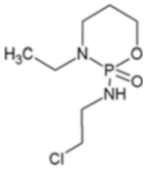
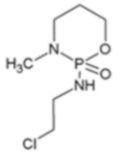
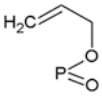
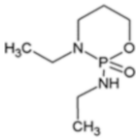
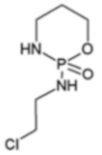
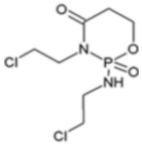
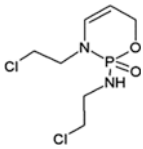
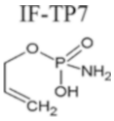
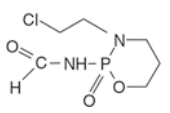
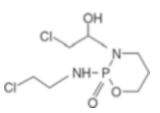
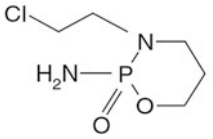
AOP	Identified TPs		Reference	
	CP-TP4 			
UV and UV/H_2O_2	3-dechloroethyl-CP 	Keto-CP 	Imino-phosph-amide (only UV/H_2O_2) 	Česen et al. (2016)
	CP-TP5 	CP-TP6 		
UV/TIO_2 and UV/Pt-TiO_2	Inorganic species: NH^{4+} PO_4^{3-} Cl^-	Keto-CP 	Unidentified TP $[M + H]^+ = 213$	Ofiarska et al. (2016)
UV and UV/H_2O_2	CP-TP7 	CP-TP8 		Zhang et al. (2017)

Table 12.11 Reported TPs of CP during various AOPs

AOP	Identified TPs		Reference	
UV/TiO_2	Keto-IF 	IF-TP1 (loss 1 Cl) 	IF-TP2 (loss CH_2) 	Lai et al. (2015)
	3-dechloroethyl-ifosfamide 	IF-TP3 (loss 1 Cl) 	IF-TP4 (loss CH_3-Cl) 	
	IF-TP5 	IF-TP6 (loss 2 Cl) 	2-chloroethylamine 	
UV and UV/H_2O_2	3-dechloro-ethyl-IF 	Keto-IF 	Imino-IF 	Česen et al. (2016)
	IF-TP7 			

(continued)

Table 12.11 (continued)

AOP	Identified TPs		Reference	
UV/TIO_2 and $UV/Pt\text{-}TiO_2$	Inorganic species: NH^{4+} PO_4^{3-} Cl^-	IF-TP8 	IF-TP9 	Ofiarska et al. (2016)
	2-dechloroethyl-IF 			

namely, 2- and 3-dechloroethyl and imino derivatives of CP and IF formed during UV/H_2O_2 and UV/TiO_2 treatments (Tables 12.10 and 12.11). Certain treatments result in the same TPs, which is expected due to the similarity in the chemical structure CP and IF. These include, for example, a short chain TP (2-chloroethylamine), CP-TP4/IF-TP5 and CP-TP5/IF-TP7 (Table 12.10). Interestingly, Ofiarska et al. (2016) identified IF-TP9, which has the same molecular weight as CP-TP8, a TP identified by Zhang et al. (2017). Both TPs were identified as the hydroxylation products of parent compounds, where Ofiarska et al. (2016) left the exact position of hydroxyl group undetermined. Since no spectra are available for the comparison of both TPs, it is hard to conclude whether they share the same structural formula or not. As CP and IF typically occur together, the amount and potency of the formed species might be higher than one would assume based on the degradation of the individual compound. This should be investigated by studies addressing toxicity, where both compounds shall be treated simultaneously. Interestingly, Ofiarska et al. (2016) report the formation of NH^{4+}, PO_4^{3-}, and Cl^- formed from CP and IF when using UV/TiO_2 (Tables 12.10 and 12.11). As these inorganic species might have an adverse effects on aqueous biota, further studies addressing their formation during other treatments and an evaluation of the toxicity of UV/TiO_2-treated samples shall be studied in the future.

12.4 Conclusions

This chapter describes the analysis, occurrence, removal efficiency, and transformations of two cytostatic drug residues, CP and IF, in the aqueous environment. The most common method for the determination of CP and IF in aqueous samples is SPE with further LC-MS analysis. Their presence has been confirmed in

WWs on a global scale, while in SW, levels are typically below the LOD. Both compounds are recalcitrant to biodegradation and, for this reason, a number of studies have addressed their removal efficiency during abiotic treatments. So far, AOPs seem to be the most promising; however, their suitability for WW treatment is limited due to the high costs involved. Therefore, they require further optimization before they can be used in real world applications, for example, to treat highly contaminated hospital WWs. In addition, stable TPs have been confirmed during various abiotic treatments, which have structures similar to that of the parent compounds. These species might, besides CP and IF, also have adverse effects on aqueous biota. Therefore, environmental occurrence, fate, and effects of all CP and IF residues including identified TPs must be assessed in the future in order to evaluate the overall risks they pose to the environment.

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