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Application of Chemical Oxidation Processes for the Removal of Pharmaceuticals in Biologically Treated Wastewater

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Application of chemical oxidation processes for the removal of pharmaceuticals in biologically treated wastewater

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2013

Academic thesis which, by due permission of the Faculty of Engineering of Lund University, will be publicly defended on 21 February 2013 at 10:15 am in lecture hall K:G at the Center for Chemistry and Chemical Engineering, Getingevägen 60, Lund, for the degree of Doctor of Philosophy in Engineering. The Faculty opponent is Research Professor (1st Class) Marie-Noëlle Pons, Université de Lorraine, France.

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Abstract

The discharge of effluents from wastewater treatment plants (WWTPs) is considered to be the major source of residual pharmaceuticals frequently found in aquatic environments. The complex nature of such compounds tends to make conventional biological treatments aimed at their removal ineffective. The present thesis concerns the removal of 62 different active pharmaceutical ingredients commonly detected in Swedish wastewater effluents by means of chemical oxidation techniques. Techniques with potential to be effective are in particular peracetic acid (PAA), chlorine dioxide (ClO_2), ozone (O_3) and a combination of ozone and hydrogen peroxide (O_3/H_2O_2), which all were included in this study. The performance of a given treatment was evaluated in terms of the degree of pharmaceutical removal achieved and the oxidant demand of the wastewater. The effects of the characteristics of the wastewater have on the degree of removal efficiency of different pharmaceuticals were also evaluated.

Ozone is considered to be the most efficient chemical oxidant for reducing the concentrations of a large number of different pharmaceuticals, the ozone dose required for this being fairly low (5-10 mg/L), depending upon the characteristics of the effluent. Over 90% of the pharmaceuticals investigated in most of the effluents could be eliminated to 90-100% by use of ozone, while several of the pharmaceuticals being observed to be recalcitrant to chlorine dioxide treatment. The addition of small amounts of hydrogen peroxide during wastewater ozonation, although not enhancing the removal of pharmaceuticals, was found to increase ozone decomposition, presumably resulting in the formation of hydroxyl (OH) radicals as secondary oxidants. The addition of small amounts of H_2O_2 in this way is seen as being advantageous in terms of its reducing both the treatment time and the reaction tank volume which is needed.

Of the various water quality parameters investigated, the organic carbon content was found to have a particularly strong effect on the removal of pharmaceuticals, due to its competitive behavior towards the oxidant. PAA appears to have the lowest degree of pharmaceutical removal, making it not a suitable treatment option for removing pharmaceuticals in the effluents. Although chlorine dioxide and ozone appeared quite similar in their manner of removing pharmaceuticals, both of them reacting with electron-rich functional groups such as those of the phenolic and amino type, some of the pharmaceuticals reacted more slowly with chlorine dioxide than with ozone, given the same reactive substituent and structural similarities. Thus, a decision regarding the possible use of chlorine dioxide for tertiary treatment should take account of how strongly the pollutant or pollutants in question are affected by it. The use of chlorine dioxide appeared to be particularly beneficial when a small-scale WWTP is involved or when treatment is required for only a limited period of time. Although ClO_2 is slightly more expensive to produce than ozone, the preparation system and the reaction chamber

for treatment that are required are far simpler and less expensive to build than those needed for ozone treatment. It was noted that energy costs connected with ozonation are a function both of the ozone demand of the wastewater and the contaminant or contaminants to be removed. It appeared that, in view of the high degree of reactivity of ozone to a broad range of the pharmaceuticals that were investigated, ozonation of secondary effluent is the most suitable alternative for most WWTPs.

Populärvetenskaplig sammanfattning

Den största källan till läkemedelsrester i vattenmiljön är utgående renat avloppsvatten från våra kommunala reningsverk. Läkemedel är utvecklade för att ha olika typer av biologiska effekter. Vilka dessa är i människan är relativt välkänt, medan effekterna på vattenlevande organismer och andra djur till stor del är okända. Detta i kombination med deras resistens mot de kemiska och biologiska nedbrytningsprocesser som pågår i reningsverken gör att de utgör en potentiell risk för miljön eftersom de inte avlägsnas i reningsverken utan följer med utgående vatten till miljön.

I denna avhandling undersöks om läkemedelsrester som finns i renat avloppsvatten från olika typer av avloppsreningsverk i Sverige kan avlägsnas med hjälp av några olika kemiska oxidationsmedel. De som ingick i studien var klordioxid, perättiksyra och ozon. Den senare enskilt och i kombination med väteperoxid. Bland de undersökta läkemedelsresterna ingick antiinflammatoriska, analgetiska, antiepileptiska och antidepressiva preparat, hormonstyrande substanser och betablockerare. Reningseffektiviteten kvantifierades genom hur mycket av läkemedlen som kunde nedbrytas vid en viss dos, definierat som att hur mycket av ursprungssubstansen som försvann. Ska dock noteras att detta inte säger något om hur långt nedbrytningen går, dvs om endast en del av molekylen förändras eller om omvandling sker ända ned till koldioxid och vatten.

Resultaten av experimenten, som genomfördes som batch experiment i laboratoriet, visade att användning av ozon är det mest effektiva sättet att genom kemisk oxidation bryta ned (>90%) de flesta av de studerade läkemedelsresterna i utgående avloppsvatten. För att uppnå >90% reduktion krävdes en ozon dos på 5 - 10 mg/L. Där dosen både var beroende av vilken substans som studerades och vilken kvalitet som vattnet hade (primärt innehåll av organiskt kol (DOC) och graden av aromatisitet hos detta). Det kunde inte fastställas att en ökad effektivitet kan uppnås genom tillsättning av små mängder väteperoxid tillsammans med ozon. Däremot visades dessa experiment att en sådan tillsättning innebar en ökad reaktionshastighet vilket i sin tur innebär minskad behandlingstid och därmed också minskad volym av reaktionsbehållaren. Något som kan ha stor betydelse vid implementering av tekniken i praktiken.

Användning av klordioxid kan jämföras med ozon då båda reagerar med elektronrika funktionella fenol- och amino grupper. Emellertid visade experimenten att för vissa av de studerade läkemedelsresterna att reaktionen med klordioxid är långsammare än motsvarande reaktion med ozon. Detta betyder att potentialen för användning av klordioxid som behandlingsmetod kommer att bero på vilka läkemedelrester som är i fokus och på om det kan vara fördelaktigt ut andra aspekter. Här kan nämnas att klordioxidtekniken skulle kunna vara fördelaktig för småskaliga avloppsreningsverk eller vid reningsverk där behandling endast krävs under en begränsad tid. Anledningen är att

anläggningarna för klordioxid är enklare och billigare att bygga både med avseende på klordioxidgeneratorn som reaktionskammaren, jämfört med motsvarande anläggningar för ozonbehandling.

List of publications

Paper I Hey, G., Ledin, A., la Cour Jansen, J., Andersen, H.R. 2012. Removal of pharmaceuticals in biologically treated wastewater by chlorine dioxide or peracetic acid. Environmental Technology 3(9), 1041-1047.

Paper II Hey, G., Grabic, R., Ledin, A., la Cour Jansen, J., Andersen, H.R. 2012. Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater. Chemical Engineering Journal 185-186, 236-242.

Paper III Antoniou, M.G., Hey, G., Vega, S.R., Spiliotopoulou, A., Fick, J., Tysklind, M., Ledin, A., la Cour Jansen, J., Andersen, H.R. Required ozone doses for removing pharmaceuticals from wastewater effluents. Manuscript.

Paper IV Hey, G., Vega, S.R., Fick, J., Tysklind, M., Ledin, A., la Cour Jansen, J., Andersen, H.R. Removal of pharmaceuticals in WWTP effluents by ozone and hydrogen peroxide. Submitted for publication.

My contribution to the publications

Paper I I planned the experiment together with my supervisors. I carried out the laboratory work at the Department of Environmental Engineering of the Technical University of Denmark (DTU). I wrote the paper and was provided comments by my supervisors and co-authors. The analysis of pharmaceuticals was performed by the Department of Environmental Engineering of DTU.

Paper II I planned the experiment together with my supervisors. I did the laboratory work at the Department of Environmental Engineering of DTU. I wrote the paper, receiving comments from my supervisors and co-authors. The analysis of pharmaceuticals was performed by the Department of Chemistry of Umeå University (UMU).

Paper III I helped conducting the experiments at the Department of Environmental Engineering of DTU. I wrote parts of the manuscript. The analysis of pharmaceuticals was performed by the Department of Chemistry of UMU.

Paper IV I planned the experiment together with my co-author and supervisor and carried out the laboratory work at the Department of Environmental Engineering of DTU. I wrote the paper and received comments from my supervisors and co-authors. The analysis of pharmaceuticals was performed by the Department of Chemistry of UMU.

Other related publication

Moradas, G. (Now Hey, G.), Auresenia, J., Gallardo, S., Guieysse, B. 2008. Biodegradability and toxicity assessment of trans-chlordane photochemical treatment. Chemosphere 73(9), 1512-1517.

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1. Introduction

1.1 Background

Pharmaceuticals in the environment

The high standard of living, in highly developed countries in particular, and the increasing availability and affordability of medical treatment in many countries, has led to an increased production and consumption of different classes of pharmaceuticals, both those that require a prescription and those that do not. In recent years, a number of pharmaceuticals have been reported to be potentially toxic substances often found rather widely in the environment (Singh et al., 2011; Albrecht et al., 2012). Hundreds of pharmaceutical substances of differing therapeutic class, together with their metabolic by-products, have been detected in different environmental matrices (Ternes et al., 1998; Kolpin et al., 2002; Kinney et al., 2006; Snyder, 2008; Lubick, 2010; Fick et al., 2010; Al-Odaini et al., 2010; Kassinos et al., 2011; Fram and Belitz, 2011), these threatening the health of many sensitive living organisms including, including humans (Pomati et al., 2006; Filby et al., 2007; Pomati et al., 2008; Schultz et al., 2010; Albrecht, 2012).

The major sources of pharmaceuticals in aquatic environments are discharges of WWTP effluents, the pharmaceuticals these contain stemming mainly from their use in households and in hospitals, and from discharges of wastewater from drug producers (Figure 1.1) (Kolpin et al., 2002; Ternes and Joss (eds), 2006; Wu et al., 2009; Albrecht, 2012). Pharmaceuticals of up to levels of several µg/L have been detected in WWTP effluents globally (Ternes, 1998; Bendz et al., 2005; Batt et al., 2006; Zorita et al., 2009; Zhang and Geissen, 2010; Falås et al., 2012; Lacey et al., 2012). These pharmaceuticals, often referred to as `emerging pollutants´, are not yet regulated in terms of their occurrence in water bodies and wastewater effluents (Bell et al., 2011). It has been proposed by the European Commission, however, that certain pharmaceuticals, such as diclofenac and the hormones ethinyl estradiol (EE2) and estradiol (E2), be regarded as priority substances in terms of the water policies established in accordance with the EU Water Framework Directive (EC, 2012).

Removal of pharmaceuticals during wastewater treatment

The majority of WWTPs in Europe operate with use of physical and biological treatments alone, due to high investment costs associated with the introduction of an additional, more advanced tertiary step (Zorita et al., 2009; Bolong et al., 2009). In Sweden, the introduction of biological wastewater treatment began 60 years ago, and nowadays the majority of the municipal WWTPs operated with use of the following processes: *i*) mechanical treatment, *ii*) biological treatment, *iii*) chemical treatment (mainly for phosphorus removal), and *iv*) filtration as a final step (Swedish EPA Naturvårdsverket Report, 2009; Rudén et al. (eds), 2010). Biological treatment comes in different process configurations involving activated sludge (with and without extended nitrogen removal), biofilm, and a combination of activated sludge and biofilm (Falås et al., 2012). The efficiency of the removal of pharmaceuticals varies, depending upon the treatment process involved. In most cases, use of activated sludge with extended nitrogen removal provides the highest level of efficiency (Falås et al., 2012). The possibilities for operating with extended biological nitrogen removal depends upon the size and location of the plant (Falås et al., 2012). Generally, WWTPs located in the northern part of the country operate without extended nitrogen removal, due to the low temperatures.

A number of studies have confirmed conventional biological methods not being effective enough to provide for the complete removal of residual pharmaceuticals in wastewaters (Ternes and Hirsch, 2000; Kimura et al., 2005; Vieno et al., 2005; Suarez et al., 2008; Hollender et al., 2009), due to the recalcitrance of the pharmaceuticals to biodegradation or to the limited biological activity taking place, especially in cold climates. Accordingly, new treatment approaches aimed at improving the process efficiency of wastewater treatment need to be employed.

The addition of a tertiary step such as chemical oxidation, following secondary biological treatment (Figure 1.1), is a suitable treatment alternative. This additional step can be followed by another process, such as a polishing step, if the effluent quality desired calls for it. The potential of this process for treating organic micropollutants, pharmaceuticals included, that both water generally and wastewaters can contain has been investigated on a worldwide basis. Chemical oxidation following biological treatment has been found to be an appropriate option for eliminating to large extent pharmaceuticals of ecotoxicological concern and reducing the probability of their occurrence in the environment.

The various observations just referred to represent the basis for the major hypothesis of the thesis and its main objectives as presented below.

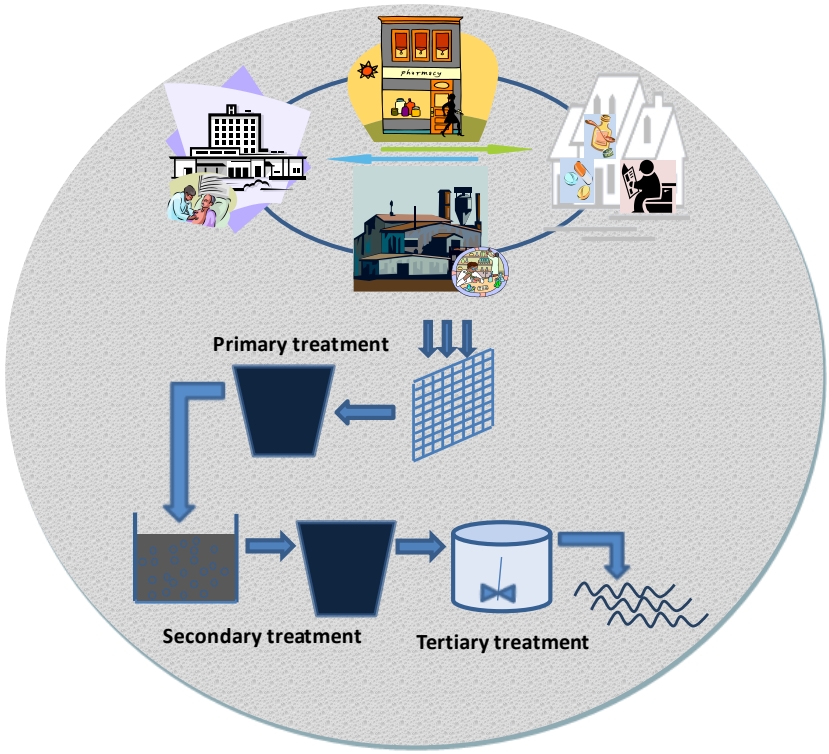

Figure 1.1 - Sources and flow of pharmaceuticals in a wastewater treatment plant.

1.2 Hypothesis and objectives

The main hypothesis tested in the thesis is the following: *Chemical oxidation is an efficient method for the removal of residual pharmaceuticals in WWTP effluents*. "Efficient" as conceived here is efficiency in decreasing the concentration of the target compounds to an acceptable level, without increasing the costs and the use of other resources (such as energy and various chemicals) for the wastewater treatment, above that can be regarded as acceptable levels. For testing this hypothesis, a number of questions were posed:

1. What oxidation method is the most efficient here?
2. How much of the oxidant is needed to effectively remove the pharmaceuticals?
3. How are the pharmaceuticals removed during chemical oxidation?
4. What factors affect the removal efficiency?

5. Which treatment method is most appropriate under the conditions present, taking into account in particular the climate, the location within the country and the size of the WWTP?

These questions led to the formulation of what is regarded as the major objective:

To develop an appropriate treatment technology for the removal of pharmaceuticals in biologically-treated wastewater by means of chemical oxidation.

In addition, a number of more specific objectives, related to the main objective, were formulated. These include the following:

- to compare the efficiency of several quite promising appearing methods involving use of peracetic acid (PAA), chlorine dioxide (ClO_2) and ozone-based processes (O_3) as oxidants for removing pharmaceuticals,
- to determine the most suitable dose of an oxidant, one resulting in >90% removal of the pharmaceuticals,
- to examine the effects of the chemical structure of the pharmaceuticals on their reactivity towards the oxidants, and
- to assess variations in the removal efficiency of different WWTP effluents in terms of the degree to which they are affected by the wastewater characteristics such as the amount of organic matter they contain, and their alkalinity, UV absorbance and pH.

1.3 Thesis Outline

The present work is based on four papers that are appended to the thesis.

A brief presentation of state-of-the-art within chemical oxidation of waters of various types is presented in Chapter 2, followed by a brief description of the methodologies employed (Chapter 3). The relevant results obtained are presented in the various sections included in Chapter 4 (with reference to the specific papers involved): *i*) Chapter 4.1 – Comparison of different chemical oxidants, *ii*) Chapter 4.2 – Removal of pharmaceuticals by ozonation: reactivity of the functional groups, and *iii*) Chapter 4.3 – Effects of the water matrix on the removal of pharmaceuticals by ozonation. Chapter 5 presents a discussion of the results obtained**.** The major conclusions are presented in Chapter 6, and what appear to be future research needs in relation to this work are taken up in Chapter 7.

2. Chemical Oxidation for water and wastewater treatment

In recent years, the potential of chemical oxidation for removing organic micropollutants in water and wastewater that cannot be degraded efficiently by conventional biological methods has been widely recognized (Ternes et al., 2003; Buffle et al., 2006; Kosjek et al., 2009; Lee and von Gunten, 2010; Benitez et al., 2011). Oxidation can be an efficient treatment option employing a variety of chemical oxidants, such as chlorine, chlorine dioxide, peracetic acid, ozone, fenton and hydrogen peroxide, its efficiency depending upon the target pollutants, the water matrix and the effluent quality aimed at. Chemical oxidants are known to react preferentially with electron-rich organic functional groups such as aromatic compounds (phenol, aniline, and polycyclic aromatics, for example), organosulfur compounds, and deprotonated amines (Hoigne and Bader, 1994; Huber et al., 2005a; Lee and von Gunten, 2010).

Chlorine has for many years been one of the most commonly used disinfectants for both water and wastewater treatment, due to its strong bactericidal effects and its cost-effectiveness (Aieta et al., 1980; Lee and von Gunten, 2010). Various studies have shown however, that use of chlorine can lead to the formation of chlorinated by-products that can be of concern in terms of public health (Isacson et al., 1985; Pehlivanoglu-Mantas et al., 2006; Watson et al., 2012). Therefore, treatment with chlorine may not be an appropriate option here.

It appears that *chlorine dioxide*, which is comparable to chlorine in its disinfection efficiency, is a better alternative, since it limits the formation of unwanted disinfection by-products (Aieta et al., 1980). ClO_2 can be used either alone or in combination with other oxidants, such as ozone. It has been employed for water disinfection and for oxidation to remove taste- and odor-causing compounds (Danielescu, 2007; EPA). The potential of ClO_2 as an oxidant makes it particularly suitable for the treatment of drinking water, surface water and wastewater for the removal of pharmaceuticals, due to its high reactivity. For example, the anti-inflammatory drug diclofenac, reported as being one of the most frequently detected compounds in water at concentrations of up to the μg/L level (Ternes, 1998), is among the pharmaceuticals completely degraded during drinking and surface water treatment at the lowest ClO_2 dose employed (Huber et al., 2005b). Additional studies have shown the effectiveness of low doses of ClO_2 in removing

pharmaceuticals in wastewater (Andersen et al., 2007; Andersen, 2010; Lee and von Gunten, 2010).

Peracetic acid (PAA) has often been employed for wastewater disinfection due to its high degree of efficiency in the inactivation of disease-causing microorganisms such as bacteria, viruses and spores (Baldry and French, 1989; Gehr et al., 2003; Dell'Erba et al., 2007). Aside from its common use as a disinfectant, PAA can be regarded as a potential oxidant for the removal of pharmaceuticals, due to its strong oxidation potential, which is greater than that of chlorine and of chlorine dioxide (Kitis et al., 2004; Koivunen and Heinonen-Tanski, 2005). In contrast to other oxidants, PAA is not known to produce any harmful by-products in being used to treat water (Erba et al., 2007).

Ozonation is considered to function efficiently in the disinfection and oxidation of pollutants in water. Traditionally, ozone has been used for treating drinking water for disinfection purposes and for the removal of odor and taste. In WWTPs, ozonation has been used as a pretreatment step for biological processes of different types or as a final disinfection step. Ozonation used for post-treatment purposes has been shown to be effective in removing trace organics, including a number of different pharmaceuticals (Ternes et al., 2003; Huber et al., 2005a; Bahr et al., 2007; Hansen et al., 2010). An advantage of the use of ozone is the production of hydroxyl (OH) radicals that occurs through the self-decomposition of ozone, usually at pH values above 7 (Hoigne and Bader, 1981; Klavarioti et al., 2009). OH radicals are known to react non-selectively with a number of organic compounds in water (Lee and von Gunten, 2010). The addition of hydrogen peroxide also catalyzes the decomposition of ozone to produce OH radicals (von Gunten, 2003), termed a peroxone process, which is an advanced oxidation process (AOP). This technique provides non-selective oxidation that leads to an enhancement of the rate of oxidation of O_3-resistant compounds and to a reduction in treatment time (Prado and Esplugas, 1999; Zwiener and Frimmel, 2000; Huber et al., 2003). The efficiency of ozone-based processes has also been confirmed by the high degree of TOC reduction they can achieve (Rosal et al., 2008). In addition, ozone can be employed for wastewater treatment in combination with UV light (O_3/UV, also an AOP) such that at a UV radiation of 254nm ozone decomposes to produce OH radicals. This combined technique leads to such reactions as photolysis, direct ozonation and radical oxidation (Kim and Tanaka, 2010). It has been employed for the removal of various organic compounds in water and wastewater (Chen et al., 2007; Zou and Zhu, 2008; Kim and Tanaka, 2010).

Another method in which hydroxyl radicals play a central role is the combined use of *UV and* H_2O_2, a method found able to remove both naproxen and TOC from wastewater (Felis et al., 2007).

Fenton oxidation, a catalytic process involving the combined use of hydrogen peroxide and ferrous ions (Fe^{2+}), is an AOP that has been studied very extensively.

Its use for the removal of organics and improvement in their biodegradability has been tested in different wastewaters (Bautista et al., 2008; Trapido et al., 2009). The main disadvantage in the use of this method, however, is the high costs of the peroxide and of the additional treatment required for removing the iron sludge from the treated water (Bautista et al., 2008). Development of the photo-fenton process, which utilizes either UV or solar light, has resulted in a reduction in the amounts of the waste sludge produced and an increase in the efficiency of treatment (Kim and Vogelpohl, 1998).

UV/TiO_2 heterogeneous photocatalysis, which is also among the most widely studied water treatment processes for the removal of contaminants consisting in part of pharmaceuticals (Dimitroula et al., 2012; Rodriguez et al., 2012) offers the advantage of the photocatalyst (TiO_2) employed being low in cost and being chemically stable. The use of solar radiation as a UV source is recommended however, due to the high costs associated with the use of lamps producing artificial UV (Rodriguez et al., 2012).

Chemical oxidation methods have been tested both in pilot- and in full-scale studies in many different regions around the world (Table 2.1). This work has demonstrated the versatility of the chemical oxidants involved in the treatment of water generally and of wastewater for disinfection and/or for micropollutant oxidation purposes. Ozone's first full-scale application in the treatment of drinking water took place prior to the 1900s in the Netherlands (Langlais et al., 1991). Ozone became popular then as a disinfectant and an oxidant in wastewater treatment. Full-scale applications of chlorine dioxide have been mostly concerned with treatment of drinking water and with wastewater disinfection. Ozone in combination with hydrogen peroxide has also been employed full-scale for groundwater remediation. In addition, advanced oxidation processes involving use of TiO_2, UV and Fenton have been tested for the removal of organic pollutants, mostly on a pilot-scale.

The transformation of micropollutants during oxidation is affected by the nature and characteristics of the wastewater involved, such as the presence of dissolved organic (DOC) and inorganic species, as well as alkalinity and pH, and the reactivity of the oxidant to the target compounds (Lee and von Gunten, 2010). For example, when ozone is applied to wastewater containing a wide range of organic matter, the reactivity of the organic material affects the efficiency of ozone, especially in the case of micropollutant oxidation. Carbonate alkalinity also acts as a scavenger of OH radicals, this affecting the lifetime of ozone in water, such as through its leading to a decrease in the decomposition of ozone as alkalinity increases (Elovitz et al., 2000). Another relevant factor to consider is the pH of the wastewater. Low pH favors reaction with molecular ozone, whereas high pH levels result in an increase in ozone decomposition which favors the formation of OH radicals and allows the degradation of substances less reactive to ozone (von Sonntag and von Gunten, 2012).

Table 2.1 - Examples of oxidation technologies applied in pilot- or full-scale water and wastewater treatment.

Treatment	Application	Size	Country	Reference
Chlorine dioxide	Combined sewer overflow disinfection	Pilot-scale	USA	Geisser et al., 1979
Chlorine dioxide	Groundwater remediation	Pilot-scale	China	Kun et al., 1998
Chlorine dioxide	Drinking water treatment	Full-scale	Israel	Limoni and Teltsch, 1985; Richardson and Thruston, 2003
Chlorine dioxide	Drinking water treatment	Full-scale	USA	Volk et al., 2002
Chlorine dioxide	Drinking water treatment	Full-scale	China	Tao et al., 2004
Chlorine dioxide	Drinking water treatment	Full-scale	Italy	Buschini et al., 2004
Chlorine dioxide	Wastewater disinfection	Pilot-scale	Italy	Veschetti et al., 2005
Ozone	Wastewater disinfection	Full-scale	USA	Rakness and Hegg, 1980; Rakness et al., 1988
Ozone	Drinking water treatment	Full-scale	USA	Escobar and Randall, 2001; Lee et al., 2003
Ozone	Drinking water treatment	Full-scale	Netherlands	Langlais et al., 1991
Ozone	Wastewater pharmaceuticals removal	Pilot-scale	Switzerland	Ternes et al., 2003; Huber et al., 2005a
Ozone	Drinking water treatment	Full-scale	Switzerland	Hammes et al., 2006
Ozone	Wastewater pharmaceutical removal	Full-scale	Japan	Nakada et al., 2007
Ozone	Wastewater micropollutant oxidation	Pilot-scale	USA	Wert et al., 2009
Ozone	Municipal wastewater treatment	Pilot-scale	Italy	Ried et al., 2009
Ozone	Wastewater micropollutant oxidation	Full-scale	Switzerland	Hollender et al., 2009
Ozone	Drinking water treatment	Full-scale	Belgium	Audenaert et al., 2010

Ozone	Wastewater disinfection, Micropollutant oxidation	Full-scale	Switzerland	Zimmermann et al., 2011
Ozone	Tertiary treatment of wastewater	Pilot-scale	Austria	Altmann et al., 2012
Ozone/hydrogen peroxide	Groundwater remediation	Pilot-scale	USA	Zappi et al., 1998
Ozone/hydrogen peroxide	Groundwater remediation for removal of organics	Full-scale	Vienna	Werderitsch, 2007
Ozone/hydrogen peroxide	Wastewater pharmaceutical removal	Pilot-scale	Switzerland	Ternes et al., 2003
Ozone/hydrogen peroxide	Drinking water treatment	Pilot-scale	Canada	Irabelli et al., 2008
Ozone, Ozone/hydrogen peroxide	Wastewater pharmaceutical removal	Pilot-scale	Japan	Kim and Tanaka, 2010
Ozone/UV	Wastewater pharmaceutical removal	Pilot-scale	Switzerland	Ternes et al., 2003
Fenton	Groundwater remediation by oxidation	Pilot-scale	USA	Bergendahl et al., 2003
Fenton	Wastewater pharmaceutical removal	Full-scale	Turkey	Tekin et al., 2006
Photo-Fenton	Industrial wastewater treatment	Pilot-scale	Austria	Bauer and Fallman, 1997
Photo-Fenton	Leachate pesticides removal	Pilot-scale	Spain	Navarro et al., 2011
UV/TiO2, Fenton, photo-Fenton	Pesticides treatment in water	Pilot-scale	Spain	Maldonado et al., 2007

To summarize, although the use of oxidation methods for the removal of pharmaceuticals appears very promising, the removal and reactivity of a number of pharmaceuticals has not been investigated extensively at all in real wastewater. It is also important to investigate matrix effects on the removal of pharmaceuticals in greater detail, since the proper dosage is dependent upon the characteristics of the water matrix, such information being highly important to evaluating the potential of the methods in question for full-scale implementation.

3. Methodology

Wastewater effluents

The WWTP effluents used in the investigation were taken after secondary treatment from different treatment plants in Sweden, which differ in the quality of the wastewater and the types of biological treatment employed. The WWTP processes are described briefly below.

Description of WWTPs

Källby WWTP in Lund receives what is mainly domestic wastewater from 80,000 inhabitants. The incoming wastewater has annual average concentrations of approximately 180 mg/L BOD_7 and 40 mg/L Total Nitrogen (TN). The wastewater is treated mechanically (screening, grit removal, and sedimentation), followed by a low-loaded activated sludge process operated with pre-denitrification. Side-stream hydrolysis is also performed so as to provide an additional carbon source and thus enhance biological phosphorous removal. Post-precipitation is used as a complementary process when biological phosphorous removal is insufficient. The samples for the present study were taken after the activated sludge process.

Sjölunda WWTP in Malmö receives wastewater from 300,000 inhabitants and from a wide range of industries. The incoming wastewater has annual average concentrations of approximately 220 mg/L BOD_7 and 40 mg/L TN. The wastewater is first treated mechanically (screening, grit removal, and pre-precipitation). The subsequent, high-loaded activated sludge process operates for BOD removal, but there is an anaerobic/anoxic zone at the inlet for denitritation of aerobically-treated or nitritated reject water from the sludge-handling facilities. Nitrification takes place in a subsequent nitrifying trickling filter, this being followed by a moving-bed biofilm reactor (MBBR) for denitrification. Flotation constitutes the final particle separation step. The samples for the present study were taken from the outflow of the high-loaded activated sludge plant.

Öresundsverket WWTP in Helsingborg receives wastewater from 120,000 inhabitants and from various industries. The incoming wastewater has annual average concentrations of approximately 180 mg/L BOD_7 and 30 mg/L TN. The wastewater is first treated mechanically (screening, grit removal, and

sedimentation). The primary sedimentation tanks are operated with primary sludge hydrolysis for the production of a carbon source for enhanced biological phosphorous removal. Nitrogen removal and enhanced biological phosphorous removal take place in a traditional UCT process. No chemicals for phosphorus removal are used at the plant. Biological sand filtration is used as the polishing step. In the present study, samples were taken after the UCT process.

Björnstorp WWTP in Lund is a very small plant that only receives domestic wastewater from about 200 persons. The incoming wastewater is diluted and has annual average concentrations of approximately 70 mg/L BOD_7 and 21 mg/L TN. The wastewater passes through a cutting pump prior to sedimentation in a pre-precipitation process, followed by passage through activated sludge for BOD removal. The treated water is then soil-infiltrated. In the present study, samples were taken following activated sludge treatment.

Nykvarnsverket WWTP in Linköping receives wastewater from about 135,000 inhabitants and from several industries. The incoming wastewater has annual average concentrations of approximately 280 mg/L BOD_7 and 45 mg/L TN. The wastewater is first treated mechanically (screening, grit removal, and pre-precipitation). Passage through a low-loaded activated sludge plant in which nitrification alone takes place follows. Part of the nitrified effluent is diverted into a post-denitrification unit (Moving Bed Biofilm Reactor), in which ethanol is used as the carbon source. Finally all of the wastewater is treated in a post-precipitation plant for final polishing. In the present study, samples were taken after the final post-precipitation stage.

Klagshamn WWTP in Malmö receives wastewater from 70,000 inhabitants. The incoming wastewater, which has annual average concentrations of 130 mg/L BOD_7 and 30 mg/L TN, was treated mechanically. This is followed by a low-loaded activated sludge process which is mainly for BOD removal and nitrification, but can also be operated for partial pre-denitrification. Denitrification takes place mainly in a moving-bed biofilm reactor process that follows the activated sludge treatment, the samples were taken from the MBBR process.

Käppala WWTP in Stockholm receives wastewater from 700,000 inhabitants. The incoming wastewater, which has annual average concentrations of approximately 230 mg/L BOD_7 and 44 mg/L TN is treated mechanically (screening, grit removal, and primary sedimentation), followed by an activated sludge process for nitrogen and enhanced biological phosphorous removal. Sand-filtration is applied as polishing step and subsequent post-precipitation with iron-sulphate as a complementary process in case of insufficient biological phosphorous removal. The samples for the present study were taken after the activated sludge process.

Uppsala (Kungsängsverket) WWTP in Uppsala receives wastewater from 200,000 inhabitants. The incoming wastewater has annual average concentrations of approximately 160 mg/L BOD_7 and 42 mg/L TN. The incoming wastewater is

treated mechanically (screening, grit removal, and primary sedimentation) with subsequent primary precipitation for carbon and phosphorous removal in the primary clarifier. Activated sludge process is applied for nitrogen removal and thereafter sand-filtration as a polishing step. Post-precipitation as a complementary process is applied in case of insufficient phosphorous removal. The samples for the present study were taken after the activated sludge process.

Chemicals

The methanol, acetonitrile, sodium hydroxide and sulfuric acid employed were purchased from Merck (Germany). The hydrogen peroxide solution (30%) was purchased from Sigma-Aldrich. All the pharmaceutical reference standards were purchased from the suppliers as analytical grade (>98%) solids. The stock solutions of the pharmaceuticals were prepared in methanol. Chlorine dioxide was synthesized using hydrochloric acid, sodium chlorite and deionized water (Figure 3.1). The ozone stock solution was prepared according to methods described in Antoniou and Andersen (2011) (Figure 3.2).

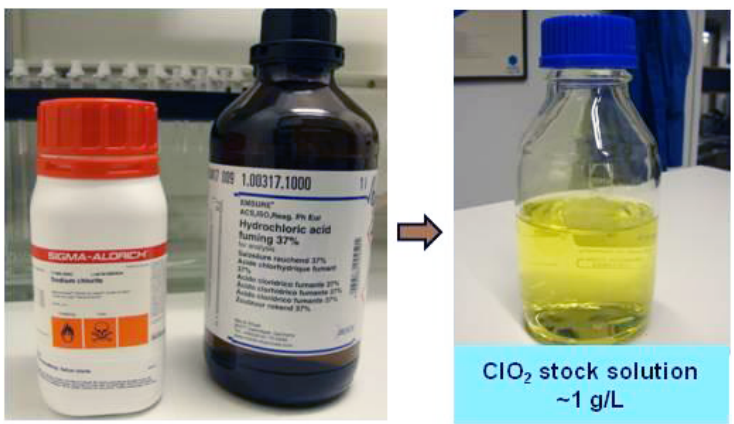

Figure 3.1 - ClO_2 (greenish yellow color) produced in the laboratory.

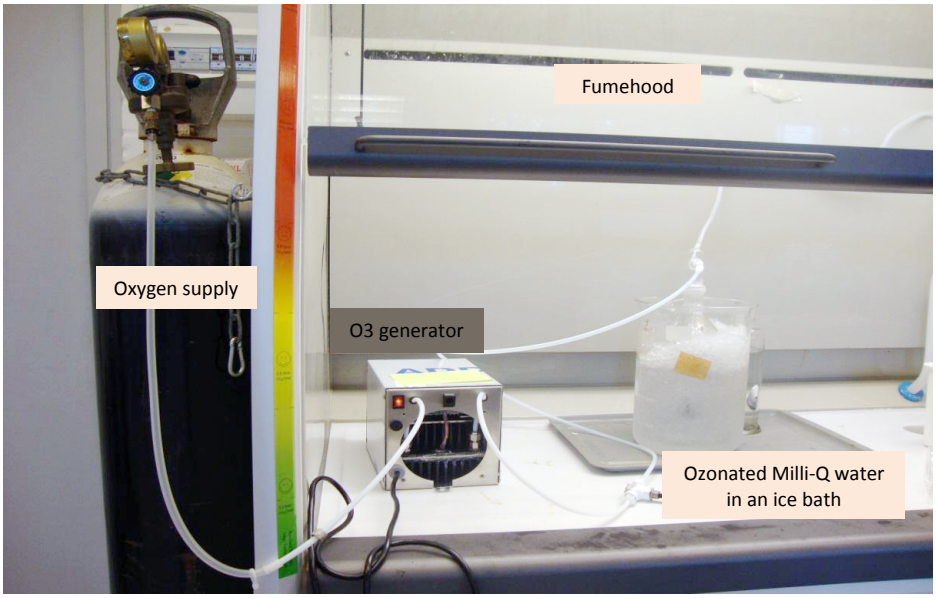

Figure 3.2 - Laboratory set up used in the preparation of ozone stock solution.

Oxidation Experiment

The oxidation of biologically-treated WWTP effluents was carried out using different techniques, such as chlorine dioxide, peracetic acid and ozone-based processes (Table 3.1). The pharmaceuticals selected represent different classes of pharmaceuticals commonly sold and used in Sweden, all of them likely to end up in WWTP effluents due to their low degree of sorption to sludge (Hörsing et al., 2011). The list of the pharmaceuticals investigated and the corresponding oxidation treatment employed is presented in Table 3.2.

PAA and ClO_2 treatment

The effluent samples were prepared in borosilicate glass bottles and were spiked with the pharmaceuticals to the initial concentrations desired. The oxidant (PAA or ClO_2) was then added to the samples at different concentrations. All of the samples were stored in the dark and were allowed to react overnight at room temperature, after which the pH and the oxidant concentrations in the samples were measured. The oxidant consumed by the effluent was followed the whole time and the oxidant remained after treatment was taken note of.

Table 3.1 - Effluent source and treatment(s) applied.

WWTP	PAA	ClO_2	O_3	O_3/H_2O_2
Källby	x	x	x	
Björnstorp			x	
Sjölunda	x	x	x	
Öresundsverket			x	
Nykvarnsverket			x	
Klagshamn			x	
Käppala			x	x
Uppsala			x	x

O_3 and O_3/H_2O_2 treatment

The wastewater effluents were spiked with pharmaceuticals and were then transferred into glass bottles to which different volumes of O_3 stock solution were added. The bottles were covered with aluminum foil and were placed for 2 hours in a 15°C water bath. For the O_3 and H_2O_2 experiments that were conducted, the H_2O_2 was added just prior to adding the ozone.

Water quality analysis

Measurements of COD and NH_4^+-N were conducted by use of Hach Lange test kits. Total suspended solids (SS-EN 872:2005), total P (SS-EN ISO 6878:2005) and total N (SS-EN ISO 11905-1) were analyzed using Swedish standard methods. Alkalinity was measured by titrating 25 ml sample with 0.05 M HCl to a pH of 4.5 and was calculated as mg HCO_3^-/L. DOC was measured on the basis of wet chemical oxidation, using a Shimadzu TOC-Vwp analyzer. The UV-absorbance at 254 nm was measured using a Varian CARY50 Bio UV-Vis spectrophotometer. The specific UV absorbance (SUVA) was determined by normalizing the UV absorbance at 254 nm to the DOC concentration (Weishaar et al. 2003). The effluent water quality parameters are given in Table 3.3 below. In some of the treatment, 2 samples from the same WWTP were taken at different period (for example in Sjölunda, the samples denoted as 1 and 2).

Table 3.2 - The pharmaceuticals investigated and the treatments employed.

Pharmaceuticals	PAA	ClO_2	O_3	O_3/H_2O_2
Alfuzosin		x		x
Alprazolam		x		x
Amitryptiline		x	x	x
Atracurium		x	x	x
Beclomethasone		x	x	x
Bezafibrate		x		x
Biperiden		x	x	x
Bisoprolol		x	x	x
Budesonide		x		x
Buprenorphine		x		x
Bupropion		x	x	x
Carbamazepine		x	x	x
Cilazapril		x	x	x
Ciprofloxacin		x		x
Citalopram		x	x	x
Clindamycine		x		x
Clofibric acid	x	x		
Clomipramine			x	x
Clonazepam		x		x
Codeine		x	x	x
Cyproheptadine		x		x
Desloratidine		x		x
Diclofenac	x	x	x	x
Dicycloverin		x		x
Diltiazem		x	x	x
Diphenhydramine		x		x
Dipyridamole		x		x
Eprosartan		x	x	x
Estriol		x		x
Estrone		x		x
Ethinyl estradiol		x	x	x
Ezetimibe			x	
Fexofenadine		x	x	x
Finasteride		x		x
Fluconazole		x	x	x
Fluoxetine		x	x	x
Flutamide		x	x	x
Glimepiride			x	
Gemfibrozil	x	x		x
Haloperidol		x	x	x
Hydroxyzine			x	x
Ibuprofen	x	x	x	x
Irbesartan		x	x	x
Ketoprofen		x	x	x
Levonorgestrel			x	x
Loperamide			x	x

Maprotiline		x	x	x
Mefenamic acid	x	x		
Memantine		x	x	x
Metoprolol		x	x	x
Mianserin		x		x
Mirtazapine		x		x
Naloxone		x		x
Naproxen	x	x	x	x
Orphenadrine		x	x	x
Oxazepam			x	x
Paroxetine		x		x
Pizotifen		x		x
Promethazine		x		x
Repaglinide		x	x	x
Risperidone		x	x	x
Rosuvastatin			x	x
Sertraline			x	x
Sotalol		x		x
Sulfamethoxazole		x	x	x
Telmisartan		x		x
Tramadol		x	x	x
Trihexyphenidyl		x		x
Trimethoprim		x	x	x
Venlafaxine		x	x	x
Verapamil			x	
Zolpidem		x		x

Analysis of the oxidants: chlorine dioxide, peracetic acid and ozone

The concentration of ClO_2 in each of the samples was quantified on the basis of its reaction with DPD (N,N-diethyl-p-phenylenediamine) using a spectrophotometer with a built-in calibration line for ClO_2 (**Paper I and Paper II**). PAA was also analysed on the basis of its reaction with DPD at a neutral pH value that prevented its oxidation by H_2O_2 in contrast to the normal use of DPD, which is based on its reaction with the oxidants at low pH. PAA was quantified on the basis of the photometric standard curve for total chlorine (Cl_2), the values obtained being recalculated to the PAA concentrations by multiplying by a factor of 1.07, which is based on the relative masses of the two oxidants (**Paper I**).

The O_3 doses delivered were analyzed by use of the colorimetric method of indigo (λ = 600 nm), using a UV spectrophotometer, preparing bottles of indigo trisulfonate solution in Milli-Q water in parallel with the treatment samples (Bader and Hoigne, 1981; Antoniou and Andersen, 2012) **(Paper III and Paper IV)**.

Table 3.3 - Quality parameters of the effluent wastewaters studied. (TP = total phosphorus; TN = total nitrogen; Alk = alkalinity as HCO_3^-; UVA = UV absorbance at 254nm)

Parameters	pH	COD	TSS	TP	TN	DOC	Alk	NH_4^+-N	UVA	SUVA
		---------- in mg/L----------							m^{-1}	L/mg.m
WWTP										
PAA and ClO_2										
Källby	6.7	31	-	-	-	-	-	-	-	-
Sjölunda 1	7.0	49	-	-	-	-	-	-	-	-
Sjölunda 2	7.0	60	-	-	-	-	-	-	-	-
ClO_2										
Källby	6.8	35	5	0.26	7.5	6.8	-	-	-	-
Sjölunda	7.2	55	8	0.28	8.0	9.9	-	-	-	-
O_3										
Källby 1	6.6	29	-	-	-	7.5	244	1.36	-	-
Källby 2	6.7	51	-	-	-	6.5	154	2.98	-	-
Sjölunda	6.7	90	-	-	-	13.7	256	1.86	-	-
Björnstorp	7.0	30	-	-	-	5.2	185	0.77	-	-
Öresundsv	7.2	36	-	-	-	8.1	229	4.93	-	-
Nykvarnsv	6.8	44	-	-	-	8.4	164	5.98	-	-
O_3 or O_3/H_2O_2										
Öresundsv	7.2	42	-	-	-	9.2	348	0.04	16.4	1.78
Klagshamn	7.6	32	-	-	-	9.0	427	0.29	24.8	1.78
Uppsala	6.6	18	-	-	-	6.9	80	0.02	16.0	2.31
Käppala	6.3	35	-	-	-	12.5	65	3.60	29.5	2.36

Analysis of pharmaceuticals

Prior to pharmaceutical analysis, solid-phase extractions (SPE) of the samples were conducted. For the PAA and ClO_2 tests, the samples were filtered through a glass microfiber filter (GFC, Whatman) and were then acidified to pH 3, using a phosphate acid buffer. An internal standard, Mecoprop, was then added. The SPE columns (Oasis® HLB 3 cc/60 mg, Waters) were conditioned serially by use of 5 ml each of methanol, ethyl acetate and acidified water. The samples were extracted at a rate of 2 ml/min. The SPE columns were dried completely by drawing air through the columns for at least 30 min (**Paper I and Paper II**). For O_3 experiments, the frozen samples were sent directly to a laboratory partner for SPE extraction prior to pharmaceutical analysis.

Two different analytical procedures for pharmaceutical analysis were employed. In **Paper I**, the analytical method used was based on Kosjek et al, 2009. After SPE extraction of the samples, analyses were carried out by gas chromatography-mass spectrometry (GC-MS), using an Agilent 5973N Mass Selective Detector. The

pharmaceuticals were quantified based on standard calibration curves, the retention times, the target and qualifier ions, and the qualifier-to-target ratios determined have to be within 20% range.

In **Paper II, Paper III, and Paper IV** the analytical method employed was one based on Grabic et al. (2012). After SPE extraction, LC/MS/MS (liquid chromatography-tandem mass spectrometry) analysis of the extracts was carried out, using a triple-stage quadrupole MS/MS TSQ Quantum Ultra EMR (Thermo Fisher Scientific, San Jose, CA, USA) coupled with an Accela LC pump (Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) having a Hypersil GOLD aQ^{TM} column (50 mm x 2.1 mm ID x 5 µm particles, Thermo Fisher Scientific, San Jose, CA, USA). Both heated electrospray (HESI) and atmospheric pressure photoionization (APPI) in the positive and the negative ion modes were employed for ionization of the target compounds. The method of analysing the pharmaceuticals employed was also used earlier by Hörsing et al. (2011) and Hey et al. (2012). A detailed description and a full method evaluation of it are presented in Grabic et al. (2012).

4. Removal of pharmaceuticals by chemical oxidation

4.1 Comparison of different chemical oxidants

As presented in Figure 4.1 and in **Paper I, Paper II and Paper III**, the removal of pharmaceuticals in real wastewater effluents can be carried out by employing any of the chemical oxidants, such as peracetic acid, chlorine dioxide or ozone. However, their efficiency was dependent upon the pharmaceutical in question. The selected pharmaceuticals shown in Figure 4.1 are the nonsteroidal anti-inflammatory drugs (NSAID) diclofenac, naproxen and ibuprofen, these are frequently found at high levels in Swedish WWTP effluents (Falås et al., 2012). Figure 4.1 shows the degree of removal of these compounds from the wastewater effluent of Källby WWTP, which has a COD content of around 30 mg/L. In comparing their removal efficiencies, both diclofenac and naproxen were found to show a high degree of removal (>90%) using ClO_2. While at low doses of ClO_2 (between 1 to 4 mg/L), a high degree of diclofenac removal was achieved as compared to O_3 in this effluent. In contrast, ibuprofen did not show any removal using ClO_2 of up to 20 mg/L. A significant improvement in the removal of both naproxen and ibuprofen was observed when they were treated with ozone.

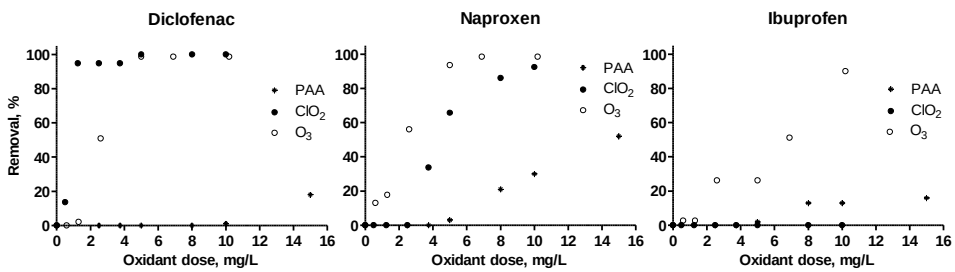

Figure 4.1 - Removal of NSAID pharmaceuticals after treatment with different doses of PAA, ClO_2 and O_3.

Based on these results, it appears that PAA is not an option for removing these pharmaceuticals from the wastewater effluent due to its low reactivity. For some of the pharmaceuticals investigated, however, PAA was found to be an effective oxidant, when high doses are employed (>25 mg/L) (**Paper I**).

Ozone was found in general to be a more efficient oxidant than chlorine dioxide for removing a large number of pharmaceuticals. As shown in Figure 4.2, over 90% of the pharmaceuticals in the effluent that were investigated could be eliminated to up to 90-100% by ozone dose of ~10 mg/L, which is equivalent to 1.3 g O_3/g DOC. The compounds carbamazepine (antiepileptic drug), metoprolol (beta-blocker), irbesartan (angiotensin receptor blocker) and bupropion (antidepressant), which have been shown to be recalcitrant to ClO_2 (**Paper II**), are among those that were eliminated to over 90% by ozone treatment (**Paper III**). With use of ClO_2, about half of the pharmaceuticals investigated could not be removed effectively even when the oxidant dose was increased to 20 mg/L, suggesting there to be only a low degree of reactivity between these compounds and ClO_2 (**Paper II**).

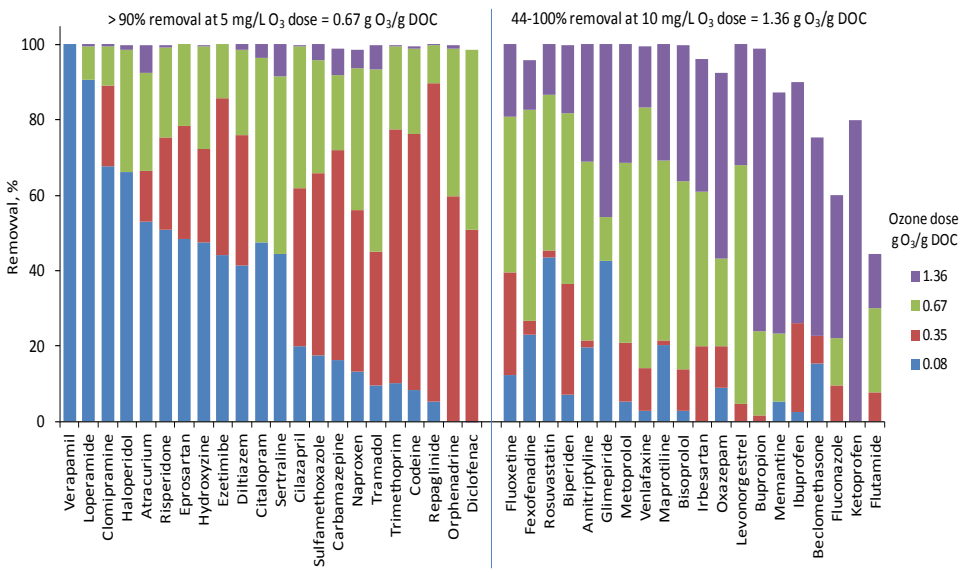

Figure 4.2 - Removal of pharmaceuticals at different ozone doses.

4.2 Removal of pharmaceuticals by ozonation: reactivity of the functional groups

In general, the efficiency of mono- and polyaromatic pharmaceutical removal by chemical oxidation, through ozonation, has been found to be affected by the nature of the compound involved, particularly as concerns the functional groups attached to the aromatic ring. For example, ozone reacts very rapidly with compounds bearing phenolic functions (von Sonntag and von Gunten, 2012). Tertiary amines and C=C functionalities are also known to be ozone-reactive sites (Huber et al., 2005a; Nakada et al., 2007; Hollender et al., 2009). In contrast, for compounds that react slowly with ozone, hydroxyl (OH) radicals can be important for mediating removal mechanisms (von Sonntag and von Gunten, 2012). The outcome of the ozone experiments carried out in the present work (**Paper III**) is considered here in discussing the impact of the chemical structure of the pharmaceuticals involved on the removal efficiencies.

One of the most reactive pharmaceuticals (see Figure 4.2), the calcium channel blocker verapamil (see chemical structure, Figure 4.3), possesses 4 electron-rich methoxy groups on its benzene rings, making it react, very readily with ozone. The tertiary amine function can also be considered as an additional ozone-reactive site. The antidiarrheal drug loperamide was likewise found to react quickly with ozone, this being presumably due to ozone attack on either the amine or the two benzene rings or both. The third benzene ring is deactivated in the presence of the chlorine substituent, in which an ozone attack is unlikely to occur. For carbamazepine, there can also be expected to be a high degree of ozone reactivity, due to its possessing a C=C double bond (Nakada et al., 2007).

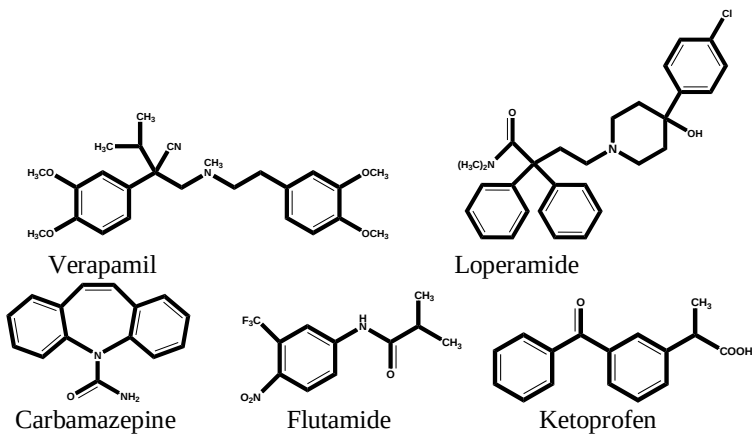

Figure 4.3 – Chemical structures of some of the pharmaceuticals investigated.

Electron-withdrawing groups (EWG) reduce the electron density of pharmaceuticals and affect their reactivity towards ozone negatively (von Sonntag and von Gunten, 2012). For example, the antiandrogen drug flutamide has two EWGs, its trifluoromethyl ($-CF_3$) and its nitro ($-NO_2$) substituents, these contributing to the extremely low ozone reactivity of this compound. The electron-withdrawing carbonyl group of the nonsteroidal anti-inflammatory drug ketoprofen in conjunction with its two benzene rings can be thought to be the basis for the low ozone reactivity found.

On the basis of the results discussed above, the rates of reaction of ozone with the different pharmaceuticals can vary widely, depending upon the nature of the substituents. For less reactive compounds having no electron-donating functional groups, it has been found that efficient elimination can be achieved by reactions involving hydroxyl radicals (von Sonntag ang von Gunten, 2012).

4.3 Effects of the water matrix on the removal of pharmaceuticals by ozonation

Table 4.3 shows the estimated ozone dose necessary to remove to at least 90% some of the most commonly detected pharmaceuticals (together with the therapeutic class to which each of them belongs) in two Swedish WWTP effluents. The pharmaceuticals can be ranked from easily- to poorly-oxidizable based on the ozone dose required. The two effluents involved showed a high degree of variation in terms of DOC and alkalinity content, one with low DOC and low alkalinity levels and one with high DOC and high alkalinity levels. A low COD level reduces the competition for ozone between the pharmaceuticals and the organic components of the water matrix.

Table 4.3 shows clearly that a lesser ozone dose is needed for pharmaceutical removal when the effluent contains relatively low levels of COD and of alkalinity (Effluent 1). As observed in other effluents that were investigated (**Paper III**), however, the alkalinity content did not seem to have any negative effect, as compared with the DOC content, on removal of the pharmaceuticals. This also provides an indication that most of the pharmaceuticals studied were oxidized by ozone directly. In addition, due to the low pH level of the effluents (between pH 6.6 to 7.2), a high degree of production of OH radicals could not be expected; otherwise these could have resulted in the increased removal of ozone-refractory pharmaceuticals. Thus, for ozone-refractory compounds present in these effluents, a much higher ozone dose would be needed for their complete elimination.

Table 4.3 - Estimated ozone dose for 90% removal of pharmaceuticals in the wastewater effluent. (NA = not available)

		O_3 dose, mg/L	
		Effluent 1	Effluent 2
DOC, mg/L		5.2	13.7
Alkalinity, mg/L HCO_3^-		185	256
pH		7.0	6.7
Pharmaceuticals	Class		
Risperidone	antipsychotic	0.9	12.1
Codeine	narcotic analgesic	2.4	9.2
Carbamazepine	antiepileptic	2.2	10.8
Naproxen	NSAID	2.5	10.0
Diclofenac	NSAID	NA	10.0
Tramadol	narcotic analgesic	3.4	13.0
Citalopram	antidepressant	2.0	15.0
Sertraline	antidepressant	1.7	12.0
Metoprolol	β-blocker	3.8	18.2
Fluoxetine	antidepressant	3.1	20.0
Oxazepam	anxiolytic	7.1	18.4
Ketoprofen	NSAID	5.5	23.9
Ibuprofen	NSAID	7.3	27.0

The effects of different pH levels as well as of the addition of H_2O_2 on the ozone lifetime and on the removal of pharmaceuticals were likewise investigated. Two effluents of relatively high pH (pH 8.0) were treated with ozone, whereas two other effluents, of low pH (pH 6.0), were treated with ozone in combination with H_2O_2 (at a H_2O_2/O_3 ratio of 0.10). Treatment was carried out at these pH levels since they correspond to the upper and the lower part of the typical range of pH values found in Swedish WWTP effluents. The effluents also differed in the origin of the potable water and in such chemical characteristics as those of alkalinity, and ammonium ion and organic matter content (**Paper IV**).

As can be expected (Figure 4.4), a rapid decomposition of ozone was observed in both the high pH and the low pH effluents, where small amounts of H_2O_2 were added, indicating an enhanced production of OH radicals to occur. On the other hand, as shown for the two effluents at different pH (Figure 4.5), the degree of removal of pharmaceuticals was higher in the effluent at pH 6.0 (without H_2O_2) than in the one at pH 8.0, especially at low ozone doses. This can be explained on the basis of the low degree of DOC content of the low pH effluent, which results in there being less competition for ozone between the water matrix and pharmaceuticals. In addition, the pH 8.0 effluent has a relatively high level of alkalinity which could increase the scavenging of the OH radicals available for pharmaceutical oxidation. In comparing those effluents (at pH 8.0), the DOC levels of which were about the same, the effect of the specific UV absorbance (SUVA) on the pharmaceutical removal efficiency was found to be significant

(**Paper IV**). The effluent, for which SUVA content is higher, showed to have poor removal of pharmaceuticals even when the O_3 dose was increased (**Paper IV**).

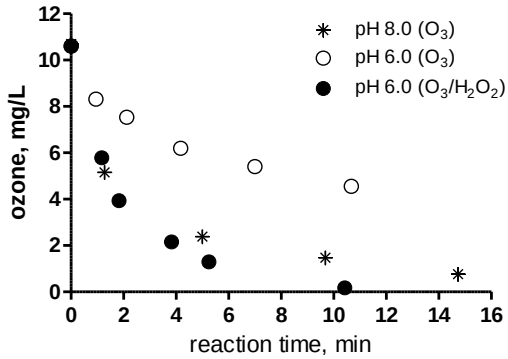

Figure 4.4 – Ozone consumption in WWTP effluents at pH 8.0 (O_3 only) and at pH 6.0 (O_3 and O_3/H_2O_2); pH 8.0 effluent: DOC 9.2 mg/L, SUVA 1.8 L/mg·m; pH 6.0 effluent: DOC 6.9 mg/L, SUVA 2.3 L/mg·m.

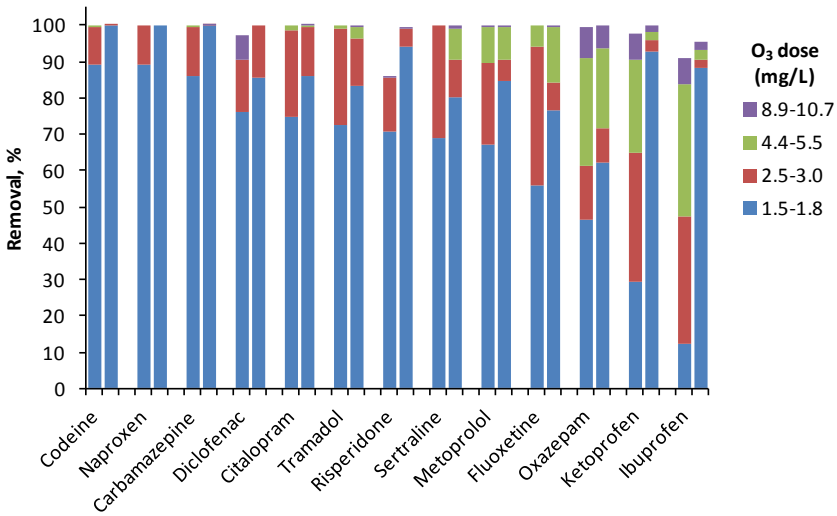

Figure 4.5 – Comparison of the pharmaceutical removal efficiency of pH 6.0 (right bar) and pH 8.0 (left bar) effluents in response to different levels of ozone dosage (for the pH 6.0 effluent: DOC 6.9 mg/L; for the pH 8.0 effluent: DOC 9.2 mg/L).

The addition of small amounts of H_2O_2 did not have any significant effect on the removal of pharmaceuticals, especially those less reactive to ozone. For certain of the pharmaceuticals- levonorgestrel, sulfamethoxazole and ketoprofen- only a slight increase in removal (<20%) was observed under such conditions (**Paper IV**).

5. Discussions

Of the 3 oxidants investigated, PAA appears to have the lowest efficiency to remove pharmaceuticals, making it not a suitable treatment option (**Paper I**). On the other hand, the oxidation of pharmaceuticals by chlorine dioxide was found to be comparable to the oxidation by molecular ozone, since both of these are selective oxidants, their capability of transforming pharmaceuticals depending upon their reactivity and the characteristics of the effluent (**Paper II and Paper III**). However, even for pharmaceuticals of the same functional group, the reaction between ClO_2 and certain of the pharmaceuticals was much slower than their reaction with ozone. Thus, it appears that ozone is the most efficient chemical oxidant of those that were investigated, its being shown to be capable of removing a large fraction of the pharmaceuticals present in most of the wastewater effluents, doing so at fairly low ozone doses (of 5-10 mg/L), and the size of the fraction removed depending upon the quality of the effluent. In employing ozonation, it is important to investigate the initial ozone demand of the wastewater in question, due to matrix effects (**Paper III and Paper IV**).

Although the addition of H_2O_2 (at a H_2O_2/O_3 ratio of 0.08-0.13) to an initial ozone dose of 10 mg/L cannot be expected to have any appreciable impact on pharmaceutical removal, the overall findings suggest that the reaction time can be reduced through combining ozone, at low pH, with small amounts of H_2O_2, which would clearly be advantageous when the technology is implemented in practice. This allows the size of the reaction tank employed for treatment to be reduced (**Paper IV**).

When chlorine dioxide is employed for tertiary treatment, there can be doubts about its use, due to the inherent toxicity of produced by-products such as chlorite. This can be controlled by minimizing the dose of ClO_2 or by employing a post-treatment step such as using ferrous iron (Fe^{2+}) or sulfite (SO_3^{2-}) (Griese et al., 1991; Katz and Narkis, 2001) **(Paper II)**. This method can reduce the ClO_2 and chlorite residuals to chloride, allowing higher levels of ClO_2 to be used for treatment and providing for more effective pharmaceutical removal. The use of ClO_2 in WWTP effluents also depends upon whether the target pharmaceuticals are sensitive to ClO_2. In addition, running costs need to be taken account of, since ClO_2 is slightly more expensive to produce than ozone, whereas it is much simpler and less expensive to build both the preparation system and the reaction chamber for ClO_2 than those for ozone. Thus, it would appear best for treatment purposes to

make use of ClO_2 mainly in small-scale WWTPs (<2,000 person equivalent) or when treatment is required for only a limited period of time **(Paper II)**.

Treatment with ozone requires more energy, such as the energy needed for ozone production, for a destruction unit and for on-site oxygen generation, the installation costs and maintenance costs required also being higher (Hollender et al., 2009). The energy costs can be seen as roughly proportional to the ozone demand of the wastewater and of the contaminant which is to be removed. In fact, according to Hollender et al. (2009), the total energy consumption of a secondary-treated wastewater (~5mg/L DOC) subjected to ozone can be estimated to be around 0.04 kWh/m^3 wastewater, equivalent to 12% of the energy required to operate a typical nutrient removal plant. Yet given the high degree of reactivity of ozone to a wide range of pharmaceuticals, the ozonation of a secondary effluent can be seen as probably being the most suitable alternative for most WWTPs while at the same time improving the microbiological quality of the effluent.

During chemical oxidation, the pharmaceuticals are not expected to be fully mineralized, but partly degraded and therefore transformed into so called transformation products. These products may have lower or higher toxicity than the parent compound. As they are expected to be more easily degraded biologically, an additional treatment step such as a polishing step in a biologically active sand filter could be a good option.

6. Conclusions

The following conclusions can be drawn on the basis of the results of the present study:

Of the chemical oxidants investigated, PAA appears to have the lowest potential for pharmaceutical efficient removal, making it not a suitable treatment option for removing pharmaceuticals in the effluents.

The oxidation of pharmaceuticals by chlorine dioxide was found to be comparable to the oxidation by molecular ozone, since both are selective oxidants, their capability of transforming pharmaceuticals depending upon their reactivity and the characteristics of the effluent.

Ozone was found to be the most efficient chemical oxidant for removing most pharmaceuticals commonly found in Swedish wastewater effluents.

Ozone decomposition to OH radicals can be stimulated by the addition of small amounts of hydrogen peroxide at low pH. This reduces the treatment time and, accordingly, the reaction volume needed. Since the addition of hydrogen peroxide has only a limited impact on the removal of pharmaceuticals, it has no appreciable negative effects in terms of reducing the reactor volume needed.

Of the various water quality parameters, the organic carbon content was found to have a particularly strong influence on the removal of pharmaceuticals, due to its competitive behavior towards the oxidant.

The decision of whether to use either chlorine dioxide or ozone can be considered as depending upon the sensitivity of the target compounds to be removed. Chlorine dioxide treatment can be particularly appropriate for small-scale wastewater treatment plants or in cases in which treatment is needed for only a short period of time.

The energy costs associated with ozone treatment are dependent upon the ozone demand of the wastewater (matrix effects) and on the contaminants to be removed. The high level of reactivity of ozone to a wide range of the pharmaceuticals that were investigated suggests that the ozonation of secondary effluents is the most suitable alternative for WWTPs.

7. Suggestions for further work

It would be of interest in future investigations to assess the applicability of ozone to full-scale tertiary treatment for the removal of pharmaceuticals from wastewaters, with the aim of better understanding the impact of ozone oxidation on the quality of the effluent, so as to ensure in so far as possible, the safety of the water that has been treated prior to its discharge. The addition of a polishing step, such as one involving biological filtration, can be employed to reduce the possible toxicity caused by oxidation by-products.

It would be of interest to develop a simple approach to performing a toxicity assay of the treatment as a whole, since it is almost impossible to identify either the types of toxic transformation products that have occurred or oxidation by-products that have been created when the wastewater contains a large number of different micropollutants.

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Paper I

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Removal of pharmaceuticals in biologically treated wastewater by chlorine dioxide or peracetic acid

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Removal of six active pharmaceutical ingredients in wastewater was investigated using chlorine dioxide (ClO_2) or peracetic acid (PAA) as chemical oxidants. Four non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, diclofenac and mefenamic acid) and two lipid-regulating agents (gemfibrozil and clofibric acid, a metabolite of clofibrate) were used as target substances at 40 μg/L initial concentration. Three different wastewaters types originating from two wastewater treatment plants (WWTPs) were used. One wastewater was collected after extended nitrogen removal in activated sludge, one after treatment with high-loaded activated sludge without nitrification, and one from the final effluent from the same plant where nitrogen removal was made in trickling filters for nitrification and moving-bed biofilm reactors for denitrification following the high-loaded plant. Of the six investigated compounds, only clofibric acid and ibuprofen were not removed when treated with ClO_2 up to 20 mg/L. With increasing PAA dose up to 50 mg/L, significant removal of most of the pharmaceuticals was observed except for the wastewater with the highest chemical oxygen demand (COD). This indicates that chemical oxidation with ClO_2 could be used for tertiary treatment at WWTPs for active pharmaceutical ingredients, whereas PAA was not sufficiently efficient.

Keywords: pharmaceuticals; chlorine dioxide; peracetic acid; wastewater effluent

Introduction

The presence of active pharmaceutical ingredients (APIs) in effluents from wastewater treatment plants (WWTPs) has raised awareness as a result of the increasing usage of human pharmaceuticals and improved analytical ability to detect their occurrence in the effluents of WWTPs and receiving surface waters [1–3]. Insufficient treatment may lead to surface and groundwater contamination, compromising the health of the aquatic ecosystems and the surrounding environment [4, 5].

In cases where APIs are not sufficiently degraded by biological processes during wastewater treatment, either because of a high persistence to biodegradation or limited biological activity during treatment, as can be found in cold areas, e.g. northern Scandinavia, improvement at the WWTPs by addition of further treatment technology such as chemical oxidation is a probable solution [6–8]. Oxidation techniques have proven effective to quantitatively remove potential pollutants in wastewater that cannot be degraded biologically. An added benefit of oxidative treatment is the disinfection effect [9, 10].

Currently, chemical oxidation is widely employed in the treatment of drinking water and wastewater, for disinfection and oxidation, involving the use of oxidants such as ozone (O_3), chlorine, chlorine dioxide (ClO_2) and peracetic acid (PAA). Among these four oxidants, ozone has been considered to be the most promising oxidation method for removal of micropollutants [2,8,11]. Unlike ozonation, ClO_2 as well as PAA, has not been extensively studied for the removal of pharmaceuticals in wastewater effluents. So far, a study on drinking and surface water using chlorine dioxide showed promising results for removal of pharmaceuticals, where for example diclofenac was completely degraded even at the lowest ClO_2 dose [12]. Navalon *et al.* [13] also demonstrated the reactivity of ClO_2 to remove several antibiotics in artificial raw water. Andersen *et al.* [14, 15] found that estrogens and xenoestrogens could be removed quickly and with a high selectivity from wastewater effluents by very small doses of ClO_2 in the order of 2–4 mg/L, which was consumed by the wastewater constituents in less than 30 seconds, leaving no ClO_2 residues. This is interpreted as being due to very fast oxidation of the phenolic groups, which nearly all estrogens contain, compared with slower reactions with the general matrix in wastewater effluents.

Although PAA has not been applied in wastewater treatment to remove pharmaceuticals, it is believed to have a strong oxidizing power, with an oxidation potential ranking next to ozone [16], and it is used for disinfection of

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wastewater [17]. Thus, aside from its disinfection effect, PAA has the potential to be an alternative technique to treat pharmaceuticals in wastewater.

When used for treatment, ClO_2 is mainly reduced to chlorite by reaction with organic matter. Chlorite reacts more slowly with organic matter, to be reduced to chloride. Chlorite residuals can potentially be problematic for the treatment depending on the concentration and degradation rate. Chlorine dioxide differs from chlorine in that it produces very little chloro-organic by-products [9,12,14]. Peracetic acid reacts in water mainly to become acetic acid, and oxygen or hydrogen peroxide, which are all quickly degraded by bacteria in treated wastewater [16,17].

This study aims to investigate the effectiveness of ClO_2 and PAA on the removal of six anionic, active pharmaceutical ingredients (APIs) in biologically treated wastewater. The APIs were the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen, diclofenac and mefenamic acid, and the lipid-regulating agents gemfibrozil and clofibric acid (the pharmaceutically active form of the drug clofibrate). The oxidants' consumption of the wastewater effluent was also followed as well as the oxidant remaining after treatment of the APIs. Results were compared with those of ozonation based on previous studies on wastewater, drinking and surface water.

Materials and methods

Chemicals

All chemicals except ClO_2 were analytical grade and purchased from Sigma-Aldrich. Chlorine dioxide was synthesized by mixing 400 mL of demineralized water with 25 mL each of 9% HCl and 7.5% $NaClO_2$. The reaction mixture was allowed to react overnight and was then diluted to 1000 mL with demineralized water. This resulted in an approximately 1 g/L ClO_2 solution.

Oxidation experiments

Wastewater effluents were collected from two treatment plants in Sweden, namely Källby and Sjölunda WWTPs. Effluent 1 was from Källby WWTP, operating with extended nitrogen removal in activated sludge. Effluent 2 was from Sjölunda WWTP, also operating full nitrogen removal but carried out in biofilm systems after a high-loaded activated sludge treatment plant. Nitrification is carried out in trickling filters, and denitrification in moving-bed biofilm reactors with addition of external carbon. Effluent 3 was also taken from Sjölunda WWTP after the high-loaded activated sludge plant. This wastewater is typical for many Swedish WWTPs operating without nitrogen removal owing to their location in the northern part of the country.

To characterize the wastewater, the pH and chemical oxygen demand (COD), measured spectrophotometrically by standardized Dr. Lange DR 2800 COD LCK 114 cuvette test, of the effluents were determined. Based on its respective COD value, the wastewater effluent was classified as low (effluent 1), medium (effluent 2) or high (effluent 3) COD.

An experiment was made to determine how fast PAA and ClO_2 react with a wastewater sample. An effluent from Källby WWTP with extended nitrogen removal was used.

For experiments with removal of APIs, an effluent sample of 300 mL was prepared in Schott Duran® bottles, spiked with each API to a final concentration of 40 μg/L and covered with aluminium foil. Each dose of the oxidants was added to duplicate samples in the range 0–20 mg/L and 0–50 mg/L for ClO_2 and PAA, respectively. Samples were stored in the dark without stirring and allowed to react overnight (18 h); thereafter the pH and oxidant concentration of the samples were measured. Residual oxidants were removed by addition of 50 mg/L Na_2SO_3.

Chlorine dioxide and peracetic acid analysis

The concentration of ClO_2 or PAA residuals in all samples was quantified by reaction with DPD (N,N-diethyl-p-phenylenediamine) using an Allcon spectrophotometer (Alldos, GmbH) with a built-in calibration line for ClO_2. The analysis of ClO_2 with DPD was performed according to the photometer manufacturer's instructions.

Peracetic acid was quantified by the photometer's standard curve for total chlorine (Cl_2), which was recalculated to PAA concentration by multiplying by a factor of 1.07, which is based on the relative masses of the two oxidants. Peracetic acid was analysed by reaction with DPD at neutral pH, which prevented oxidation by H_2O_2 contrary to the normal use of DPD, which is based on reaction with the oxidants at low pH. This was necessary since PAA is delivered as a mixture with the synthesis precursors H_2O_2 and acetic acid. The selectivity of the reaction was tested by measuring a sample spiked with 50 mg/L H_2O_2 only. The quantification of PAA was shown not to be biased by the presence of H_2O_2 in water, as a wastewater sample to which was added 50 mg/L H_2O_2 measured less than 0.05 mg/L PAA.

API analysis

The analytical procedure was based on Kosjek *et al*. [18]. Samples of 250 mL were filtered with a glass microfibre filter (GFC, Whatman) and then acidified to pH 3 using phosphate acid buffer. An internal standard (IS), mecoprop (40 μg/L), was added before solid-phase extraction (SPE). The SPE columns (Oasis® HLB 3 cc/60 mg, Waters) were conditioned serially with 5 mL each of methanol, ethyl acetate and acidified water. Samples were extracted at a maximum flow rate of 2 mL/min. The SPE columns were dried completely by drawing air through the columns for at least 30 min.

Samples were eluted with 1.5 mL of ethyl acetate and evaporated in a thermal heating block at 35°C with a

Table 1. Retention times, target ion, qualifier ion(s) and ratio of qualifier ion(s)/target ion of the APIs and the IS, and the LOD determined in a typical biologically treated wastewater.

API	Retention time(min)	Target ion	Qualifier ion(s)	Ratio (%)	LOD (μg/L)
Ibuprofen	7.02	143	271, 273	43, 16	0.8
Clofibric acid	7.40	263	117	10	0.8
Mecoprop (IS)	7.55	225	199	45	NA
Naproxen	11.55	287	185, 141	31, 13	1.0
Gemfibrozil	11.95	243	307	24	0.8
Diclofenac	13.55	214	352, 354	120, 86	1.1
Mefenamic acid	14.35	224	298	86	0.8

gentle stream of nitrogen until approximately 250 μL was left. Samples were transferred to GC vials and 25 μL of the derivatization reagent, N-(t-butyldimethylsilyl)-N-methyltrifluoroacetamide (MTBSTFA), was added. The vials were allowed to react for 60 min at 60°C. Analyses of the samples were done with gas chromatography–mass spectrometry (GC-MS, Agilent 5973N Mass Selective Detector). The capillary column was an Agilent HP 5-MS (30.0 m × 250 μm × 0.25 μm) with a 1 μL injection volume in splitless mode. The GC oven temperature programme was as follows: 100°C for 1 min, 30°C/min up to 190°C, 3°C/min up to 204°C, 30°C/min up to 245°C, 5°C/min up to 265°C, and finally 30°C/min up to 300°C for 1 min. The APIs were quantified based on standard calibration curves with the retention times, the target and qualifier ions, and the determined qualifier-to-target ratios, which have to be within 20%. The limit of detection (LOD) of the method was between 0.8 and 1.1 μg/L, as determined in a representative WWTP (Table 1). The method had a linear response between the LOD and at least 50 μg/L.

Statistics

GraphPad Prism [19] was used for both graphical and statistical analyses.

Results and discussion

Effluent 1 with extended nitrogen removal has the lowest COD at 31 mg/L, followed by effluent 2 at 49 mg/L, and effluent 3 without nitrogen removal with COD at 60 mg/L. From the COD values, the effluents were classified as low, medium and high in COD, respectively. The initial pH of effluent 1 was 6.7 and effluent 2 and 3 had a pH at 7.0. The pH did not change a lot in any of the effluents after treatment even for the highest oxidant dose where pH remained slightly acidic (~pH 6). The decrease in pH is expected since the stock solutions of ClO_2 contain some HCl residual from their synthesis, and likewise the PAA stock solution contains acetic acid.

The profiles of consumption of the two oxidants in a biologically treated wastewater effluent (Figure 1) revealed

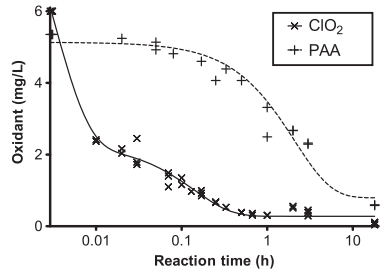

Figure 1. Profiles of oxidant consumption with time in a biologically treated wastewater. The fitted lines represent a one-phase exponential decay model for PAA and a two-phase exponential decay model for ClO_2.

that ClO_2 reacts faster than PAA in wastewater effluents. About 90% of 6 mg/L ClO_2 had disappeared 30 min after addition, whereas the same removal was reached after 18 h reaction for PAA. The profile of ClO_2 decay resembled profiles shown in other investigations on biologically treated wastewater [8,14,15]. The profile of ClO_2 decay fitted ($R^2 = 0.996$) a two-phase exponential decay model, which could be explained by ClO_2 reacting fast with a minor part of the dissolved material in the effluent, which consumes about 3.5 mg/L ClO_2 within 0.5 min. After this reactive fraction of the solutes in the water is consumed, a slow reaction with the bulk of the solutes follows. Compared with this, the PAA profile fitted ($R^2 = 0.952$) a one-phase exponential decay model, which indicates that PAA reacts equally well, but more slowly, than ClO_2, with all the solutes. The PAA degrades relatively slowly in treated wastewater, which makes it less attractive for treatment of effluents, unless the residual is removed with a chemical before it is released to surface water. Both oxidants are essentially stable (>95% remain) in distilled water at the same pH and time range (18 h; results not shown). These results show that the oxidant consumption of the wastewater alone was significant compared with that needed to oxidize the APIs in the batch experiments.

The residual concentrations of ClO_2 and PAA in the three effluents spiked with APIs and increasing oxidant doses are shown in Figure 2. Chlorine dioxide was almost completely consumed in all samples with added ClO_2 dose up to 10 mg/L. However, when the dose was doubled, the oxidant remaining in effluent 1 (low COD) was much higher than in the two other effluents. Spiked with the same amount of pharmaceuticals, the difference in ClO_2 removal could be attributed to the differences in the COD. Effluents 2 (medium COD) and 3 (high COD) contained more COD than effluent 1; therefore more oxidant was needed to remove a fraction of the COD. As shown in this test, oxidant consumption was mostly due to the presence of organic components in the wastewater rather

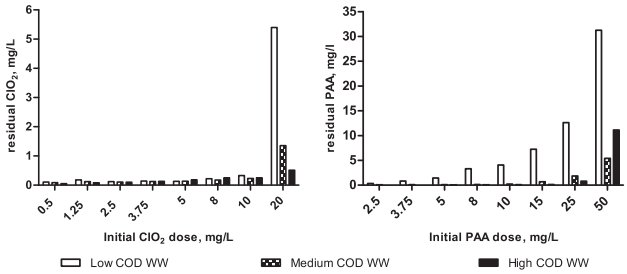

Figure 2. Residual concentrations of ClO_2 (left) and PAA (right) in the three effluents after treatment with different initial doses of ClO_2 or PAA.

than the pharmaceuticals. Peracetic acid oxidation followed the same trend as ClO_2 except that effluent 1 had much lower consumption of PAA in all treatment doses, which is consistent with the fact that effluent 1 has the lowest COD.

Residual concentrations of pharmaceuticals in all effluents treated with ClO_2 are shown in Figure 3. Clofibric acid and ibuprofen appeared to be recalcitrant to oxidation in wastewater and did not react with ClO_2 even at the 20 mg/L treatment dose. Gemfibrozil was removed only when treated with 20 mg/L ClO_2 in the low COD effluent 1, whereas higher removal was observed in effluents 2 and 3 at much lower ClO_2 dose. On the other hand, more than 60% of mefenamic acid was removed with just 0.5 mg/L ClO_2, and, by treatment with a dose of 1.25 mg/L, 90–95% of mefenamic acid was removed from all effluents. More than 90% diclofenac and naproxen were removed in all effluents with 2.5 and 20 mg/L ClO_2, respectively, whereas, in the medium COD effluent, diclofenac was completely removed with 3.75 mg/L ClO_2. A similar study on drinking water by Huber *et al.* [3] showed complete oxidation of diclofenac and 50% naproxen removal at 0.95 mg/L ClO_2; ibuprofen and clofibric acid did not show reactivity up to 11.5 mg/L ClO_2, whereas gemfibrozil showed 40% removal [3]. As presented in these studies, oxidation of

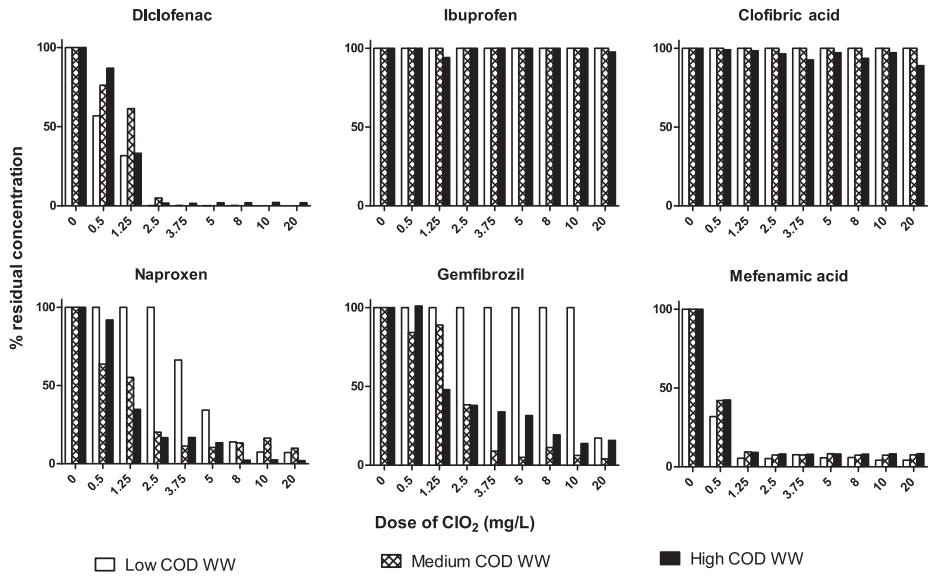

Figure 3. Percentage residual concentrations of APIs in the effluents after treatment with different initial ClO_2 doses.

pharmaceuticals in drinking water normally consumes less ClO_2 than in wastewater, which could be attributed to the presence of higher concentrations of organic compounds with high ClO_2 demand in the wastewater.

Comparing this to the ozonation process, Ternes *et al.* [6] reported that, during ozone treatment of municipal sewage treatment plant effluent, diclofenac and naproxen were completely removed with 5 mg/L O_3, while increasing the O_3 dose to 10 and 15 mg/L effectively removed ibuprofen and clofibric acid. In the study by Huber *et al.* [3], diclofenac and naproxen were also oxidized to more than 90% during ozonation of municipal wastewater effluents at O_3 dose $\geq$ 2 mg/L. On the other hand, ibuprofen residual of 20% was still detectable at higher O_3 dose [3]. Furthermore, ozonation of surface water with 0.2 mg/L O_3 was sufficient to completely oxidize diclofenac, whereas a much higher dose of 2 mg/L O_3 was needed to remove 40–60% of ibuprofen [11]. In contrast to wastewater, surface water typically contains lower concentrations of organic matter; therefore a much lower O_3 dose was needed to oxidize the same type of compound. In addition, the presence of other inorganic components in the wastewater may also deplete the oxidant, and this affects the removal of the target compounds [8]. Thus, for wastewaters with a high load of organic or inorganic matter, a rather high dose of oxidants is required to significantly remove the pollutant of concern.

The oxidation reaction mechanism for ClO_2 appears to be similar to the oxidation by molecular ozone. Diclofenac and naproxen, which were removed by the lowest doses of ClO_2, were also removed by the lowest ozone doses, whereas ibuprofen and clofibric acid, which were not effectively removed by ClO_2, required higher ozone doses. Both ozone and ClO_2 are selective oxidants that transform organic pollutants depending on their reactivity and the presence of other components in the water (i.e. the dissolved organic matter). They react with electron-rich functional groups of organic compounds such as phenolic and amino groups (i.e. aniline group for diclofenac) [3,8,20,21]. However, compared with ozonation, the reaction of ClO_2 was much slower even with the same reactive functional group, as shown previously in a number of studies.

These studies demonstrated the potential of ozonation for removing certain pharmaceuticals, such as ibuprofen and clofibric acid, that exhibit no reactivity to ClO_2 as shown in the present study. In addition to its higher oxidative capacity, ozone can react with water to create the unselective reacting hydroxyl radical, which can compete in removing the APIs, which ozone itself does not react quickly [6,11]. However, for small WWTPs where an ozonation system could be too expensive and complicated to implement, the more simple dosing of ClO_2 can be an alternative option to remove some of the most potentially problematic pharmaceuticals present in the wastewater effluents.

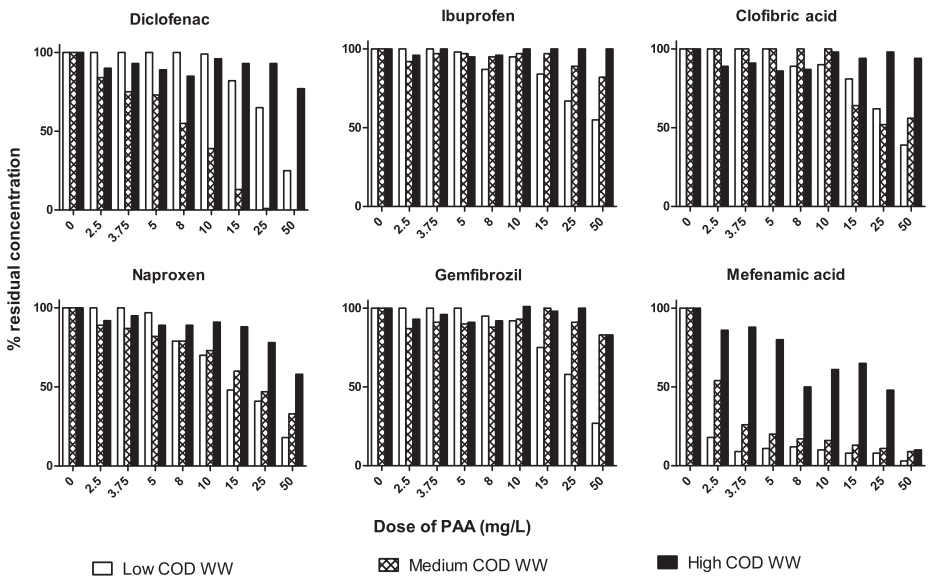

Figure 4. Percentage residual concentrations of APIs in the effluents after treatment with different initial PAA doses.

In the case of PAA, Figure 4 shows that mefenamic acid was most reactive at lower PAA dose in both low and medium COD effluents, as compared with the rest of the APIs, which were gradually removed with increasing PAA dose. Diclofenac was more reactive in effluent 2 at higher oxidant dose, with more than 90% removal for 25 mg/L PAA, compared with only 75% when treated with 50 mg/L PAA in effluent 1. On the other hand, in effluent 3 with high COD, no significant degradation was observed in most of the APIs investigated, even at the highest oxidant dose, except mefenamic acid, which was removed by 90% at 50 mg/L PAA. The results of this study indicated that ibuprofen and clofibric acid are more recalcitrant to both ClO_2 and PAA oxidation compared with the other four compounds investigated. Higher doses of PAA allow removal of APIs such as diclofenac and mefenamic acid in lower COD effluents. Nevertheless, PAA showed its potential to remove some compounds in wastewater that may pose a threat to the environment, especially the aquatic ecosystem. To our knowledge, no literature references exist regarding the reaction of pharmaceuticals with PAA in wastewater.

In comparison to PAA, ClO_2 is more effective at low doses in removing pharmaceuticals, especially naproxen and diclofenac, which have low biodegradability and are of ecotoxicological concern; for instance diclofenac, tagged as among the most devastating environmental toxicants, caused the poisoning and decline of Indian vultures [22,23]. Other APIs such as ibuprofen are not so easily removed by oxidation, but they can be degraded biologically [24]. Therefore it appears that PAA is not a candidate oxidant for treatment of APIs in biologically treated sewage effluents, though it remains an interesting disinfectant chemical for both sewage effluents and combined sewer overflows [17].

Conclusions

This study showed that ClO_2 is more effective than PAA at removing pharmaceuticals in wastewater. However, removal of APIs varies between the two oxidants and the matrix of the wastewater. Some of the pharmaceuticals react selectively with ClO_2 and are therefore removed even with a low dose, almost independently of the matrix, whereas others do not react. Peracetic acid generally reacts more uniformly with the APIs from effluent 1 containing low COD but requires high doses to achieve significant removal. The exception was mefenamic acid, which was degraded by low doses of PAA. Owing to its high selectivity, ClO_2 can be applied, as an alternative to ozone, during wastewater treatment to remove pharmaceuticals of ecotoxicological concern, such as diclofenac, as long as the residual ClO_2 is minimized and does not exceed the standard; this requires a minimal reaction time before contact with the receiving waters. Oxidation with ClO_2 could be a potential solution for removal of pharmaceutical at smaller treatment plants where ozonation may be too expensive and complicated to operate. Furthermore, evaluation of the ecological toxicity of the oxidation products and the treatment by-products should be carried out, and the economic aspect of the treatment operation should be investigated.

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Paper II

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Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater

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ABSTRACT

Biologically treated wastewater spiked with a mixture of 56 active pharmaceutical ingredients (APIs) was treated with 0–20 mg/L chlorine dioxide (ClO_2) solution in laboratory-scale experiments. Wastewater effluents were collected from two wastewater treatment plants in Sweden, one with extended nitrogen removal (low COD) and one without (high COD). About one third of the tested APIs resisted degradation even at the highest ClO_2 dose (20 mg/L), while others were reduced by more than 90% at the lowest ClO_2 level (0.5 mg/L). In the low COD effluent, more than half of the APIs were oxidized at 5 mg/L ClO_2, while in high COD effluent a significant increase in API oxidation was observed after treatment with 8 mg/L ClO_2. This study illustrates the successful degradation of several APIs during treatment of wastewater effluents with chlorine dioxide.

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1. Introduction

One of the pressing problems in wastewater treatment plants (WWTPs) is the inability of conventional methods to completely remove active pharmaceutical ingredients (APIs) due to their high resistance to biodegradation and/or limited biological activity, especially in cold climates such as that in Sweden [1,2]. The extensive usage and hence release of traces of many pharmaceuticals in wastewater effluents may lead to surface and groundwater contamination compromising the aquatic ecosystem and the environment [3,4].

Where biological treatment is not sufficient, improvement in WWTPs can be achieved by an additional chemical oxidation step to remove potential pollutants that cannot be degraded biologically [5–8]. Among the chemical oxidants applied in water treatment reported in the literature, chlorine dioxide is one that merits further investigation regarding its potential to remove APIs in wastewater. As in the case of ozonation, the application of chlorine dioxide to treat drinking water, surface water and wastewater effluents has shown promising results for the removal of pharmaceuticals. The non-steroidal anti-inflammatory drug diclofenac, reported as one of the most frequently detected compounds in water at concentrations up to the μg/L level [9], is among the pharmaceuticals completely degraded during drinking and surface water treatment at the lowest ClO_2 dose applied [10]. In wastewater effluents, steroid estrogens and industrial estrogenic chemicals, as well as personal care products, were removed by low doses of ClO_2 between 1.25 and 3.75 mg/L, and the removal of estrogenic potency was observed at the same time [11]. The removal of several antibiotics found in water has also demonstrated the ability of ClO_2 as an oxidant [12,13].

When ClO_2 was used for selective oxidation of organic micropollutants in other investigations on biologically treated wastewater, it was found that smaller doses, e.g. up to 4 mg/L (depending on the concentrations tested and the matrix) were consumed in less than a minute through reactions with the soluble components in the water, while still completely removing many of the reactive micropollutants. This fast consumption of the oxidant in wastewater has been observed in previous studies by Andersen [11], Hey et al. [14], Lee and von Gunten [6] and Andersen et al. [15]. Based on ClO_2 reactivity in wastewater effluents, it has been suggested that ClO_2 could be used as an alternative to ozone for the removal of micropollutants. It is easy to introduce a ClO_2 dosing step in a WWTP since ClO_2 is produced as a solution in water by mixing aqueous solutions of the reactants in a simple reactor; furthermore, the ClO_2 stock solution is semi-storable. This is much simpler than treatment with ozone, which requires on-site delivery of dry oxygen and considerable electric power to run an expensive and complicated ozone generator which produces an ozone gas mixture with less than 20% ozone yield. Following the generation of ozone, the gas must be transferred to the water using a gas contact reactor, usually with 5–20 min hydraulic retention time [5,7,16].

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When ClO_2 is used for oxidation of water with low NOM (natural organic matter), most of the ClO_2 is reduced to chlorite by reactions with the organic matter. Chlorate is also formed as a by-product, but at a much lower concentration than chlorite [17–19]. According to Korn [18] and Lee [19], the formation of chlorite and chlorate accounts for about 70% and 10%, respectively, of the chlorine dioxide applied. In drinking water with low NOM, chlorite reacts slowly with organic matter and is reduced to chloride, while in wastewater, significantly more NOM is available to reduce the chlorite. Toxicity derived from chlorite residuals after treatment may be problematic depending on the concentration and degradation rate [20]. ClO_2 differs from chlorine in that it produces very little chloro-organic by-products [11,15,21]. The formation of undesirable by-products can be controlled by minimizing the dose of ClO_2 and applying post-treatment using, for example, ferrous iron (Fe^{2+}) or sulfite ($SO_3{}^{2-}$), which reduces ClO_2 and chlorite residuals to chloride [22,23]. The removal of ClO_2 and chlorite residuals allows higher levels of ClO_2 to be used for treatment providing effective micropollutant removal.

In this study, the removal of 56 different APIs in biologically treated wastewater was investigated in both low- and high-COD effluents using different doses of chlorine dioxide. The APIs were chosen to represent different classes of pharmaceuticals commonly sold and used in Sweden, which will most likely end up in WWTP effluents due to their low sorption to sludge [24]. The effectiveness of the treatment was evaluated by monitoring the oxidant consumption and the amount of APIs oxidized. Oxidation by-products were not evaluated in this study as the aim was to determine the most suitable oxidant dose and identify which APIs can be removed. Once the relevant dose has been determined, attention can be turned toward investigating the ClO_2 by-products.

2. Materials and methods

2.1. Chemicals

All pharmaceutical reference standards were purchased as solids of analytical grade (>98%) from different suppliers. All APIs investigated are listed in Supplementary Information Table S1. Methanol and acetonitrile were of LC/MS grade (Merck, Darmstadt, Germany). Ultrapure water was prepared from deionized water using a Milli-Q Gradient system (Millipore, Billerica, MA), equipped with a UV radiation source. A stock solution of APIs was prepared in methanol at concentration of about 100 mg/L. Solutions for spiking and analysis were prepared by precise dilution of the stock solution. Chlorine dioxide was synthesized by adding equal volumes (25 mL each) of 9% HCl (Merck, Darmstadt, Germany) and 7.5% $NaClO_2$ (Sigma–Aldrich, Steinheim, Germany) to 400 mL deionized water. The solution was allowed to react in the dark for at least 10 h and then diluted to 1000 mL with water. This resulted in an approximately 1 g/L ClO_2 stock solution.

2.2. Analytical methods

The concentration of residual ClO_2 was quantified by reaction with DPD (N,N-diethyl-p-phenylenediamine) using an Allcon spectrophotometer (Alldos, GmbH, Germany) with a built-in calibration line for ClO_2. The analysis of ClO_2 with DPD was performed according to the manufacturer's instructions.

For the analysis of the APIs, samples of 100 mL treated effluent were filtered using a 0.45 μm membrane filter (Millipore, Ireland) then acidified to pH 3 using sulfuric acid. Five ng of ^{13}C- and ^{2}H-labeled APIs was added as internal standards, to each sample (see Supplementary Table 1 for the complete list) before solid-phase extraction using Oasis HLB columns (200 mg, Waters). LC/MS/MS analysis of the extracts was carried out using a triple-stage quadrupole mass spectrometer (MS/MS TSQ Quantum Ultra EMR) coupled to an Accela LC pump (both from Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) with a Hypersil GOLD aQ™ column (50 mm × 2.1 mm ID × 5 μm particles). Both heated electrospray and atmospheric pressure photoionization were used in positive and negative ion modes for the ionization of target compounds. Two MS/MS transitions were measured for each API. Samples were quantified using isotope dilution or internal standard methods. Six points calibration curve corresponding to concentration ranges 10–2500 ng/L were measured before, in the middle and at the end of sample analysis sequence to monitor response factor stability. Recoveries and the relative standard deviation of triplicate analyses of effluent from the Sjölunda WWTP spiked at 1 μg/L are given in Supplementary Information Table S2. Maximum difference between results at quantification and qualification mass transition was set to 30% as criterion for positive identification of the analyte. The same method is used by Hörsing et al. [24] and Grabic et al. (unpublished results) [25].

2.3. Experimental setup

2.3.1. Wastewater effluents

Wastewater effluents were collected after secondary treatment from two WWTPs in southern Sweden. Effluent 1 was collected from Källby WWTP after the activated sludge system which is operated with extended nitrogen removal.

Effluent 2 was obtained from Sjölunda WWTP after a high loaded activated sludge process before nitrogen removal. This wastewater is typical of that in many Swedish WWTPs which are operated without nitrogen removal due to their location in the northern part of the country where the climate is colder. Sjölunda also employs full nitrogen removal but using a biofilm system after a highly loaded activated sludge plant. Nitrification is achieved in trickling filters and denitrification in moving bed biofilm reactors with the addition of external carbon.

Table 1 gives the characteristics of the effluents. The effluents were analyzed using standard Swedish methods for total suspended solids (SS-EN 872:2005), total P (SS-EN ISO 6878:2005) and total N (SS-EN ISO 11905-1), while COD was determined with the Dr. Lange LCK 114 kit. The effluents were classified as low COD (Effluent 1) or high COD effluent (Effluent 2) based on their COD levels.

2.3.2. Oxidation experiments

Effluent samples of 150 mL each were prepared in Schott Duran® bottles and spiked with mixed APIs to a final concentration of approx. 1 μg/L. ClO_2 was added to duplicate samples at concentrations ranging from 0 to 20 mg/L. All samples were stored in the dark and allowed to react overnight (approx. 18 h) at room temperature, after which the pH and oxidant concentration in the samples

Table 1
Effluent characteristics.

	pH	COD (mg/L)	TSS (mg/L)	Total P (mg/L)	Total N (mg/L)
Effluent 1 (Källby)	6.8	35	5	0.26	7.5
Effluent 2 (Sjölunda)	7.2	55	8	0.28	8.0

were measured. Residual oxidants were removed by the addition of 50 mg/L sodium sulfite.

3. Results and discussion

Table 2 lists the APIs investigated, including information on the class of drug, arranged according to the ease with which they were oxidized by ClO_2 (based on Effluent 1).

No further pH adjustments were made during the entire experiment. The pH of the samples did not change significantly after treatment, even with the highest oxidant dose of 20 mg/L, where the sample remained slightly acidic (~pH 6.2–6.5). This slight decrease in pH is expected since the stock solutions of ClO_2 contain some residual HCl from the synthesis.

Fig. 1 shows the residual concentration of ClO_2 in the two effluents spiked with APIs as a function of the initial ClO_2 dose. It can be seen that the high COD effluent consumed more oxidant than the low COD effluent, especially when the dose was 8 mg/L ClO_2 and above.

Table 3 gives the number of APIs that can be effectively oxidized (i.e. by more than 90%) at each ClO_2 dose in both effluents. It can be seen that a dose of 8 mg/L ClO_2 to Effluent 1 was able to oxidize 38 of 56 APIs, and that only 1 more API was oxidized when the dose was increased to 20 mg/L. In Effluent 2, 33 APIs were oxidized with a dose of 8 mg/L ClO_2, and increasing the ClO_2 dose to 20 mg/L oxidized further 4 APIs. The remaining APIs (about one third) could not be degraded effectively (at least 90%) with a dose of 20 mg/L ClO_2.

Table 2
Name and chemical structure of the APIs investigated (www.fass.se). The therapeutic class, and in the case of the easily and moderately oxidizable APIs the reactive functional group are given in brackets.

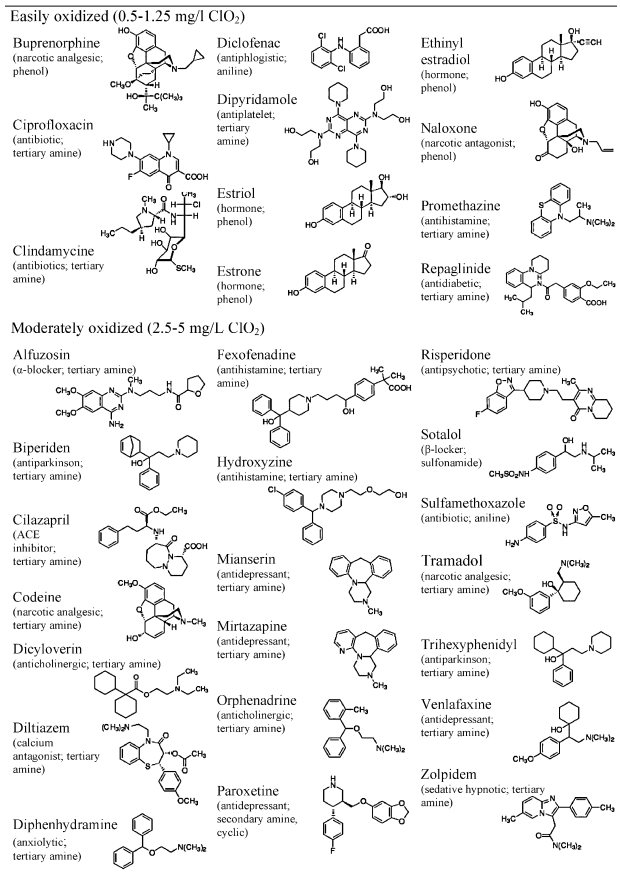
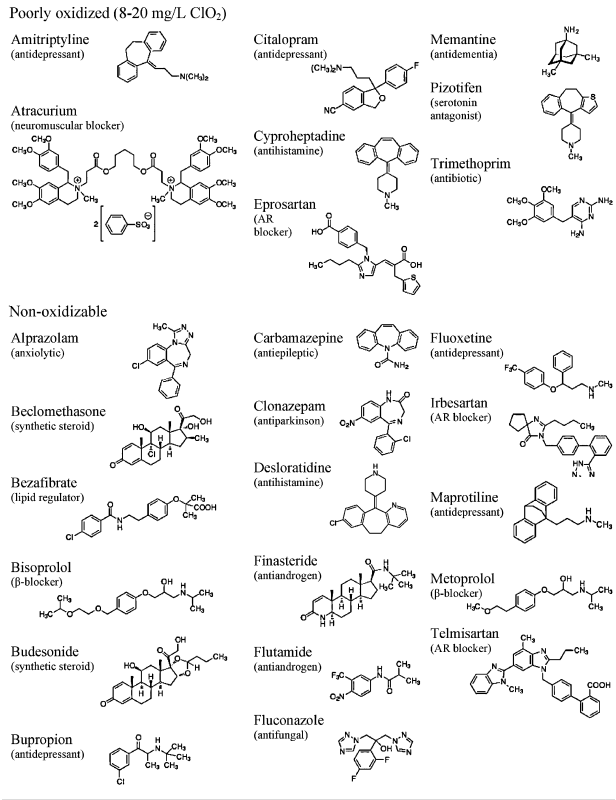


Table 2 (*Continued*)



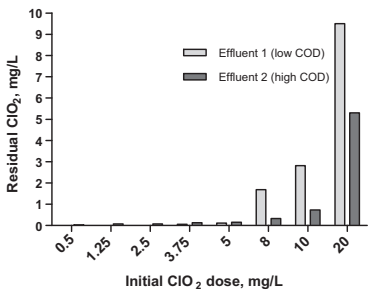


Fig. 1. Residual concentration of ClO_2 in the 2 effluents after treatment with different doses of the oxidant.

Table 3
The number of APIs tested (of a total of 56) that could be effectively oxidized (at least 90%) at each ClO_2 dose.

ClO_2 dose (mg/L)	No. of APIs oxidized by >90%	
	(Effluent 1)	(Effluent 2)
0.5	4	0
1.25	11	4
2.5	15	8
3.75	24	12
5	31	18
8	38	33
10	38	36
20	39	37

Only few APIs were oxidized by more than 90% at the lowest dose of ClO_2 (0.5 mg/L), while high oxidative degradation was observed with higher doses (8–20 mg/L). The degree to which each API was oxidized at different ClO_2 doses is shown in Fig. 2A and B for Effluents 1 and 2, respectively. The vertical lines divide the APIs into easily, moderately, poorly (based on the ClO_2 dose required to

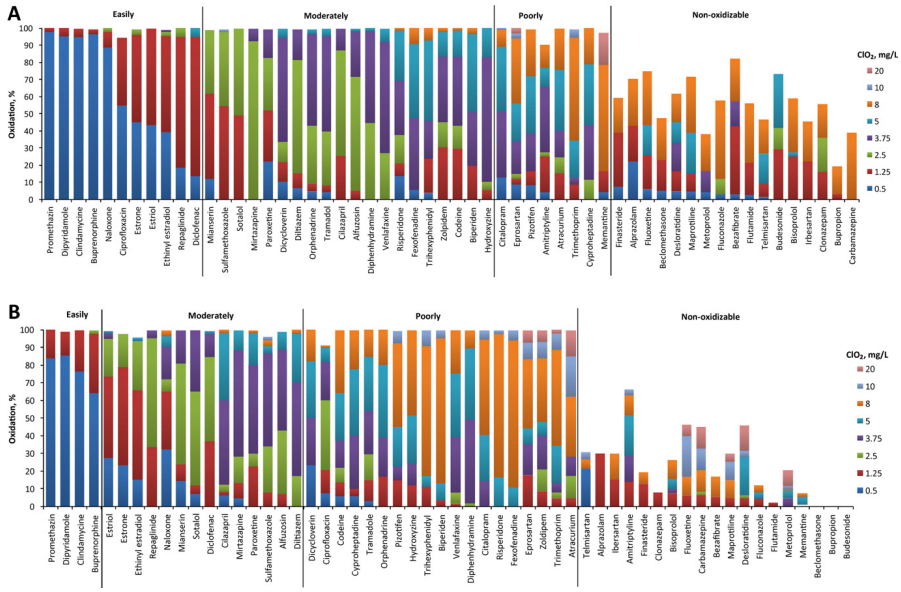


Fig. 2. Fraction of APIs oxidized in Effluent 1 (A) and Effluent 2 (B) at different ClO2 doses. The vertical lines divide the APIs into groups according to their ease of oxidation.

achieve 90–100% degradation) and non-oxidizable APIs (less than 90% degradation with 20 mg/L ClO_2).

As shown for Effluent 1 (Fig. 2A and Table 2), 11 of the APIs from 8 different therapeutic classes could be oxidized by more than 90% with 0.5–1.25 mg/L ClO_2. These include all 3 hormones, 2 antibiotics, 1 antihistamine, and 1 narcotic analgesic, as well as the antiplatelet, antidiabetic, antiphlogistic and narcotic antagonist compounds. The common reactive and electron-rich functional groups in these APIs are aniline in diclofenac, phenol in hormones, buprenorphine, and naloxone, and tertiary amines in promethazine, clindamycine, dipyridamole, repaglinide and ciprofloxacin. The high reactivity of ClO_2 with aniline, phenolic and tertiary amine functional groups has been reported in a number of studies [6,10,26]. The reactivity of ClO_2 with the piperazine ring of the antibiotic ciprofloxacin has also been reported by Wang et al. [13]. Similarly, Navalon et al. [12] also showed high reactivity of ciprofloxacin with ClO_2 in both surface water and wastewater effluent.

APIs requiring doses of 2.5–5 mg/L ClO_2 for oxidation are considered to be moderately oxidizable (Table 2). Most of the APIs from 13 of the different therapeutic classes belong to this category including 4 antidepressants, 2 antihistamines, 2 antiparkinson drugs, 2 narcotic analgesics, 2 anticholinergics, 1 antibiotic, 1 beta blocker, 1 sedative-hypnotic, 1 anxiolytic, and the representative compound from different classes, namely angiotensin converting enzyme (ACE) inhibitor, alpha blocker, antipsychotic and calcium antagonist. The most common functional group in this category of moderately oxidizable APIs is the tertiary amino group, which is also found in the structures of easily oxidizable APIs. However, despite belonging to the same therapeutic class, the behavior of the APIs differed significantly, depending largely on the reactivity of electron-rich functional groups. The removal of pharmaceuticals at fairly low oxidant doses (1.25–3.75 mg/L ClO_2) has also been observed in previous studies on surface and drinking water [10] and in wastewater effluents [6,11].

The resistance of poorly and non-oxidizable APIs to oxidation by ClO_2 could be attributed to the presence of the electron-withdrawing functional groups such as the chloro (in clonazepam, bupropion, desloratidine, alprazolam, bezafibrate, and beclomethasone), fluoro (in citalopram, flutamide, fluoxetin, fluconazole), nitro (in flutamide and clonazepam), olefin or C=C double bonds (in eprosartan and amitriptyline), amide carbonyl (in bezafibrate and finasteride) and keto group (in bupropion, beclomethasone and budesonide) [7,26–29]. The secondary amine-containing beta blockers, metoprolol and bisoprolol are also considered less susceptible to ClO_2 oxidation. Lee and von Gunten [6] reported the poor transformation of the beta blocker atenolol which has a secondary amine functional group. However, the oxidizability of the beta blocker sotalol can be explained by the presence of the ClO_2 reactive sulfonamide functional group in its structure. The same degree of API oxidation can be achieved in the high COD effluent (2) as in the low COD effluent (1), but higher ClO_2 doses are required. This is due to consumption of the ClO_2 competitively with the APIs by other organic components in the wastewater [6]. In addition, the presence of inorganic components in the wastewater also consumes some of the oxidant and this could affect the removal of the target micropollutants [6].

The results of this study showed that about 20 APIs cannot be oxidized effectively, even at the highest dose investigated (20 mg/L ClO_2), suggesting low reactivity between these APIs and ClO_2. In Effluent 1, 13 of these APIs (alprazolam, finasteride, fluoxetine, beclomethasone, desloratadine, maprotiline,

fluconazole, bezafibrate, flutamide, telmisartan, budesonide, bisoprolol, and clonazepam) were oxidized by 50–80%, while the remaining 4 APIs metoprolol, irbesartan, bupropion, and carbamazepine were degraded less (20–40%). On the other hand, in Effluent 2, most of these APIs were oxidized by less than 50%, while 3 APIs (the synthetic steroids beclomethasone and budesonide, and the antidepressant bupropion) did not show any degradation at all. Bezafibrate and carbamazepine have been shown in previous investigations to be recalcitrant to ClO_2 oxidation during water and wastewater treatment [6,10,28]. As mentioned above, the presence of electron-withdrawing functional groups results in low reactivity of some APIs to ClO_2 oxidation, and thus a much higher dose of ClO_2 would be needed for oxidation.

APIs such as diclofenac, sulfamethoxazole and estrogens have been found to be oxidized by more than 90% during ozonation of municipal wastewater effluents at O_3 doses of $\geq$2 mg/L, while a much higher O_3 dose was required for the effective removal of bezafibrate [30]. Ternes et al. [7] also found significant removal (>90%) of sulfamethoxazole, diclofenac, carbamazepine, and sotalol during treatment of municipal sewage effluent with 5 mg/L O_3, while a higher O_3 dose of 10–15 mg/L was required to effectively remove the beta blocker metoprolol, which also exhibits low reactivity to ClO_2. In the present study, ClO_2 was able to oxidize several APIs effectively at doses comparable to those of ozone. The reactivity of carbamazepine was very different since it could be removed by low ozone doses, while it is almost completely resistant to ClO_2.

The oxidation of APIs by ClO_2 is comparable to oxidation by molecular ozone as both are selective oxidants and are capable of transforming organic micropollutants based on the reactivity of the structure and the characteristics of the water matrix. These chemical oxidants react with electron-rich functional groups such as phenolic and amino groups, which can be found in the structures of most of the APIs investigated [6,10,31–33]. However, the reaction between ClO_2 and some APIs was much slower than ozonation, even with the same reactive functional group. Therefore, the usefulness of ClO_2 end-of-pipe treatment of WWTP effluents will depend on whether the micropollutants deemed to be critical for the receiving water are sensitive to ClO_2. Running costs must also be considered since ClO_2 is slightly more expensive to produce than ozone, while it is far simpler and less expensive to build both the generator and reaction chamber for ClO_2 treatment. The treatment perspective then is mainly to use ClO_2-treatment for small scale WWTP (<2000 person equivalent) effluents or where treatment is required only for a limited time.

Two of the APIs investigated here may be of considerable concern regarding the discharge of wastewater effluents into surface water. Both ethinyl estradiol, a pharmaceutical with a high endocrine-disrupting ability [34], and diclofenac, identified as a contaminant that causes direct toxic effects in the environment [35,36], were found to be very sensitive to ClO_2 oxidation. However, if other less reactive APIs, e.g. bezafibrate or carbamazepine, were found to be of concern regarding aquatic life in the receiving water body of the WWTP effluent, ClO_2 treatment would not be a suitable treatment option.

4. Conclusions

The results of this study show that ClO_2 can be used to treat wastewater effluents to oxidize various APIs belonging to different therapeutic classes. However, there was considerable variation in the reactivity of the investigated APIs to ClO_2. The degree of oxidation was found to be dependent on the type of wastewater; API removal is better from the low COD wastewater from the plant with extended nitrogen removal, than the one without (high COD wastewater), at the same oxidant dose. In addition, the reactivity of the APIs depends on the reactive functional group present. APIs with electron-withdrawing functional groups appear to be more resistant to ClO_2 oxidation.

ClO_2 oxidation by-products and toxicity must be investigated before this method can be considered for application in wastewater treatment. The use of ClO_2 oxidation for the removal of pharmaceuticals may be beneficial in small wastewater treatment plants where ozonation could be too expensive and complicated.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cej.2012.01.093.

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Paper III

Required ozone doses for removing pharmaceuticals from wastewater effluents

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Abstract

The aim of the present study was to investigate the ozone dosage required to remove active pharmaceutical ingredients (APIs) from biologically treated wastewater of varying quality originating from different raw wastewater and wastewater treatment processes. Secondary effluents from six Swedish wastewater treatment plants (WWTP) were spiked with 42 APIs (nominal concentration 1μg/L) and treated with different O_3 doses (0.5-12.0 mg/L ozone) in bench- scale experiments.

In order to obtain a parameter to compare the sensitivity of APIs in each matrix the specific dose of ozone required to achieve one decade of removal of each investigated API (DDO_3) was determined for each effluent by fitting a first order equation to the remaining concentration of API at each applied ozone dose. Ozone dose requirements were found to vary significantly between effluents depending on their matrix characteristics.

The specific ozone dose was then normalized to the dissolved organic carbon (DOC) of each effluent. The DDO_3/DOC ratios were comparable for each API between the effluents. Seventeen of the 42 investigated APIs could be classified as easily degradable ($DDO_3/DOC \leq 0.7$), while 17 were moderately degradable ($0.7 < DDO_3/DOC \leq 1.4$) and 8 were recalcitrant towards O_3-treatment ($DDO_3/DOC > 1.4$). Furthermore, we predict that a reasonable estimate of the required ozone dose required to remove any of the investigated APIs may be attained by

multiplying the experimental average DDO_3/DOC obtained with the actual DOC of any effluent.

Keywords: matrix effects; ozonation; ozone dose, pharmaceuticals, wastewater.

Introduction

The modern life-style of developed countries involves daily usage of artificial compounds such as active pharmaceutical ingredients (API), personal care products, hormones, pesticides and other environmentally persistent chemicals. As a result residues of these compounds become micropollutants in wastewater (Fick et al., 2010; Hollender et al., 2009; Richardson, 2010; Gerrity and Snyder, 2011; Huber et al., 2005; Richardson, 2010). Of all groups of micropollutants the vast majority of research activities are currently focused on the fate of active pharmaceutical ingredients during wastewater treatments (Hollender et al., 2009; Huber et al., 2003; Huber et al., 2005; Lee and von Gunten, 2010; McDowell et al., 2005; Zimmermann et al., 2011). APIs by purpose are generally designed to illicit a specific biological action. Due to their use pattern release to the environment is mainly via sewage outlets into surface waters. APIs are usually found at concentrations ranging from pg/L - µg/L in wastewater and surface waters influenced by wastewater outlets. However, in many cases chronic exposure of APIs to humans and wildlife even at these low concentrations is both of scientific and societal concern (Richardson, 2010). To address this problem many WWTPs consider incorporating an additional treatment process step to remove APIs from the effluent. Treatment with O_3 appears to be one of the most promising technologies for the removal of these compounds (Ternes et al., 2003; Hansen et al., 2010; Hollender et al., 2009; Huber et al., 2003; Huber et al., 2005; Lee and von Gunten, 2010; Zimmermann et al., 2011).

One of the first studies which showed the efficiency of ozonation for removal of micropollutants in biological treated wastewater was by Ternes et al. (2003). Ozonation was employed at 5.0 to 15.0 mg/L of O_3 to investigate the removal efficiency (Ternes et al., 2003) for selected APIs, personal care products and iodated X-ray contrast media. Pharmaceuticals and personal care products were removed sufficiently by only 5 mg/L of O_3 while the iodated X-ray contrast media were only partially removed by 15 mg/L of O_3. However, as there is not much toxicological concern for iodated X-ray contrast media results were interpreted as promising and more optimised treatment studies were conducted which reported efficient removal of pharmaceuticals and hormones in wastewater at lower O_3 doses (2.0-3.5 mg/L) (Bahr et al., 2007; Hansen et al., 2010; Huber et al., 2005). Estimating the removal efficiencies of APIs from wastewater effluents in bench and pilot scale experiments, was the main focus of subsequent studies (Hollender et al., 2009; Huber et al., 2003; Zimmermann et al., 2011). For example, Hollender et al. (2009) studied the removal efficiencies of 220 pharmaceuticals in full scale

with conventional activated sludge sewage treatment followed by ozonation and sand filtration. Kinetic studies and modeling of ozonation based on reactor hydraulics, O_3 chemistry and reaction kinetics were also performed for a full scale municipal wastewater facility (Zimmermann et al., 2011).

Generally, APIs and other micropollutants are easy to degrade, i.e. can be removed with low ozone dosage, if they react reasonable fast with molecular ozone. If a micropollutant does not react well with ozone it will still degrade with higher applied ozone dosage via a secondary oxidation mechanism by which ozone in water is converted to the hydroxyradical, $HO^{\bullet}$, which is very reactive (non-selective) to most organic molecules.

Up to now, the parameter most commonly used by researchers to determine how well an API reacts with O_3, is the second order rate constant with O_3 ($k_{O3,API}$, selective oxidation) and $HO^{\bullet}$ ($k_{HO,API}$, non-selective oxidation) (Hollender et al., 2009; Huber et al., 2003; Zimmermann et al., 2011). According to these studies, compounds with $k_{O3,API}$ greater than 10^4 $M^{-1}s^{-1}$, require low delivered O_3 doses (easily degraded). Compounds with $k_{O3,API} < 10^4$ $M^{-1}s^{-1}$, are more persistent to O_3 treatment and therefore their degradation occurs mainly via reaction with $HO^{\bullet}$, the secondary degradation route of ozonation.

However, of the several hundred APIs which have been detected in WWTP effluents (Ternes et al., 1998; Kolpin et al., 2002; Hollender et al., 2009; Fick et al., 2011; Falås et al., 2012a) very few have had their respective $k_{O3,API}$ and $k_{HO\bullet,API}$ determined (Benner and Ternes, 2009; Buffle et al., 2006a; Dodd et al., 2006; Huber et al., 2003; Huerta-Fontela et al., 2011). In fact, constants are available for less than 10% of the model APIs used in this study (Supplementary Information Table S1). Even when these two rate constants ($k_{O3,API}$ and $k_{HO,API}$) are known for an API, an experiment to determine the ozone and HO exposure that results from an ozone dose in the specific wastewater is needed before the degradation of the API can be predicted (Huber et al., 2005; Buffle et al., 2006b).

With O_3 production being an energy intensive process (Kim and Tanaka, 2011), it is important for WWTPs to use optimum O_3 doses that achieve sufficient API degradation while maintaining low operational cost (Bahr et al., 2007; Hansen et al., 2010). APIs exhibit different susceptibilities to O_3 degradation which can vary up to 10 orders of magnitude (Hoigne and Bader, 1983; Hollender et al., 2009; Huber et al., 2003). They are also competing for O_3 degradation with the organic components found in the matrix of the WWTP effluent (Hollender et al., 2009) that vary in amount and quality depending on the treatment process and origin of wastewater. This makes it particularly difficult to predict the required O_3 dosage requirements (DO_3) for satisfactory API removal in WWTP effluents, which is crucial parameter in estimating treatment design and therefore cost.

This study investigated the delivered O_3 dose (0.5 mg/L $\leq DO_3 \leq$ ~12 mg/L) needed to achieve one order of magnitude of removal of 42 APIs (at low

concentrations, μg/L, Table S1) from 6 Swedish WWTP effluents. These APIs are commonly found in the WWTP effluents of Sweden (Fick et al., 2011, 2012; Falås et al., 2012a) and have different susceptibilities to ozonation (Benner and Ternes, 2009; Buffle et al., 2006a; Dodd et al., 2006; Hoigne and Bader, 1983; Huber et al., 2003). Effluents used in the experiments were chosen to represent typical variations observed in the main traditional characteristics of effluent quality that would occur due to different treatment processes currently employed in Sweden and also variability in raw water, i.e. COD, alkalinity and NH_4^+-N content (Table 1). Since APIs reacting with ozone also compete with the matrix components of the effluent, an attempt was made to correlate the DO_3 with the effluent characteristics.

Materials and Methods

Chemicals

All pharmaceutical reference standards were of analytical grade (> 98%) purchased from different suppliers (Table S2). A stock solution of the APIs was prepared in methanol (Merck, Darmstadt, Germany) at concentration of about 100 mg/L. An O_3 stock solution was prepared in Milli-Q water (Millipore, Billerica, MA) as described in Antoniou and Andersen (2011).

Wastewater effluents

Effluents from five WWTPs in Sweden, including Källby (Effluent 1&2), Björnstorp (Effluent 3), Oresundsverket (Effluent 4), Sjölunda (Effluent 5), and Nykvarnsverket (Effluent 6) were used in this study. Effluent 1 and Effluent 2 were from the same treatment plant but were collected on separate occasions with a 3-week time interval. Although Effluent 1 and Effluent 2 came from the same WWTP, they were treated as 2 different effluents due to the variability of their characteristics. This difference is attributed to the significant rainfall events which occurred following the first sampling round. These precipitation events most likely caused a sludge wash-out, reducing the biological treatment efficiency and increasing the COD value, while at the same time alkalinity reduced because of dilution with rain water. The characteristics and treatment processes that are performed at each WWTP are listed in Table 1 and extensively described in S.I., respectively.

Table 1. Source and characterization of the wastewater effluents.

WWTP	Källby 1	Källby 2	Björnstorp	Öresundsv	Sjölunda	Nykvarnsv
	Eff 1	Eff 2	Eff 3	Eff 4	Eff 5	Eff 6
COD, mg/L	29	51	30	36	90	44
DOC, mg/L	7.5	6.5	5.2	8.1	13.7	8.4
Alkalinity, mg HCO_3^-/L	244	154	185	229	256	164
pH	6.6	6.7	7.0	7.2	6.7	6.8
NH_4^+-N, mg/L	1.36	2.98	0.77	4.93	1.86	5.98

Experimental set-up

Effluent was spiked with the APIs standard to give a nominal concentration of 1 µg/L, and then transferred into borosilicate glass vials, where different volumes of O_3 stock solution were added (in triplicate) to give nominal concentrations between 0.5 and ~12 mg/L O_3 for a total volume of 150 mL. Vials were placed in a covered water bath at 15°C.

Analysis

DOC, pH, alkalinity (mg HCO_3^-/L), COD, and $NH4^+$-N concentrations in the effluent were quantified based on standard methods. The DO_3 was measured with the colorimetric method of indigo (λ = 600nm), by preparing bottles with indigo trisulfonate solution in Milli-Q water in parallel with the treatment samples (Antoniou and Andersen, 2011; Bader and Hoigne, 1981). After SPE extraction, the APIs were quantified by LC/MS/MS using a triple-stage quadrupole mass spectrometer (MS/MS TSQ Quantum Ultra EMR) coupled to an Accela LC pump (both from Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) with a Hypersil GOLD aQTM column (50 mm x 2.1 mm ID x 5 µm particles). The same method was used to investigate the fate of APIs in wastewater treatment by Hörsing et al. (2011) and Hey et al. (2012) and a full method evaluation and detailed description of the method are given in Grabic et al. (2012).

Results and Discussion

Removal of APIs from 6 WWTP effluents: Effect of wastewater matrix

In this study, 42 APIs commonly found in WWTP effluents in Sweden were spiked in six different WWTP effluents and treated with O_3 to evaluate their removal efficiencies and the effect of the matrix. Figure 1 summarizes the contribution of each O_3 dose (0.5 to ~12.0 mg/L O_3) on the removal of the APIs in 2 (Effluent 1and 5) of the six WWTP effluents. The two wastewaters represent the 2 distinct types of wastewaters in Sweden, where Effluent 1 represents activated sludge plants with extended nitrogen and phosphorous removal present in the Southern part of the country and Effluent 5 the high loaded activated sludge plants with only removal of organic matter and phosphorous, mainly can be found in the Northern part of Sweden where no nitrogen removal is needed.The same data is also shown in Figure S1 (for all effluents) and Figures S2 to S7 but plotted in a less condensed manner allowing representation of experimental variation. A general trend can be seen whereby increasing O_3 dosage increases API removal efficiency (Figure 1). However, great variability is observed in required O_3 dose to achieve removal of different APIs within the same effluent and for the same API between effluents.

For the lowest delivered O_3 dose (0.5-0.6 mg/L), Effluent 1 has the highest number of APIs exhibiting removal efficiencies between 50-100%, possibly due to its low COD values compared to other effluents. Low COD level reduces the competition for O_3 between the pharmaceuticals and the organic matrix of the wastewater. The high alkalinity value observed in this effluent (highest in the group, Table 1) did not seem to significantly affect the API removal. The APIs in Effluent 5 appear to be the most recalcitrant to O_3 treatment, with all exhibiting < 50% removal at the lowest delivered O_3 dosage. Increasing the O_3 dosage to ~8.9 mg/L has only little effect on API removal in this effluent, removing only 18 out of 42 by > 90%. Thus it can be noted that the high COD (~90 mg/L) level present in Effluent 5 contributed to inhibiting the API removal.

The APIs in the 3 effluents (Effluent 2, 3, and 6 and Figure S1) were removed by over 50% at the highest O_3 dosage. In Effluents 1 and 4, only 1 API had less than 50% removal while 7 of the APIs were poorly removed (< 50%) in Effluent 5 even with the highest O_3 dosage. Based on the results shown here, the susceptibility of the APIs to O_3 degradation appears to be highly dependent on the characteristics of the wastewaters studied, explaining the wide range of removal efficiencies that some APIs exhibited. Specifically, the synthetic steroid beclomethasone was removed between 0-98% in all effluents. Removal of fluconazole (antifungal) and flutamide (antiandrogen) ranged between 33-77% and 13-87%, respectively, inferring that the APIs were not effectively degraded (to reach the treatment goal of 90%) in any of the tested effluents with the applied O_3 doses.

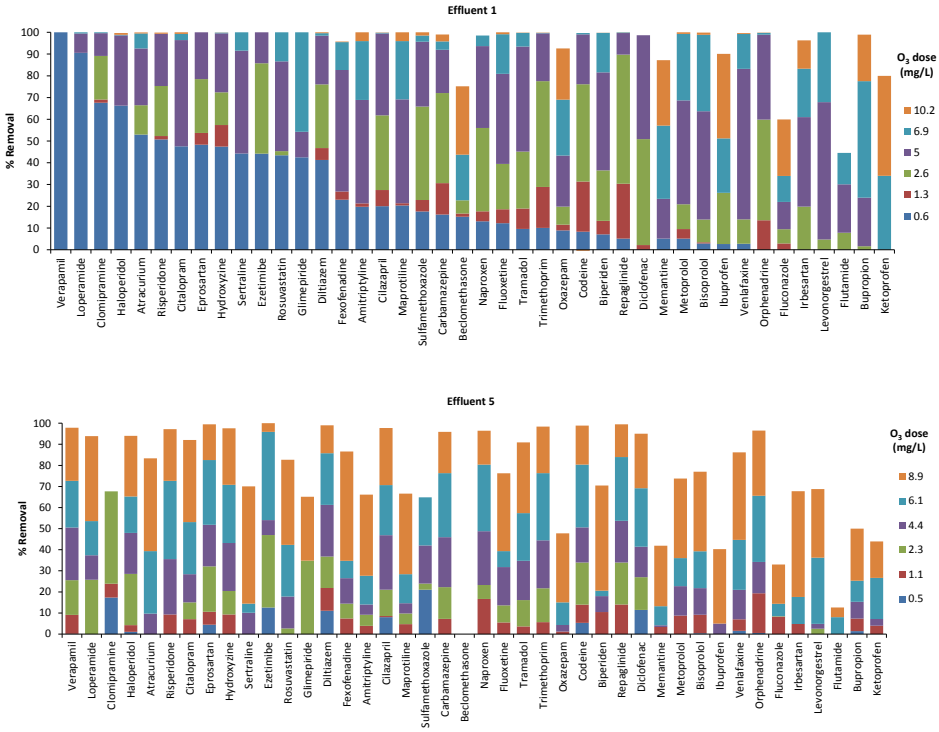

Figure 1. Profiles of dose dependency for the removal of pharmaceuticals in the 2 investigated wastewaters.

Required ozone dose to achieve 90% removal of API in WWTP effluents

In order to determine the O_3 dosage that achieves 90% removal of each API in the effluent, the data shown on Figure 1 and also in Figure S1 were fitted with Equation 1 and the results summarized in Figures S2-S7. Equation 1 is an exponential formula that describes the remaining API concentration in relation to its initial concentration after a specific O_3 dose is delivered (DO_3). It is dependent on the fact that ozone's fate in the effluent is determined by the effluent's matrix and not significantly affected by the reaction with the APIs; therefore it is independent on the API concentration. The equation contains the O_3 dose required to remove 90% of the API as a constant (here noted as decadic dose of O_3, DDO_3), allowing the determination of the standard error directly through curve fitting. The fitted parameter is named the decadic dose of O_3, DDO_3.

$$(Eq.1) \qquad \log\left(\frac{C}{C_o}\right) = \frac{-DO_3}{DDO_3} \Leftrightarrow C = C_o \cdot 10^{-\left(\frac{DO_3}{DDO_3}\right)}$$

Equation 1 resembles the general formula used for the characterization of the effectiveness of energy intensive advanced treatment methods (Equation 2) recommended by IUPAC and described by Bolton et al. (2001). Equation 2 correlates the electrical energy dose (EED) with the residual concentration of the treatment target compound and uses the constant EEO which is the EED required to achieve 90% removal (Bolton et al., 2001).

$$(Eq.2) \qquad \log\left(\frac{C}{C_o}\right) = \frac{-EED}{E_{EO}}$$

Equation 1 was suggested by Hansen et al., (2010) who used both Equations 1 and 2 to describe the effectiveness of O_3 treatment for estrogenic chemicals in WWTP effluents in terms of the O_3 and energy dosage applied. Based on the above, it was decided to use the same system of equations to describe the effectiveness of O_3-treatment for API removal from wastewater (Figures S2-S7).

In the present study, an apparent lag-phase towards degradation was observed at lower O_3 doses for some APIs and it wasn't until higher O_3 doses were applied that degradation occurred. Once the O_3 lag-phase dose was surpassed, a decrease in concentrations of the APIs with ozone dose was observed which is apparently similar to the curve shape (exponential decay) for the APIs which did not show this lag-phase. It is our belief, that the lag-phase is a result of the low reactivity of some APIs for direct reaction with O_3 in addition to competition with the wastewater matrix for O_3 degradation. Some of the matrix components react directly with O_3 and quickly consume the low O_3 doses, therefore reducing the chances of O_3 reacting with the target compounds. It is only when O_3 is added at higher doses, to satisfy the O_3 reactive part of the matrix, that enough O_3 remains for the APIs to be degraded either directly or through the secondary pathway which is mediated by HO• ($O_3 + H_2O \rightarrow 2HO\bullet + O_2$), assuming that O_3 remains in the wastewater long enough to break down to radical forms. To fit the concentration curves of the pharmaceuticals that showed an apparent lag of reactivity towards low O_3 doses, a variation of Equation 1 was developed and shown as Equation 3 (see Figure S8 for graphical representation).

$$(Eq.3) \qquad IF: DO_3 < LagO_3 \rightarrow C = C_o$$

$$IF: DO_3 > LagO_3 \rightarrow C = C_o \cdot 10^{-\left(\frac{DO_3 - LagO_3}{D}\right)}; \qquad DDO_3 = D + LagO_3$$

The resulting estimated DDO_3 values of each API in all the effluents are presented in Table 2. Significant variation is observed in the DDO_3 values of a specific API depending on the wastewater effluent matrix. For example, carbamazepine exhibited a low DDO_3 of ~2 mg/L in Effluent 3, compared to the high DDO_3 of ~ 10 mg/L in Effluent 5. This confirms the strong influence exerted by the wastewater matrix components on pharmaceuticals removal efficiencies with O_3. This has also been observed by Benitez et al. (2009) during O_3-treatment of pharmaceuticals (including metoprolol and naproxen) in surface and ground water and wastewater. Their results showed higher pharmaceutical removal in surface water (alkalinity=30 mg $CaCO_3$/L) compared to groundwater (alkalinity=388 mg $CaCO_3$/L), while the effluent containing the lowest DOC and alkalinity had the highest removal among the 3 secondary effluents tested (Benitez et al., 2009).

Based on the above, and in order to categorize the different pharmaceuticals into easily degradable, moderately degradable and recalcitrant towards O_3 degradation, the Specific DDO_3 value was calculated by dividing the DDO_3 with the effluent DOC [DDO_3/DOC]. The selection criterion for an API to be characterized as easily degraded was decided to be a [DDO_3/DOC] value of = 0.7. Seventeen out of 42 investigated APIs fulfilled this criterion including repaglinide (antidiabetic), trimethoprim (antibiotic), carbamazepine (antiepileptic) and diclofenac (antiphlogistic) and naproxen (antiphlogistics). Seventeen APIs fulfilled the moderately degradable criterion of 0.7 < [DDO_3/DOC] = 1.4 including sulfamethoxazole (antibiotic), metoprolol and bisoprolol (beta blockers) and citalopram, amitriptyline, maprotiline, venlafaxine, fluoxetine, bupropion and sertraline (antidepressants). The remaining 8 APIs, such as beclomethasone and the antiphlogistics ketoprofen and ibuprofen, were considered O_3-recalcitrant since they have [DDO_3/DOC] >1.4.

Hollender et al. (2009) and Bahr et al. (2010) have also used the O_3 dose in relation to the DOC value of the wastewater to describe the treatment efficiency. In a study conducted by Hollender et al. (2009) on the removal of organic micropollutants from wastewater with O_3 including 24 pharmaceuticals, the fast reacting APIs sulfamethoxazole, diclofenac, carbamazepine and trimethoprim were eliminated at a dose of 0.47 g O_3/g DOC (dissolved organic carbon). In our study we found that the same compounds require from 0.55 up to 0.77 g O_3/g DOC for 90% removal. Furthermore, Bahr et al., (2010) reported the complete removal of naproxen, diclofenac and carbamazepine at a specific ozone dose of 0.5 g O_3/g DOC during ozonation of secondary WWTP effluents. Our study predicts the dosage required for 90 % removal of these APIs to be in the order of 0.61-0.66 g O_3/g DOC. While for slow reacting compounds, such as ibuprofen and ketoprofen, a specific ozone dose > 1 g O_3/g DOC is required for > 95% removal according to Bahr et al., 2010. In comparison, our work showed the dosage of ozone required for 90 % removal to be 1.61 and 1.51 g O_3/g DOC, respectively, for these two APIs.

Table 2: Ozone dose for removal of the first decade of each pharmaceutical in the wastewater and the dose relative to the DOC with estimated 95% confidence intervals. (NA* = compound not quantified; NA** = out of range, either <<lowest dose or >> highest dose of ozone applied)

	DDO_3 (ppm O_3)						[DDO_3/DOC]						
API	Eff 1	Eff 2	Eff 3	Eff 4	Eff 5	Eff 6	Eff 1	Eff 2	Eff 3	Eff 4	Eff 5	Eff 6	Ave
Easily degradable													
Repaglinide	2.6	3.7	1.8	4.1	8.7	1.5	0.35	0.57	0.35	0.50	0.64	0.18	0.43
Ezetimibe	3.2	4.6	1.5	3.8	8.0	2.0	0.43	0.71	0.29	0.47	0.58	0.24	0.45
Diltiazem	3.6	3.7	2.2	4.3	8.0	3.9	0.48	0.57	0.42	0.53	0.58	0.47	0.51
Verapamil	<0.5	5.4	<0.5	5.0	10.5	7.5	0.07	0.84	0.10	0.61	0.77	0.90	0.55
Eprosartan	3.2	4.9	1.9	4.5	9.1	4.2	0.43	0.76	0.37	0.55	0.66	0.50	0.55
Trimethoprim	4.0	4.3	2.1	4.4	9.7	3.9	0.53	0.67	0.40	0.54	0.71	0.47	0.55
Clomipramine	2.3	7.3	2.4	3.7	7.5	4.2	0.31	1.13	0.46	0.45	0.55	0.50	0.57
Risperidone	3.5	4.7	0.9	5.5	12.1	5.0	0.47	0.73	0.17	0.68	0.88	0.60	0.59
Hydroxyzine	3.4	5.7	1.9	4.8	10	4.8	0.45	0.88	0.37	0.59	0.73	0.57	0.60
Codeine	4.2	4.9	2.4	4.6	9.2	5.4	0.56	0.76	0.46	0.57	0.67	0.65	0.61
Carbamazepine	5.1	5.4	2.2	4.3	10.8	3.5	0.68	0.84	0.42	0.53	0.79	0.42	0.61
Loperamide	2.0	4.5	<0.5	5.7	>12	8.7	0.27	0.70	0.10	0.70	0.97	1.04	0.63
Naproxen	5.7	5.0	2.5	6.4	10	3.7	0.76	0.77	0.48	0.79	0.73	0.44	0.66
Fexofenadine	5.2	5.8	3.0	6.5	9.1	2.9	0.69	0.90	0.58	0.80	0.66	0.35	0.66
Orphenadrine	4.5	5.0	3.4	4.8	12.1	4.0	0.60	0.77	0.65	0.59	0.88	0.48	0.66
Diclofenac	4.7	5.8	NA*	3.5	10	NA*	0.63	0.90	NA*	0.43	0.73	NA*	0.67
Cilazapril	4.5	7.1	2.7	5.7	11	4.0	0.60	1.10	0.52	0.70	0.80	0.48	0.70
Moderately degradable													
Glimepiride	7.0	7.6	3.6	6.7	>12	0.6	0.93	1.18	0.69	0.82	NA**	0.07	0.74
Rosuvastatin	5.4	5.6	3.3	5	>12	4.8	0.72	0.87	0.63	0.61	1.06	0.57	0.74
Haloperidole	4.8	7.8	1.5	6.3	11.8	5.9	0.64	1.21	0.29	0.77	0.86	0.71	0.75
Sulfamethoxazole	4.8	4.5	3.6	4.5	>12	NA*	0.64	0.70	0.69	0.55	1.28	NA*	0.77
Tramadole	5.7	5.8	3.4	6.3	>12	6.4	0.76	0.90	0.65	0.77	0.95	0.77	0.80
Citalopram	5.0	7.8	2.0	7.1	>12	5.0	0.67	1.21	0.38	0.87	1.09	0.60	0.80
Sertraline	6.4	5.2	1.7	7.9	12	11.6	0.85	0.81	0.33	0.97	0.88	1.39	0.87
Venlafaxine	5.3	6.3	3.4	6.4	>12	9.3	0.71	0.98	0.65	0.79	1.21	1.11	0.91
Maprotiline	7.3	6.9	4.1	8.3	>12	7.2	0.97	1.07	0.79	1.02	0.99	0.86	0.95
Bisoprolol	7.2	6.0	3.3	7.3	>12	7.2	0.96	0.93	0.63	0.90	1.53	0.86	0.97
Amitriptyline	7.3	9.4	3.6	8.3	>12	7.3	0.97	1.46	0.69	1.02	0.99	0.87	1.00
Metoprolol	6.9	6.9	3.8	7.4	>12	8.8	0.92	1.07	0.73	0.91	1.33	1.05	1.00
Biperiden	5.9	6.3	4.3	7.3	>12	7.4	0.78	0.98	0.83	0.90	1.68	0.88	1.01
Levonorgestrel	6.7	7.3	6.6	6.0	>12	6.5	0.89	1.13	1.27	0.74	1.33	0.78	1.02
Fluoxetine	6.6	6.8	3.1	7.7	>12	11.3	0.88	1.05	0.60	0.95	1.46	1.35	1.05
Irbesartan	8.7	7.7	5.4	11.5	>12	4.3	1.16	1.19	1.04	1.41	1.00	0.51	1.05
Bupropion	8.1	8.0	5.2	9.3	>12	12.1	1.08	1.24	1.00	1.14	NA**	1.45	1.18
Recalcitrant towards ozone degradation													
Oxazepam	12.3	11.3	7.1	>12	18.4	9.7	1.64	1.75	1.37	1.66	1.34	1.16	1.49
Ketoprofen	13.4	12.7	5.5	>12	23.9	9.7	1.78	1.97	1.06	1.62	1.74	1.16	1.56
Memantine	11.4	12.8	7.8	>12	21.3	10.2	1.52	1.98	1.50	1.78	1.55	1.22	1.59
Ibuprofen	11.5	10.9	7.3	>12	27	10.4	1.53	1.69	1.40	1.81	1.97	1.24	1.61
Beclomethasone	20	18	5.8	12	>12	9.2	2.66	2.79	1.12	1.47	NA**	1.10	1.83
Atracurium	3.7	6.2	4.4	11	11.1	3.9	0.49	3.13	0.85	1.35	0.81	0.47	1.18
Flutamide	>12	>12	11.7	>12	>12	9.4	NA**	3.87	2.25	2.20	NA**	1.12	2.36
Fluconazole	15.1	>12	10.7	20	>12	>12	2.01	2.79	2.06	2.46	NA**	2.63	2.39

Some APIs follow first-order decay with the added O_3 dose such as carbamazepine and naproxen (Figure S2-S7) while APIs such as beclomethasone and memantine exhibits an apparent lag phase before any significant degradation occurred. In Figure S2-S7, the intersection of the horizontal line with the y-axis indicates the

DDO_3 of the APIs. It is evident that Effluent 5 has the most O_3-recalcitrant pharmaceuticals and requires higher DDO_3 compared to the other effluents (Figures 2A and 2B).

Based on the data shown in Table 2, the average [DDO_3/DOC] for the majority of the APIs is = 1.2, while only a few exhibit a [DDO_3/DOC] > 1.5. Thus, an O_3 dose of 1.4 g per g DOC should be sufficient to remove (by at least 90%) more than 80% of the APIs tested in this study. However, in order to remove the most O_3-recalcitrant APIs as well, a twice as high O_3 dose ([DDO_3/DOC]> 2.4 g O_3 per g DOC) is needed which results in a significantly more costly treatment process.

Effect of chemical structure of the APIs on O_3 reactivity

The chemical structure of each API and the functional groups comprising it determine whether an API would be easy or difficult to degrade with O_3. Due to its electronic configuration, O_3 can perform different types of reactions in water including oxidation reactions, cycloadditions and electrophilic substitution reactions (Beltrán, 2004). Easily degradable APIs (relatively low [DDO_3/DOC] values) are characterized by the presence of electron-rich functional groups and they mainly react readily with O_3 through electrophilic substitution. These functional groups include C=C double bonds (found in eprosartan, carbamazepine), tertiary amines (repaglinide, clomipramine), aniline (dicofenac), phenol (ezetimibe) and methoxy groups (trimethoprim, verapamil, diltiazem, naproxen) (Hoigne and Bader, 1976; Huber et al., 2003; Huber et al., 2005; Nakada et al., 2007, Hollender et al., 2009).

APIs which are poorly removed (relatively high [DDO_3/DOC] values) generally contain electron-withdrawing functional groups, such as fluoro (flutamide, fluconazole), nitro (flutamide), chloro (beclomethasone), amide (flutamide) and carboxyl (ketoprofen) (Hey et al., 2012; Nakada et al., 2007; Acero et al., 2000; Hollender et al., 2011). Electron withdrawing groups reduce electron (e^-) density of the pharamaceutical structure inhibiting electrophilic substitution reactions to occur. In addition, the electronegative groups themselves are less likely to react with O_3 and thus cause a shielding effect.

Some easily degradable APIs such as carbamazepine and diclofenac also contain electron-withdrawing functional groups (amide in carbamazepine, chloro and carboxyl in diclofenac) but remain O_3-reactive, inferring the presence and position of the high e^- density functional groups in their structure (Nakada et al., 2007) and counteract the inhibitory effect. Ibuprofen possesses no electron-rich functional group and is recalcitrant towards O_3 treatment (Huber et al., 2005) however can be adequately removed through biological treatment (e.g. Falås et al., 2012b). In addition, effective oxidative removal of O_3-resistant APIs may be possible through

the hydroxyl radical pathway (Antoniou et al., 2008; von Sonntag and von Gunten, 2012).

Conclusions

- The effect of O_3 dose on the degradation of 42 APIs in different WWTP effluents was investigated with large variability between APIs and effluent characteristics. In order to evaluate the effect of O_3 dose on pharmaceutical degradation, the results of the remaining API concentrations were fitted with the corresponding O_3 dose and the decadic dose of O_3 (DDO_3) was determined from the resultant curve of the 42 pharmaceuticals. The DDO_3 of a specific API varied significantly among the effluents investigated.
- DDO_3 was correlated with the effluent DOC by calculating the DDO_3/DOC for each API in every effluent. This enabled ranking of the different APIs into easily degradable, moderately degradable and recalcitrant to O_3-treatment categories.
- Following this practice, the required O_3 dose can be predicted based on the target pharmaceutical and the matrix component of the wastewater (DOC) to be treated.
- An O_3 dose of 1.4 g per g DOC removed (by at least 90%) more than 80% of the pharmaceuticals investigated. To remove the most O_3-recalcitrant APIs, a dose in the order of 2.4 g O_3 per g DOC is required.

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Supplementary Information (SI): Required ozone doses for removing pharmaceuticals from wastewater effluents

Text S1: Description of WWTPs

Källby WWTP in Lund receives mainly domestic wastewater from 80,000 people. Incoming wastewater has annual average concentrations of approximately 180 mg/L BOD_7 and 40 mg/L Total Nitrogen. The wastewater is treated mechanically (screening, grit removal, and sedimentation), followed by a low loaded activated sludge process operated with pre-denitrification and enhanced biological phosphorous removal. Side stream hydrolysis is also performed in order to provide an additional carbon source and therefore enhance the biological phosphorous removal. Post-precipitation is used as a complementary process in case of insufficient biological phosphorous removal.

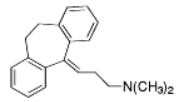
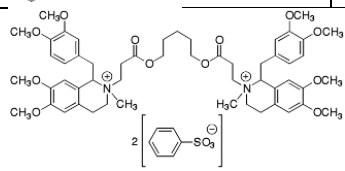
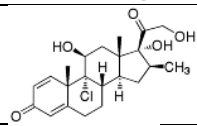
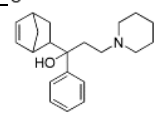
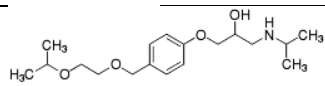
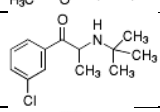
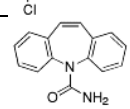
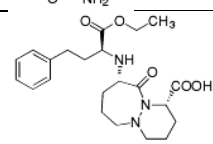
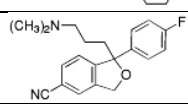
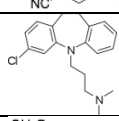
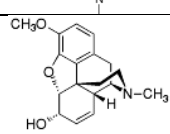
Sjölunda WWTP in Malmö receives wastewater from 300,000 people and a wide range of industries. Incoming wastewater has annual average concentrations of approximately 220 mg/L BOD_7 and 40 mg/L Total Nitrogen. The wastewater is treated mechanically (screening, grit removal, and pre-precipitation) first. The subsequent, high loaded activated sludge process is operated for BOD removal but an anaerobic/anoxic zone at the inlet is created for denitritation of aerobically treated reject water from the sludge handling facilities. Nitrification takes place in a subsequent nitrifying trickling filter followed by a moving bed biofilm reactor (MBBR) for denitrification. Flotation makes up the final particle separation step. The samples for the present study are taken after the high loaded activated sludge plant.

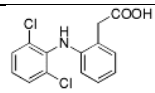
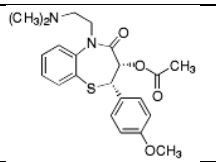
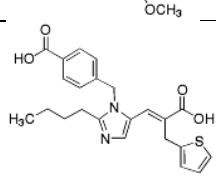
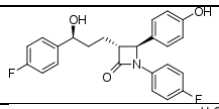
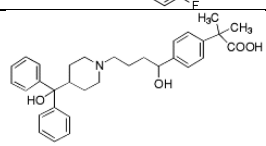
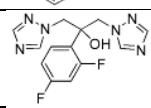
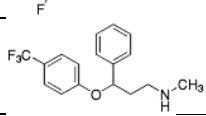
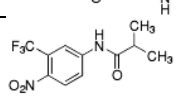
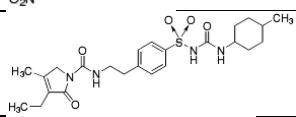
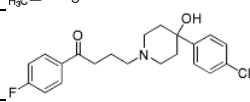
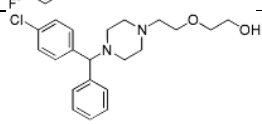
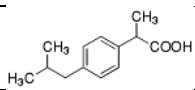
Öresundsverket WWTP in Helsingborg receives wastewater from 120,000 people and various industries. Incoming wastewater has annual average concentrations of approximately 180 mg/L BOD_7 and 30 mg/L Total Nitrogen. The wastewater is treated mechanically (screening, grit removal, and sedimentation) first. The primary sedimentation tanks are operated with primary sludge hydrolysis for the production of carbon source for enhanced biological phosphorous removal. Nitrogen removal and enhanced biological phosphorous removal takes place in a traditional UCT process. No chemicals for phosphorus removal are used at the plant.

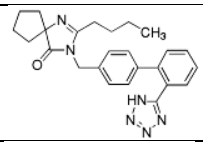
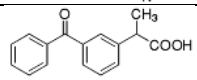
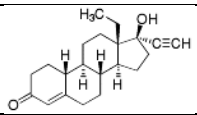
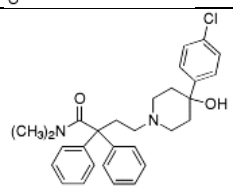
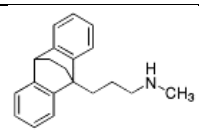
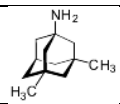
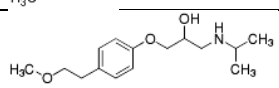
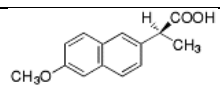
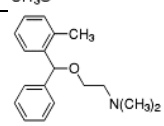
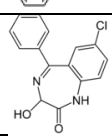
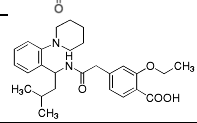
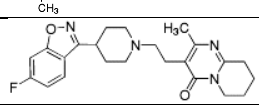
Björnstorp WWTP in Lund is a very small plant only receiving domestic wastewater from about 200 people. Incoming wastewater is diluted and has annual average concentrations of approximately 70 mg/L BOD_7 and 21 mg/L Total Nitrogen. The wastewater passes through a cutting pump prior to sedimentation in a pre-precipitation process; followed by activated sludge for BOD removal. The treated water is then soil infiltrated. In this study, samples were taken after activated sludge treatment.

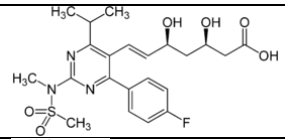
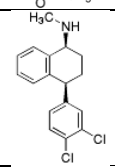
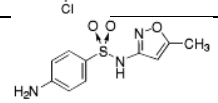
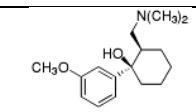
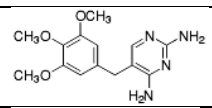
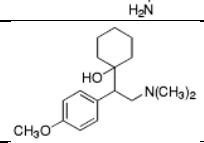
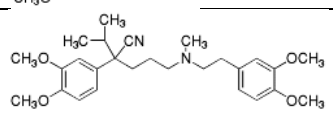
Nykvarnsverket WWTP in Linköping receives wastewater from 135,000 people and several industries. Incoming wastewater has annual average concentrations of approximately 280 mg/L BOD_7 and 45 mg/L Total Nitrogen. The wastewater is treated mechanically (screening, grit removal, and pre-precipitation) first. Then a low loaded activated sludge plant with nitrification only follows. Part of the nitrified effluent is diverted into a post-denitrification unit (Moving Bed Biofilm Reactor) where ethanol is used as carbon source. Finally all wastewater is treated in a post-precipitation plant for final polishing. In this study, samples were taken after the final post-precipitation stage.

Table S1: Structures* of the pharmaceuticals and estimated second order rate constants with O_3 and $HO^{\bullet}$.

Name	Structure	$k_{O3,API}$ ($M^{-1}s^{-1}$)	$k_{HO\bullet,API}$ ($M^{-1}s^{-1}$)	Referen-ces
amitriptyline				-
atracurium				-
beclomethasone				-
biperiden				-
bisoprol				-
bupropion				-
carbamazepine		$3 \cdot 10^5$	$(8.8 \pm 1.2) \cdot 10^9$	(Huber, 2003)
cilazapril				-
citalopram				-
clomipramine				-
codeine				-

diclofenac		10^6	$(7.5\pm 1.5)\cdot 10^9$	(Buffle, 2006; Huber, 2003)
diltiazem				-
eprosartan				-
ezetimibe				-
fexofenadine				-
fluconazole				-
fluoxetine				-
flutamide				-
glimepiride				-
haloperidole				-
hydroxyzine				-
ibuprofen		9.6	$7.4\cdot 10^9$	Buffle et al., 2006

irbesartan				-
ketoprofen		0.4±0.07		Real et al., 2009
levonorgestrel				-
loperamide				-
maprotiline				-
memantine				-
metoprolol		$(20\pm0.6)\cdot10^{3}$	$(7.3\pm0.2)\cdot10^{9}$	(Benner, 2008; Benner and Ternes, 2009)
naproxen		$2.62\cdot10^{4}$	$2.97\cdot10^{5}$	Benitez et al., 2009
orphenadrine				-
oxazepam				-
repaglinide				-
risperidone				-

rosuvastatin				-
sertraline				-
Sulfametho-xazole		$2.5 \cdot 10^{6}$	$(5.5 \pm 0.7) \cdot 10^{9}$	(Buffle, 2006; Huber, 2003)
tramadol				-
trimethoprim		$2.7 \cdot 10^{5}$	$(6.5 \pm 0.2) \cdot 10^{9}$	(Dodd, 2006)
venlafaxine				-
verapamil				-

*Chemical structures of the investigated APIs were taken from www.fass.se

Table S2: List of suppliers for APIs and the corresponding internal standards used for quantification.

APIs	Supplier	Internal standards	Supplier
Amitryptiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Atracurium	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Beclomethasone	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Biperiden	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Bisoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Bupropion	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Carbamazepine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Cilazapril	LGC Standards (Middlesex, UK)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Citalopram	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

Clomipramine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Codeine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diclofenac	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diltiazem	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Eprosartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Ezetimibe	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Fexofenadine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluconazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluoxetine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Fluoxetine	Cambridge Isotope Laboratories (Andover, MA, USA)
Flutamide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories

			(Andover, MA, USA)
Glimepiride	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Haloperidole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Hydroxyzine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ibuprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}$ - Ibuprofen	Cambridge Isotope Laboratories (Andover, MA, USA)
Irbesartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ketoprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}\,^{2}H_{3}$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)
Levonorgestrel	LGC Standards (Middlesex, UK)	$^{13}C_{2}$ – Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Loperamide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Maprotiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Memantine	Sigma-Aldrich (Steinheim,	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope

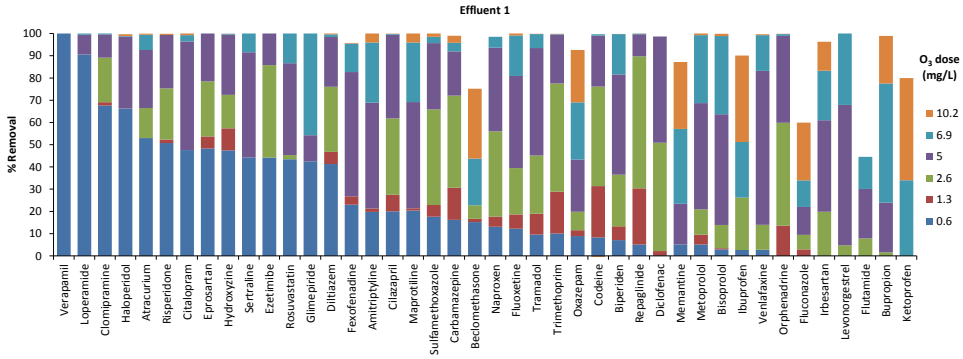
	Germany)		Laboratories (Andover, MA, USA)
Metoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Naproxen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3\ ^{2}H_3$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)
Orphenadrine	LGC Standards (Middlesex, UK)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Oxazepam	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Repaglinide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Risperidone	LGC Standards (Middlesex, UK)	$^{2}H_4$ - Risperidone	Sigma-Aldrich (Steinheim, Germany)
Rosuvastatin	CHEMOS GmbH (Regenstauf, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Sertraline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Sulfamethoxazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_6$ - Sulfamethoxazole	Cambridge Isotope Laboratories (Andover, MA, USA)
Tramadol	Sigma-Aldrich (Steinheim,	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope

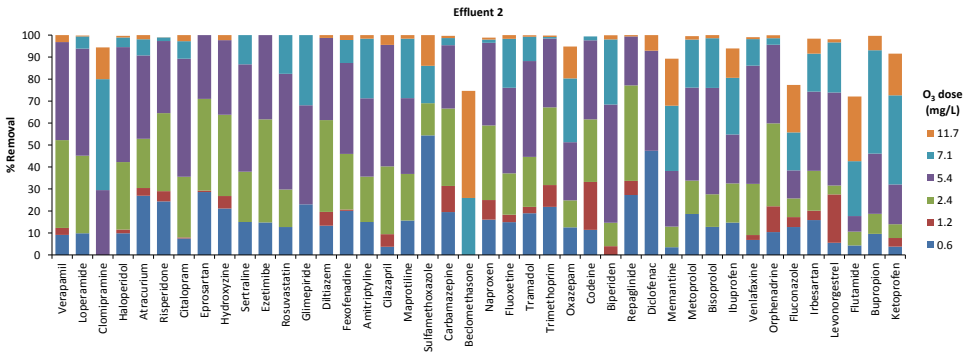
	Germany)		Laboratories (Andover, MA, USA)
Trimethoprim	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Venlafaxine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Verapamil	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

Table S3: Ionization mode, recoveries, relative standard deviation (RSD) and limit of quantification (LOQ) of the APIs.

API	Ionization mode	Recovery (average of triplicate)	RSD	LOQ
		%	%	ng/L
Amitryptiline	HESI	83.3	7.5	5
Atracurium	HESI	85.8	7.2	0.5
Beclomethasone	HESI	25.2	12.9	10
Biperiden	HESI	106	8.4	0.1
Bisoprolol	HESI	83.1	5.1	0.1
Bupropion	HESI	96.3	4.7	0.1
Carbamazepine	HESI	101	15.1	1
Cilazapril	HESI	143	5.9	1
Citalopram	HESI	83.6	8.5	5
Clomipramine	HESI	72.7	11.4	0.5
Codeine	HESI	86.7	24.0	0.5
Diclofenac	HESI	42.1	4.4	10
Diltiazem	HESI	107	3.8	0.5
Eprosartan	HESI	62.3	4.3	5
Ezetimibe	HESI	18.5	18.6	50
Fexofenadine	HESI	81.1	7.1	5
Fluconazole	HESI	89.8	12.9	0.5
Fluoxetine	HESI	97.0	11.4	5
Flutamide	HESI	91.8	3.9	5
Glimepiride	HESI	45.6	18.5	10
Haloperidole	HESI	64.0	12.7	0.1
Hydroxyzine	HESI	94.5	14.2	0.5
Ibuprofen	APPI	62.4	7.4	10
Irbesartan	HESI	109	2.6	0.5
Ketoprofen	APPI	73.2	7.4	10
Levonorgestrel	APPI	99.5	3.0	10
Loperamide	HESI	61.6	15.7	0.5
Maprotiline	HESI	84.1	7.4	5
Memantine	HESI	85.7	7.7	0.5
Metoprolol	HESI	82.9	1.3	5
Naproxen	APPI	95.5	4.5	10
Orphenadrine	HESI	94.7	11.2	0.1
Oxazepam	HESI	97.4	1.1	5
Repaglinide	HESI	93.4	8.6	0.5
Risperidone	HESI	101	2.4	0.1
Rosuvastatin	HESI	147	6.4	10

Sertraline	HESI	71.2	16.5	10
Sulfamethoxazole	HESI	97.3	4.3	5
Tramadol	HESI	129	6.3	0.5
Trimethoprim	HESI	109	10.7	0.1
Venlafaxine	HESI	96.2	7.8	0.5
Verapamil	HESI	85.5	8.8	10


Effluent 1
% Removal
O3 dose (mg/L)
10.2
6.9
5
2.6
1.3
0.6
Verapamil
Loperamide
Clomipramine
Haloperidol
Atracurium
Risperidone
Citalopram
Eprosartan
Hydroxyzine
Sertraline
Ezetimibe
Rosuvastatin
Glimepiride
Diltiazem
Fexofenadine
Amitriptyline
Cilazapril
Maprotiline
Sulfamethoxazole
Carbamazepine
Beclomethasone
Naproxen
Fluoxetine
Tramadol
Trimethoprim
Oxazepam
Codeine
Biperiden
Repaglinide
Diclofenac
Memantine
Metoprolol
Bisoprolol
Ibuprofen
Venlafaxine
Orphenadrine
Fluconazole
Irbesartan
Levonorgestrel
Flutamide
Bupropion
Ketoprofen


Effluent 2
% Removal
O3 dose (mg/L)
11.7
7.1
5.4
2.4
1.2
0.6
Verapamil
Loperamide
Clomipramine
Haloperidol
Atracurium
Risperidone
Citalopram
Eprosartan
Hydroxyzine
Sertraline
Ezetimibe
Rosuvastatin
Glimepiride
Diltiazem
Fexofenadine
Amitriptyline
Cilazapril
Maprotiline
Sulfamethoxazole
Carbamazepine
Beclomethasone
Naproxen
Fluoxetine
Tramadol
Trimethoprim
Oxazepam
Codeine
Biperiden
Repaglinide
Diclofenac
Memantine
Metoprolol
Bisoprolol
Ibuprofen
Venlafaxine
Orphenadrine
Fluconazole
Irbesartan
Levonorgestrel
Flutamide
Bupropion
Ketoprofen

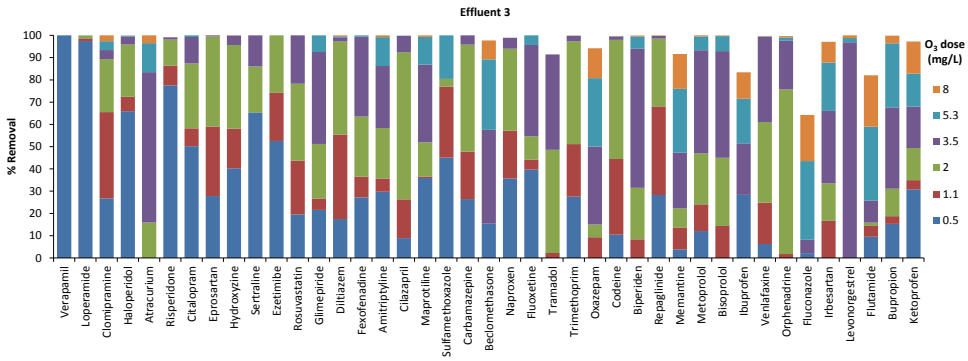

Effluent 3
% Removal
O3 dose (mg/L)
8
5.3
3.5
2
1.1
0.5
Verapamil
Loperamide
Clomipramine
Haloperidol
Atracurium
Risperidone
Citalopram
Eprosartan
Hydroxyzine
Sertraline
Ezetimibe
Rosuvastatin
Glimepiride
Diltiazem
Fexofenadine
Amitriptyline
Cilazapril
Maprotiline
Sulfamethoxazole
Carbamazepine
Beclomethasone
Naproxen
Fluoxetine
Tramadol
Trimethoprim
Oxazepam
Codeine
Biperiden
Repaglinide
Memantine
Metoprolol
Bisoprolol
Ibuprofen
Venlafaxine
Orphenadrine
Fluconazole
Irbesartan
Levonorgestrel
Flutamide
Bupropion
Ketoprofen

Figure S1: Profiles of dose dependency for the removal of pharmaceuticals in the 6 investigated wastewaters.

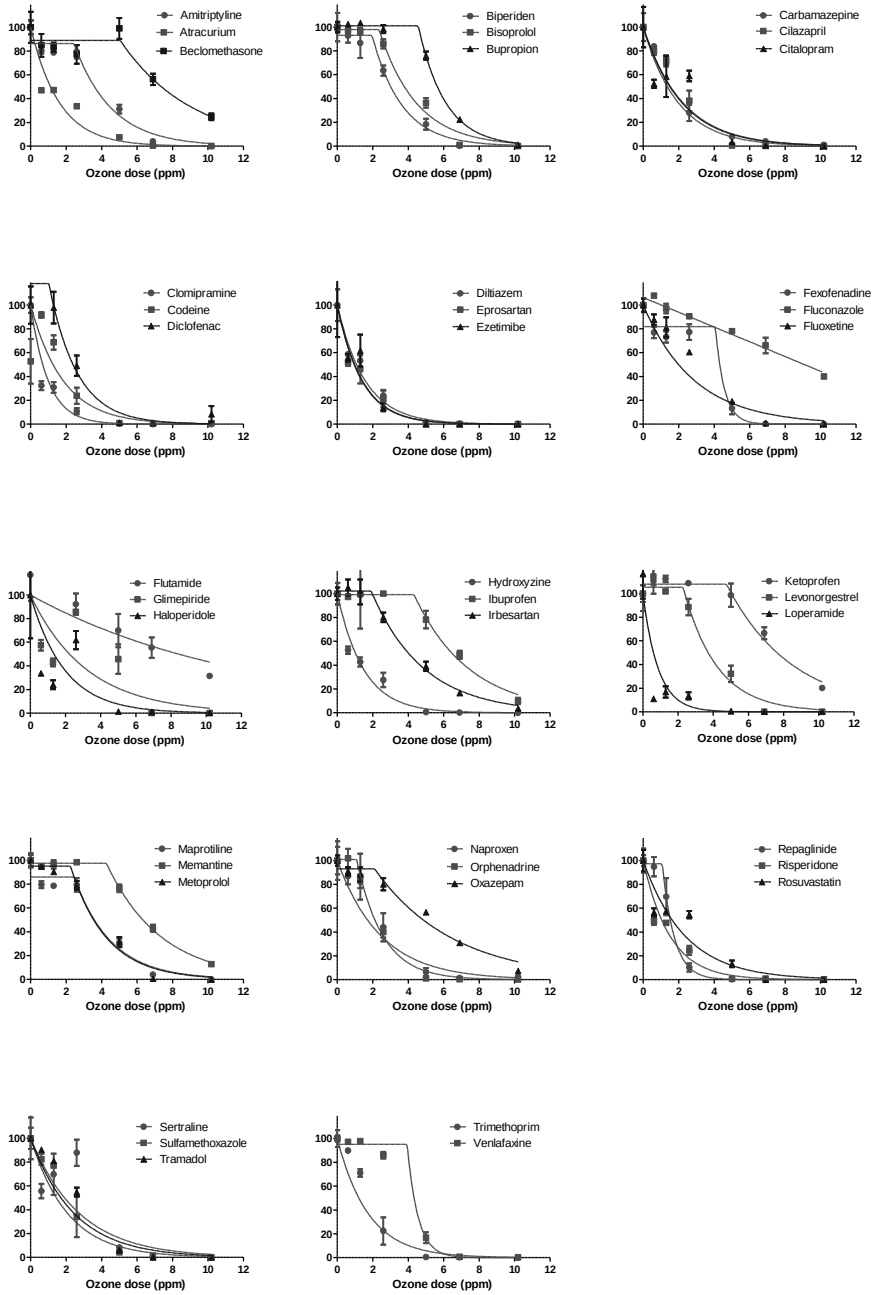


Figure S2: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 1. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

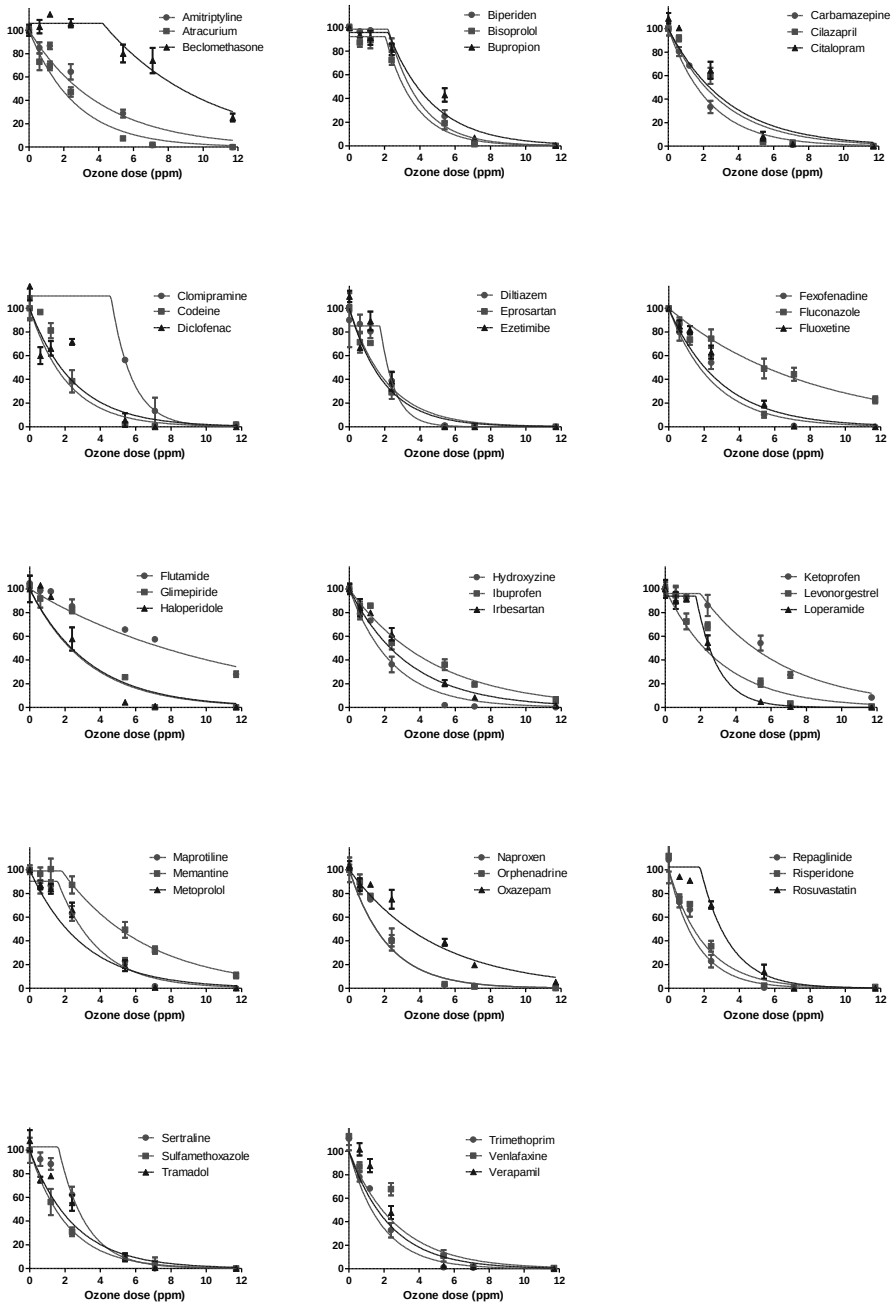


Figure S3: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 2. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

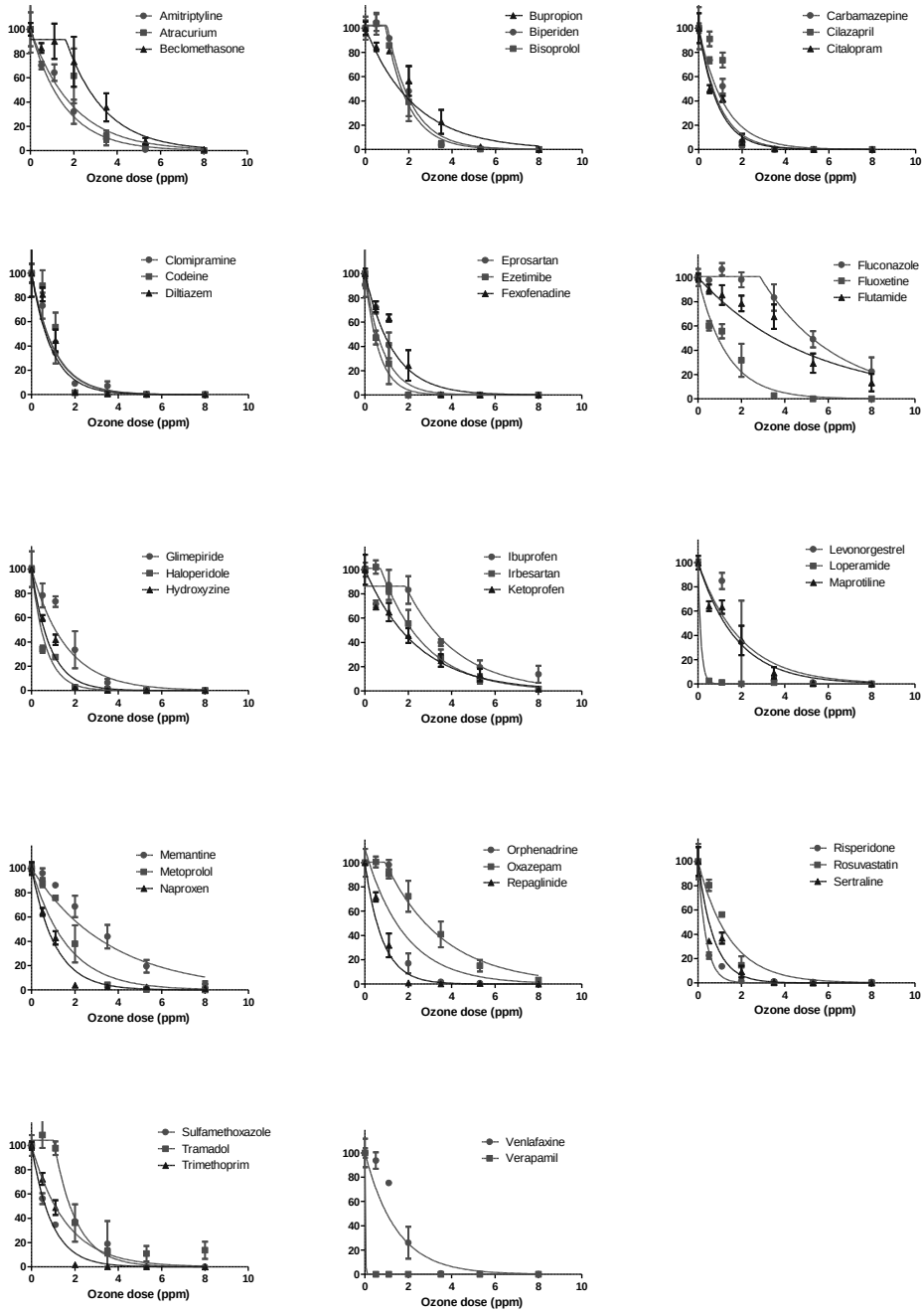


Figure S4: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 3. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

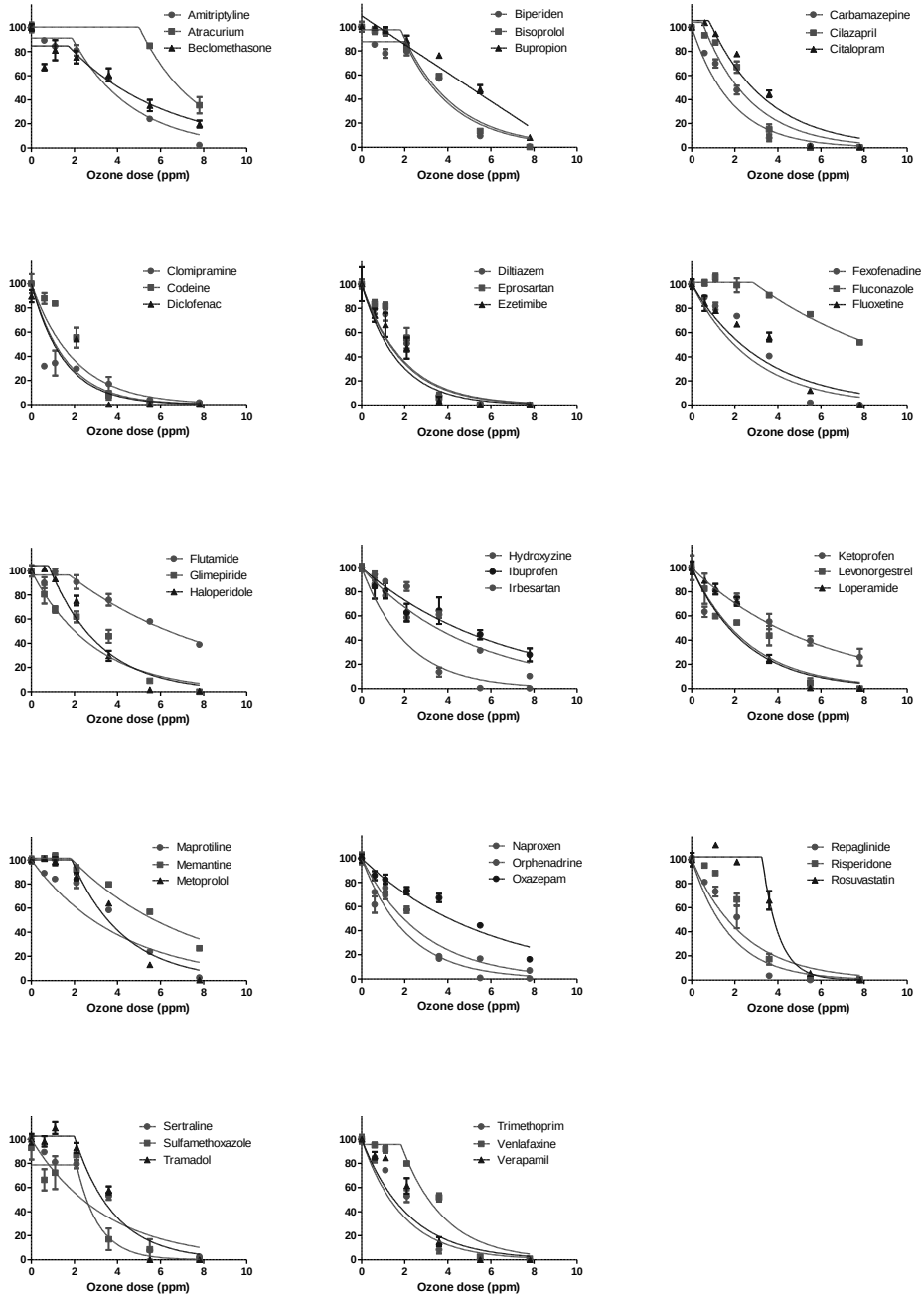


Figure S5: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 4. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

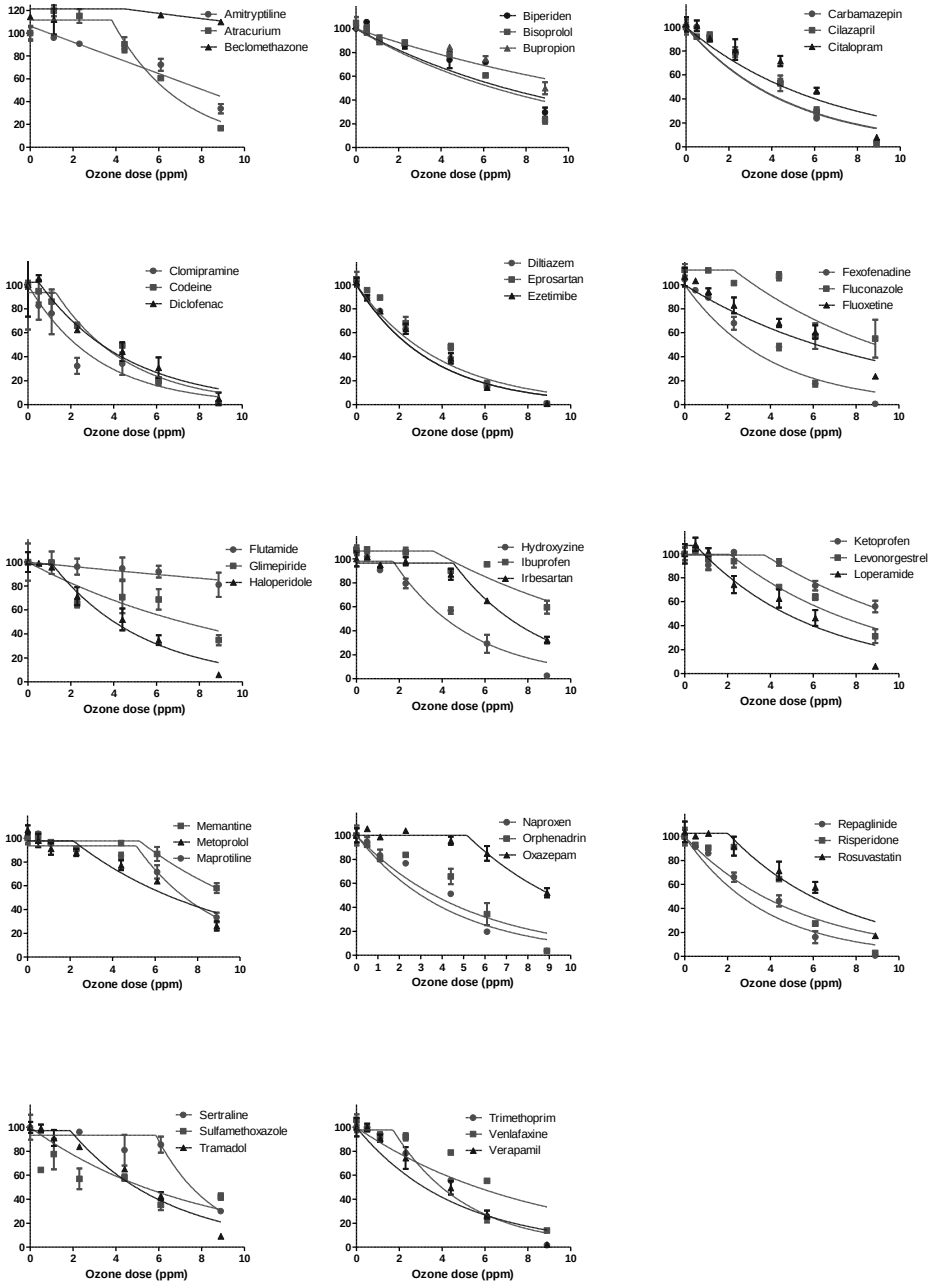


Figure S6: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 5. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

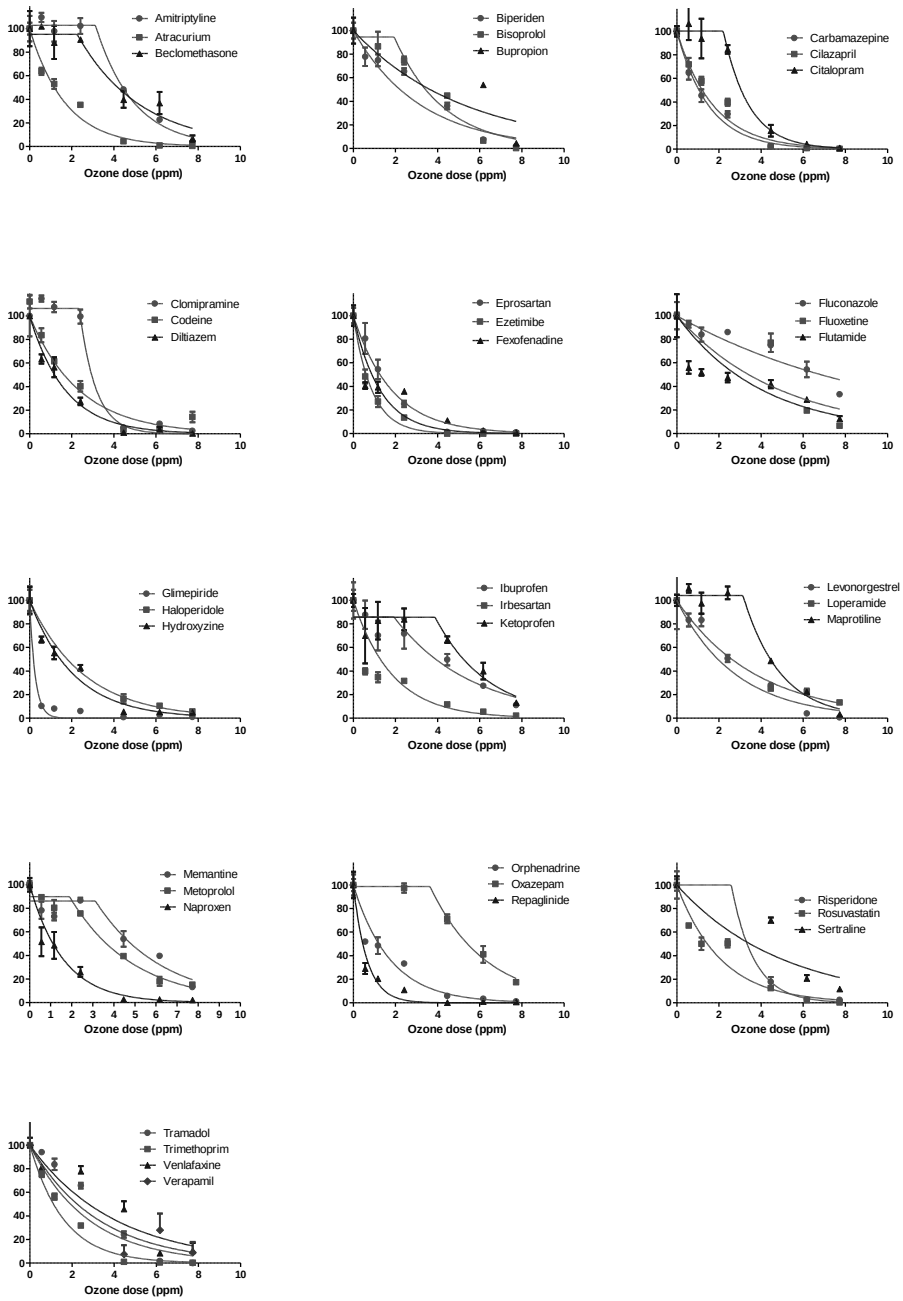


Figure S7: Fraction of remaining API concentrations (Y axis) and the corresponding ozone dose in WWTP Effluent 6. The T-bar indicates the standard error of the mean calculated from triplicate experiments performed at each ozone dose.

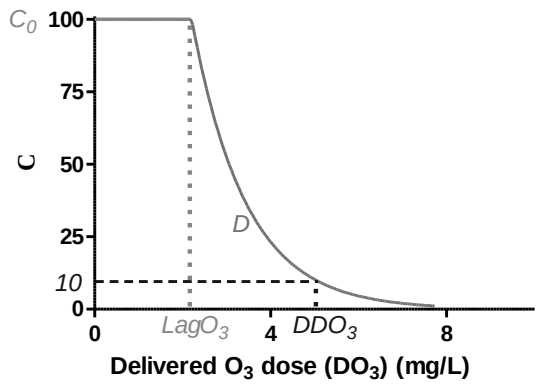


Figure S8: Graphical representation showing how the experimental data were fitted to predict the DDO3 based on Eqs. 3 and 4.

Paper IV

Removal of pharmaceuticals in WWTP effluents by ozone and hydrogen peroxide

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Abstract

The ozonation of wastewater effluents with pH values in the upper and lower part of the typical range for Swedish wastewater was investigated. The aim was to study the effects of differences in pH (6.0 and 8.0) and of small additions of H_2O_2 prior to ozone treatment on the removal of pharmaceuticals, and to evaluate the possibilities of promoting the decomposition of ozone to OH radicals and the effect this can have on the removal of pharmaceuticals. The effluents selected differed in their chemical characteristics, particularly in terms of alkalinity (65.3-427 mg HCO_3^-/L), COD (18.2-41.8 mg/L), DOC (6.9-12.5 mg/L), ammonium (0.02-3.6 mg/L) and specific UV absorbance (1.78-2.76 L/mg×m). Lower ozone decomposition rates were observed at pH 6.0 than at pH 8.0. The addition of H_2O_2 at pH 6.0 increased the decomposition rate, indicating that production of OH radicals was promoted. When pH 8.0 effluents were ozonated, a higher degree of pharmaceutical removal occurred in those with a low than in those with a high specific UV absorbance. For pH 6.0 effluents, the removal of pharmaceuticals was most efficient in the effluent with low COD and in the same range as in the pH 8.0 effluent with low specific UV absorbance. The addition of H_2O_2 had no significant effect on the removal of pharmaceuticals but enhanced the ozone decomposition

rate. Thus, the addition of H_2O_2 can reduce the reactor volume needed for the ozonation of wastewater effluents.

Keywords: ozonation; pharmaceuticals; specific UV absorbance; wastewater effluents

Introduction

A number of pharmaceuticals of differing therapeutic class together with their metabolites have been detected in aquatic environments (Ternes 1998; Kolpin et al. 2002; Fent et al. 2006; Batt et al. 2006; Snyder 2008; Verlicchi et al. 2012). The major source of these pharmaceuticals is considered to be the discharge of effluents by wastewater treatment plants (WWTPs) that are not designed for removing trace organic pollutants in view of the recalcitrance of such pollutants to biodegradation and their limited biological activity, especially in cold climates. Accordingly, additional treatment following biological treatment is called for.

Ozonation is one of the most promising technologies for the removal of organic micropollutants contained in wastewater. The efficiency of ozone in removing pharmaceuticals and personal care products both from water generally and from wastewater has been tested in both laboratory- and pilot-scale experiments (Ternes et al. 2003; Huber et al. 2005; Buffle et al. 2006a,b; Bahr et al. 2007; Benner and Ternes 2009; Hollender et al. 2009; Hansen et al. 2010; Zimmermann et al. 2011). Ozone-based oxidation can be more energy-efficient than UV-based oxidation, especially when used for treatment of waters high in UV absorbance (Rosenfeldt et al. 2006; Hansen and Andersen 2012).

One of the benefits of using ozonation in aqueous solutions is that the hydroxyl (OH) radicals that are produced react non-selectively with pharmaceuticals that are difficult to degrade (Lee and von Gunten 2010). The OH radicals can be generated through the self-decomposition of ozone in water matrix at pH levels above 7, the hydroxide ions acting as initiators (Hoigne and Bader 1983). The addition of hydrogen peroxide (H_2O_2) catalyzes the decomposition of ozone promoting the production of OH radicals (von Gunten 2003). Non-selective oxidation by highly reactive radicals usually enhances the rate of oxidation of ozone-resistant compounds, reducing the treatment time required (Zwiener and Frimmel 2000; Huber et al. 2003). Balcioglu and Ötker (2003) reported that adding H_2O_2 enhances both the UV absorbance (at 254 nm) and the COD removal of wastewater. The rapid reaction of OH radicals is preferable in practice since it reduces the reactor size needed for such treatment. The efficiency of ozone treatment for the removal of pharmaceuticals can also depend upon the reactivity of the wastewater matrix in general (Nöthe et al. 2009). Depending upon the wastewater characteristics, the removal of a large fraction of pharmaceuticals may

require a relatively large ozone dose, since ozone can be consumed by other organic compounds.

The present study aimed at investigating the impact of different pH levels on the removal of pharmaceuticals from wastewater effluents by the addition of ozone, and also at evaluating the extent to which the reactivity of ozone can be promoted by the addition of small amounts of H_2O_2 at low pH levels. Since the addition of H_2O_2 can be expected to catalyze the decomposition of ozone to OH radicals, it can be of interest to investigate the effect this has in the case of effluents with a pH below 7, where the reaction rate can be expected to be lower and the pharmaceutical removal rate lower due to the lack of hydroxide ions that promote the decomposition of ozone.

Materials and methods

Overall experimental setup

Two effluents of relatively high pH (pH 8.0) were treated with ozone, whereas two other effluents, low in pH (pH 6.0) were treated with ozone in combination with H_2O_2. Treatment was carried out at these pH levels since they correspond to the upper and the lower range of pH values typically found in Swedish WWTP effluents. The effluents selected are from plants with extended nitrogen and phosphorous removal. The difference in pH is due to the origin of the potable water (ground versus surface waters). Further, the effluents also differ with respect to other chemical parameters such as alkalinity and ammonium and organic matter content. The pharmaceuticals investigated represent different therapeutic classes commonly used in Sweden, most of them having been found to be present in WWTP effluents (Falås et al. 2012).

The production of OH radicals by ozone decomposition was followed indirectly through measuring the ozone concentration. The experiments were carried out initially in effluents with a pH range of between 5 and 8 with the aim to determine the minimum amount of H_2O_2 needed to increase the decomposition of ozone.

Chemicals

The H_2O_2 solution (30%) employed was purchased from Sigma-Aldrich, the NaOH and H_2SO_4 being purchased from Merck (Germany). The pharmaceutical reference standards were purchased from different suppliers as analytical grade (> 98%) solids (Supplementary Information Table S1). The stock solution of pharmaceuticals was prepared in methanol at a concentration of 100 mg/L. The ozone stock solution was prepared in purified water (Millipore-Billerica, MA) as described in Antoniou and Andersen (2012).

WWTP effluents

The biologically-treated wastewater effluents investigated, differing in their characteristics and representing the typical variations in alkalinity, pH, and organic matter and ammonium content, were taken from four municipal WWTPs in Sweden: Öresundsverket (Effluent 1), Klagshamn (Effluent 2), Uppsala (Effluent 3) and Käppala (Effluent 4). The effluent samples differed from one another in pH on the day of collection and were adjusted at the start of the experiment by use of either NaOH or H_2SO_4 so as to be exactly pH 6.0 or pH 8.0. Table 1 shows the quality parameters of the effluents.

Table 1. Quality parameters of the effluent wastewaters studied.

WWTPs	Öresundsverket	Klagshamn	Uppsala	Käppala
	Effluent 1	Effluent 2	Effluent 3	Effluent 4
	High pH	High pH	Low pH	Low pH
COD, mg/L	41.8	32.4	18.2	35.4
DOC, mg/L	9.2	9.0	6.9	12.5
Initial alkalinity, mg HCO_3^-/L	347.7	427	79.9	65.3
NH_4^+-N, mg/L	0.04	0.29	0.02	3.6
UV abs_{254nm}, m^{-1}	16.4	24.8	16.0	29.5
pH (initial)	7.2	7.6	6.6	6.3
pH (adjusted)	8.0	8.0	6.0	6.0
SUVA, L/mg·m	1.78	2.76	2.31	2.36

Analysis

COD and NH_4^+-N were determined by use of the Hach Lange test kits LCK 114 and LCK 304. To measure alkalinity, a 25 ml sample was titrated with 0.05 M HCl to a pH of 4.5, the alkalinity in mg HCO_3^-/L being calculated then. DOC was measured on the basis of wet chemical oxidation, using a Shimadzu TOC-Vwp analyzer. The UV-absorbance at 254 nm was measured using a Varian CARY50 Bio UV-Vis spectrophotometer. The specific UV absorbance (SUVA), an indicator of the dissolved aromatic carbon that the wastewater contains, known to affect the reactivity of DOC to ozone, was determined by normalizing UV absorbance at 254 nm to the DOC concentration (Weishaar et al. 2003). The O_3 doses delivered were analyzed by the colorimetric method of indigo (λ = 600 nm)

through preparing bottles of indigo trisulfonate solution in Milli-Q water in parallel with the treatment samples (Bader and Hoigne 1981; Antoniou and Andersen 2012).

For pharmaceutical analysis, 100 ml samples of the treated effluent were filtered through a 0.45 µm membrane filter (Millipore) and were acidified to pH 3 by use of sulfuric acid. After SPE extraction, LC/MS/MS analysis of the extracts was carried out, using a triple-stage quadrupole MS/MS TSQ Quantum Ultra EMR (Thermo Fisher Scientific, USA) coupled with an Accela LC pump (Thermo Fisher Scientific, USA) and a PAL HTC autosampler (CTC Analytics AG, Switzerland) having a Hypersil GOLD aQTM column (50 mm x 2.1 mm ID x 5 µm particles, Thermo Fisher Scientific, USA). The method of analysing pharmaceuticals was used earlier by Hörsing et al. (2011) and Hey et al. (2012). A detailed description and a full method evaluation are presented in Grabic et al. (2012). The ionization mode, recoveries, relative standard deviations (RSD) and limit of quantification (LOQ) of the pharmaceuticals are given in the Supplementary Information Table S2.

Experimental setup

For the ozone consumption experiments carried out, the biologically-treated municipal wastewater was ozonated at different pH levels and O_3 to H_2O_2 ratios. Samples were taken at different reaction times for analysis of the O_3 content. For experiments involving pharmaceutical removal, the wastewater effluents from four WWTPs were spiked with pharmaceuticals so as to provide a nominal concentration of ~1 µg/L. The spiked effluents were transferred then into borosilicate glass bottles (Schott Duran®) to which different volumes of O_3 stock solution were added to provide, in each case, a nominal concentration of between 1.4 and 10.7 mg/L O_3 for a total sample volume of 150 mL. The bottles were covered with aluminum foil and were placed for 2 hours in a 15°C water bath. For the O_3 and H_2O_2 experiments that were conducted, the H_2O_2 was added just prior to the addition of ozone. All treatment tests conducted were run in triplicates, a relative standard deviation of up to 20% between replicates being considered for data treatment.

Results and discussion

Determination of ozone concentration profiles at different pH

At each of the pH levels (pH 5-8) tested, the ozone concentration in the effluents decreased rapidly during the first minute after the addition of ozone. Thereafter, the rate of ozone decomposition decreased gradually and stabilized. This relatively fast ozone consumption was to be expected, due to the matrix components of the

wastewater consuming the oxidant. In addition, as can been seen in Figure 1, the decomposition of ozone tended to proceed faster at the highest pH value (pH 8) than at the lowest value tested (pH 5), in accordance with the results of other studies, such as those of Hoigne and Bader (1981) concerning water spiked with organic compounds and of Elovitz et al. (2000) concerning different surface and ground waters.

When H_2O_2 was added to the effluents at H_2O_2/O_3 ratios ranging from 2 to 0.25 (Figure 1), the added ozone was almost completely consumed during the first minute. As could be expected, the effluent of high pH (pH 8) exhibited the fastest ozone decomposition rate (< 1 minute) (Figure 1B). To confirm this, an additional experiment was also carried out at pH 6.0, involving use of a rather high initial ozone dose and lower doses of H_2O_2, this resulting in significantly lower H_2O_2/O_3 ratios of 0.05-0.10. As can be seen in Figure 1C, the differences between the samples in the ozone removal rate are most obvious in the first minute or so of treatment, the decomposition of ozone appearing to increase with an increase in the H_2O_2/O_3 ratio for around 2 minutes, after which nearly all of the ozone appeared to have been consumed.

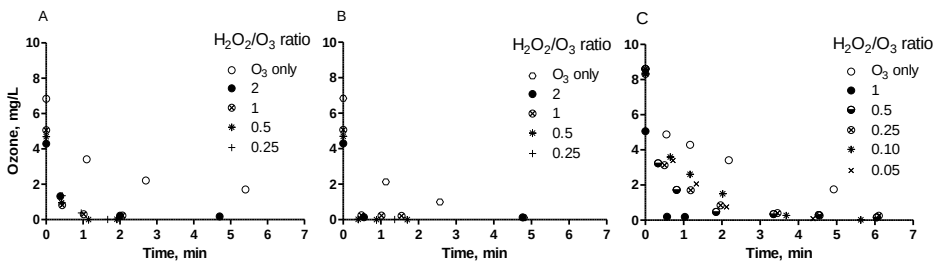

Figure 1. Ozone consumption in the WWTP effluent at pH 5 (A), at pH 8 (B) and at pH 6 (C) for different doses of H_2O_2.

O_3 concentration profiles in the WWTP effluents tested

On the basis of the findings, even the addition of relatively small amounts of H_2O_2 is able to change the ozone concentration profile appreciably. To investigate this further, a set of experiments was carried out using four different effluent wastewaters (Table 1), two having a relatively high pH and two a relatively low pH. The effluents, after pH adjustments to 8.0 and 6.0, respectively, were treated with ozone so as to follow its decomposition (Figures 2A and 2B). In the high pH effluents (Figure 2A), about half of the ozone was already consumed during the first minute, especially in the case of Effluent 2. The differences observed were found to be related to the higher SUVA content in Effluent 2 than in Effluent 1 (Table 1). The relatively high content of aromatic compounds, indicated by the

relatively high SUVA level, could explain the increased ozone consumption in the early stages of treatment, due to fast reactivity of aromatic compounds. Such was also observed by Westerhoff et al. (1999). At pH 6.0, in contrast, Effluent 3 appears to have a much lower ozone demand than Effluent 4 (Figure 2B), this probably being due to the lower organic content of Effluent 3, which is only about half that of Effluent 4. Similar to what can be seen above (Figure 1), the addition of H_2O_2 to the effluent led to an increased decomposition of ozone, measured as decline in ozone concentration.

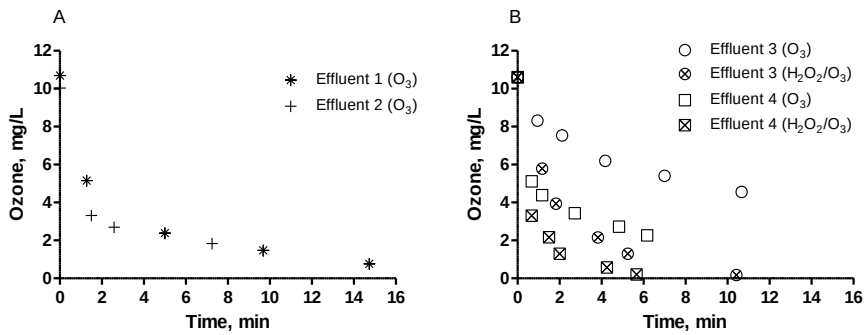

Figure 2. Ozone consumption in WWTP effluents (A) at pH 8.0 without H_2O_2 and (B) at pH 6.0, both with H_2O_2 (at a H_2O_2/O_3 ratio of 0.10) and without.

These findings show it to be important, when employing ozonation, to investigate the initial ozone demand of the wastewater. The present findings also show that at low pH the combination of ozone and H_2O_2 reduces the reaction time, this also indicating it to be possible to reduce the size of the reaction tank employed for treatment.

Removal of pharmaceuticals by O_3 and H_2O_2

In ozonation of pH 8.0 effluents there was found to be significant reduction in the different pharmaceuticals especially in the case of Effluent 1 (Figure 3A), already at relatively low doses of ozone. At the lowest dose (1.5 mg/L O_3), 9 of the 40 pharmaceuticals (clomipramine, sulfamethoxazole, repaglinide, ethinyl estradiol, fexofenadine, codeine, naproxen, diltiazem and eprosartan) were already removed to 90-100%, only 8 of the pharmaceuticals (bupropion, oxazepam, levonorgestrel, memantine, fluconazole, flutamide, ketoprofen and ibuprofen) exhibiting < 50% removal. As the ozone dose was increased, most of the pharmaceuticals including the less reactive ones too were degraded.

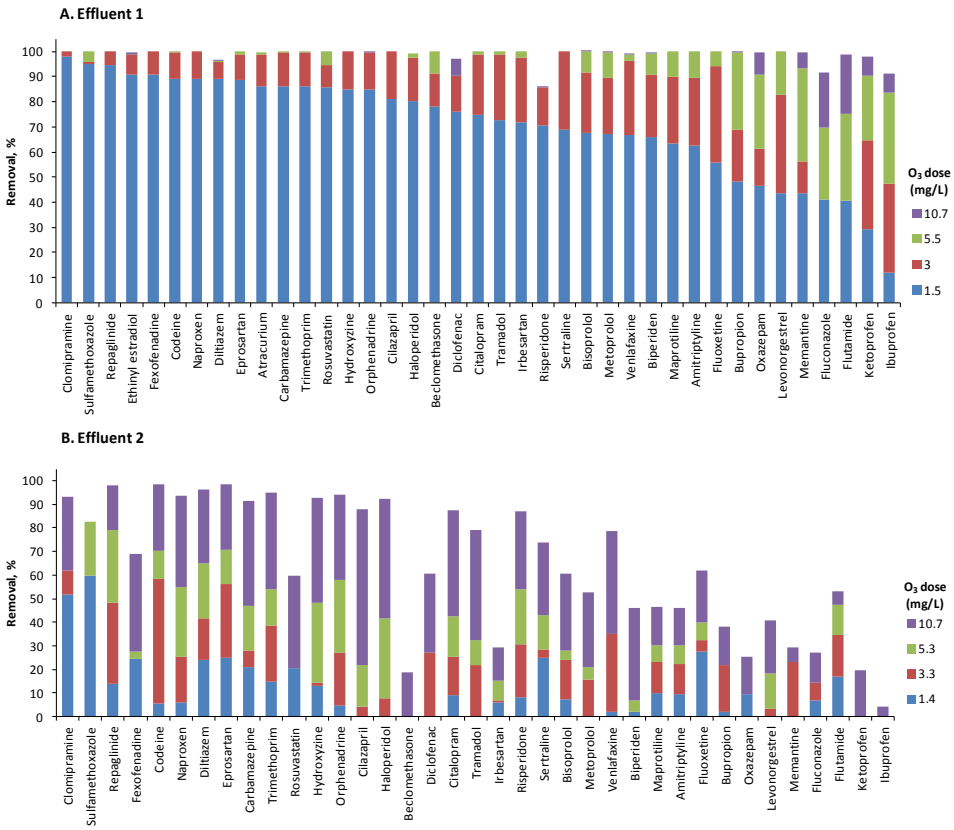

Figure 3. The contribution of each level of ozone dose to the removal of pharmaceuticals in Effluent 1 (A) and in Effluent 2 (B) during ozonation at pH 8.0.

On the other hand, in Effluent 2 (Figure 3B) the pharmaceuticals were poorly removed, even when the O_3 dose was increased. This can be attributed to the high SUVA level (2.76 as compared with 1.78) of this effluent. The high ozone reactivity of the aromatic components of the DOC may have contributed to the decrease in pharmaceutical removal in Effluent 2. In contrast, in Effluent 1, for which COD is high and SUVA is low, the pharmaceuticals appear to be more susceptible to indirect ozone reaction, initiated by secondary oxidants such as OH radicals, produced by the reaction of ozone with the organic components of the wastewater. According to Huber et al. (2003), a high concentration of organic components in the wastewater can enhance the decomposition of ozone so as to produce more OH radicals, a matter that could have a positive effect on pharmaceutical removal. Also, as can be observed in Figure 3, some of the

pharmaceuticals in Effluent 1 exhibited a high level of removal in response to the lowest ozone dose but did not follow the same pattern of removal in Effluent 2. For example, both clomipramine and repaglinide showed a high degree of removal at the lowest ozone dose, yet when treated with the same O_3 dose in Effluent 2, it was only clomipramine for which the degree of removal was significant (~50%). This shows clearly that both the level of removal and the reactivity of pharmaceuticals can vary, depending upon the composition of the wastewater involved.

The efficiency of ozone in removing pharmaceuticals from pH 6.0 effluents (Figure 4A) showed that ozone alone could remove > 90% of half of the pharmaceuticals present in Effluent 3 at the lowest ozone dose (1.8 mg/L). When the dose was increased to 4.4 mg/L, all of the pharmaceuticals except for fluconazole were degraded by over 90%. A still further increase in the ozone dose resulted in over 99% removal of all of the pharmaceuticals, except for fluconazole (93%) and ibuprofen (96%). In contrast, the ozonation of Effluent 4 resulted in > 90% degradation of the pharmaceuticals when rather high doses of ozone (> 5 mg/L) were employed (Figure 4B).

Figure 5 illustrates the contribution that the addition of H_2O_2 can make to the removal of those pharmaceuticals that have been shown to have the lowest reactivity towards ozone. For fluconazole (Effluent 3), as can be seen, there was only a slight increase in removal after the addition of H_2O_2, whereas for ibuprofen no improvement in its removal occurred. Thus, the addition of H_2O_2 (at an H_2O_2/O_3 ratio of 0.08-0.13) to an initial ozone dose of 10 mg/L could not be expected to have any appreciable impact on the removal of pharmaceuticals. For Effluent 4, the addition of H_2O_2 was found to enhance the removal of ibuprofen, fluconazole, levonorgestrel, sulfamethoxazole and ketoprofen by 4-16% but it reduced naproxen removal by ~15%. The overall findings here show that the reaction time can be reduced when ozone is combined with small amounts of H_2O_2, this being advantageous when practical implementation of the technology takes place. For most pharmaceuticals, however, this addition has no impact on the removal efficiency, i.e. neither increasing nor decreasing removal.

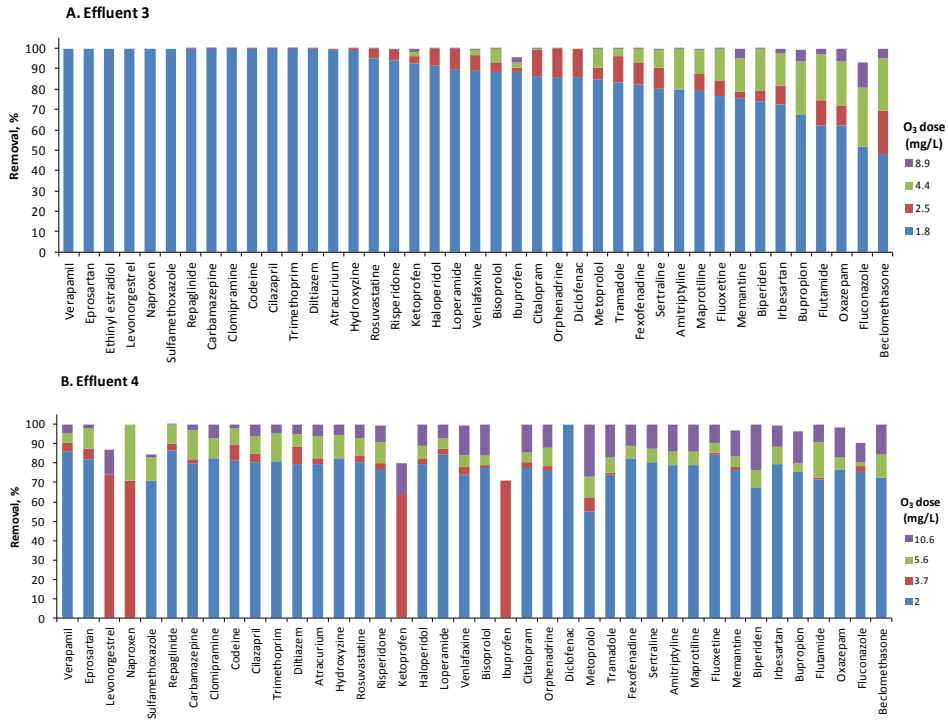

Figure 4. The contribution of each level of ozone dose to the removal of pharmaceuticals in Effluent 3 (A) and in Effluent 4 (B) during ozonation at pH 6.0.

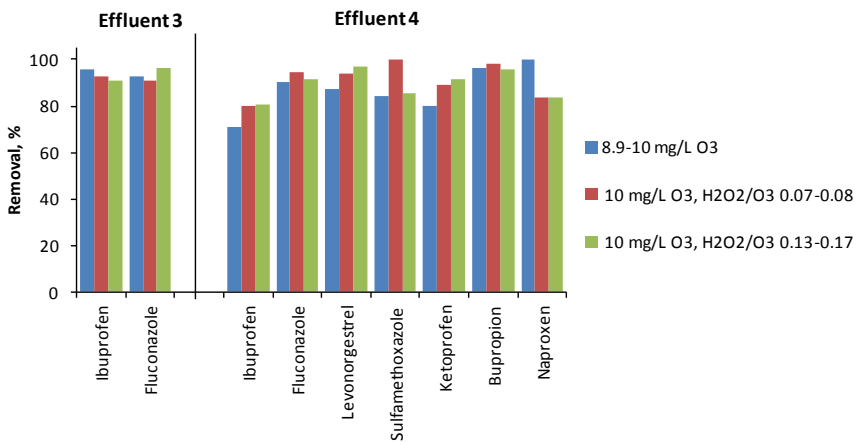

Figure 5. The contribution of the addition of H_2O_2 to the removal of pharmaceuticals less reactive to ozone in Effluent 3 and Effluent 4.

The majority of pharmaceuticals included in this study contained acidic and/or basic groups, their thus having different charges (positive, neutral or negative) and, as a result, their possibly also differing in their tertiary chemical structure as a function of pH. The pharmaceuticals that are acids are protolysed at pH 6, no further changes occurring then when pH is increased to 8. In contrast, those pharmaceuticals that are bases and thus have low pK_a values go from being unprotolysed at pH 6 to being protolysed at pH 8, the charge thus changing from positive to neutral, which can result in a change in the tertiary structure. Those pharmaceuticals having both acidic and basic groups may also undergo changes in the charge and in their tertiary structure. This can be thought to have an impact on the oxidation rate. It is not possible, however, on the basis of the experiments carried out here, to draw any final conclusions regarding this.

Table 2 provides an overview of the findings regarding removal efficiencies for the pharmaceuticals that were investigated. It can readily be seen that an ozone dose of around 5 mg/L is sufficient to remove over half of the target pharmaceuticals, except in the case of Effluent 2, in which a higher ozone dose may be required for removing a large fraction of the pharmaceuticals, this most likely being due to the higher SUVA level it posseses. At the same time, it appears that, in the case of wastewaters such as Effluent 3 that are low in pH, a reasonable dose of ozone for being able to remove over 90% of the pharmaceuticals is one of 5 mg/L.

Table 2. Pharmaceuticals for which at least 90% removal (✓) occurs in each of the effluents when treated with ~5 mg/L O_3. (NA = compound not quantified)

	(High pH)		(Low pH)			(High pH)		(Low pH)	
Pharmaceuticals	Eff 1	Eff 2	Eff 3	Eff 4	Pharmaceuticals	Eff 1	Eff 2	Eff 3	Eff 4
Amitriptyline	✓	—	✓	✓	Hydroxyzine	✓	—	✓	✓
Atracurium	✓	NA	✓	✓	Ibuprofen	—	—	✓	
Beclomethasone	—	—	✓	—	Irbesartan	✓	—	✓	✓
Biperiden	—	—	✓	—	Ketoprofen	—	—	✓	—
Bisoprolol	—	—	✓	—	Levonorgestrel	—	—	✓	—
Bupropion	—	—	✓	—	Loperamide	NA	✓	✓	✓
Carbamazepine	✓	—	✓	✓	Maprotiline	✓	—	✓	✓

Cilazapril	✓	—	✓	✓	Memantine	—	—	✓	—
Citalopram	✓	—	✓	✓	Metoprolol	—	—	✓	—
Clomipramine	✓	—	✓	✓	Naproxen	✓	—	✓	✓
Codeine	✓	—	✓	✓	Orphenadrine	✓	—	✓	✓
Diclofenac	✓	—	✓	✓	Oxazepam	—	—	✓	—
Diltiazem	✓	—	✓	✓	Repaglinide	✓	—	✓	✓
Eprosartan	✓	—	✓	✓	Risperidone	✓	—	✓	✓
Ethinyl estradiol	✓	NA	✓	NA	Rosuvastatin	✓	—	✓	✓
Fexofenadine	✓	—	✓	✓	Sertraline	✓	—	✓	✓
Fluconazole	—	—	—	—	Sulfamethoxazole	—	—	✓	—
Fluoxetine	✓	—	✓	✓	Tramadol	—	—	✓	—
Flutamide	✓	—	✓	✓	Trimethoprim	✓	—	✓	✓
Haloperidol	✓	—	✓	✓	Venlafaxine	✓	—	✓	—

The oxidation of pharmaceuticals can lead to the production of by-products. Since these can be toxic to varying degree as compared with the mother compound, toxicity evaluation of a given technology should be performed before it is considered for implementation.

Conclusions

The following conclusions can be drawn on the basis of the results of the study:

- Ozonation can be employed as an additional treatment step to enable trace pharmaceuticals to be removed effectively from wastewater effluents.
- The amount of ozone required for the removal of pharmaceuticals is dependent upon the chemical composition of the wastewater, and on the target compounds, the content of organic matter in general and its aromaticity being of considerable importance here.
- Ozone decomposition can be stimulated by adding hydrogen peroxide at low pH. This reduces the treatment time and, accordingly, the reaction volume needed. Since the addition of hydrogen peroxide has only a limited impact on the removal of pharmaceuticals, it has no negative effects in terms of reducing the reactor volume.

Acknowledgements

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Supplementary Information: Removal of pharmaceuticals in WWTP effluents by ozone and hydrogen peroxide

Table S1: List of suppliers for pharmaceuticals and the corresponding internal standards used for quantification.

Pharmaceuticals	Supplier	Internal standards	Supplier
Amitryptiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Atracurium	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Beclomethasone	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{5}$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Biperiden	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Bisoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Bupropion	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Carbamazepine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Cilazapril	LGC Standards	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge

	(Middlesex, UK)		Isotope Laboratories (Andover, MA, USA)
Citalopram	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Clomipramine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Codeine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diclofenac	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diltiazem	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Eprosartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Ethinyl estradiol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_2$ - Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Fexofenadine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories

			(Andover, MA, USA)
Fluconazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluoxetine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Fluoxetine	Cambridge Isotope Laboratories (Andover, MA, USA)
Flutamide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Haloperidol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Hydroxyzine	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ibuprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Ibuprofen	Cambridge Isotope Laboratories (Andover, MA, USA)
Irbesartan	CHEMOS GmbH (Regenstauf, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ketoprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3\,^{2}H_3$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)

Levonorgestrel	LGC Standards (Middlesex, UK)	$^{13}C_2$ – Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Loperamide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Maprotiline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Memantine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Metoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Naproxen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3\ ^{2}H_3$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)
Orphenadrine	LGC Standards (Middlesex, UK)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Oxazepam	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Repaglinide	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA,

			USA)
Risperidone	LGC Standards (Middlesex, UK)	$^{2}H_{4}$ - Risperidone	Sigma-Aldrich (Steinheim, Germany)
Rosuvastatin	CHEMOS GmbH (Regenstauf, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Sertraline	Sigma-Aldrich (Steinheim, Germany)	$^{2}H_{6}$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Sulfamethoxazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{6}$ - Sulfamethoxazole	Cambridge Isotope Laboratories (Andover, MA, USA)
Tramadol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Trimethoprim	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_{3}$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Venlafaxine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^{2}H_{3}$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

Table S2: Ionization mode, recoveries, relative standard deviation (RSD) and limit of quantification (LOQ) of the pharmaceuticals.

Pharmaceuticals	Ionization mode	Recovery (average of triplicate)	RSD	LOQ
		%	%	ng/L
Amitryptiline	HESI	83.3	7.5	5
Atracurium	HESI	85.8	7.2	0.5
Beclomethasone	HESI	25.2	12.9	10
Biperiden	HESI	106	8.4	0.1
Bisoprolol	HESI	83.1	5.1	0.1
Bupropion	HESI	96.3	4.7	0.1
Carbamazepine	HESI	101	15.1	1
Cilazapril	HESI	143	5.9	1
Citalopram	HESI	83.6	8.5	5
Clomipramine	HESI	72.7	11.4	0.5
Codeine	HESI	86.7	24.0	0.5
Diclofenac	HESI	42.1	4.4	10
Diltiazem	HESI	107	3.8	0.5
Eprosartan	HESI	62.3	4.3	5
Ethinyl estradiol	APPI	85.7	4.1	10
Fexofenadine	HESI	81.1	7.1	5
Fluconazole	HESI	89.8	12.9	0.5
Fluoxetine	HESI	97.0	11.4	5
Flutamide	HESI	91.8	3.9	5
Haloperidole	HESI	64.0	12.7	0.1
Hydroxyzine	HESI	94.5	14.2	0.5
Ibuprofen	APPI	62.4	7.4	10
Irbesartan	HESI	109	2.6	0.5

Ketoprofen	APPI	73.2	7.4	10
Levonorgestrel	APPI	99.5	3.0	10
Loperamide	HESI	61.6	15.7	0.5
Maprotiline	HESI	84.1	7.4	5
Memantine	HESI	85.7	7.7	0.5
Metoprolol	HESI	82.9	1.3	5
Naproxen	APPI	95.5	4.5	10
Orphenadrine	HESI	94.7	11.2	0.1
Oxazepam	HESI	97.4	1.1	5
Repaglinide	HESI	93.4	8.6	0.5
Risperidone	HESI	101	2.4	0.1
Rosuvastatin	HESI	147	6.4	10
Sertraline	HESI	71.2	16.5	10
Sulfamethoxazole	HESI	97.3	4.3	5
Tramadol	HESI	129	6.3	0.5
Trimethoprim	HESI	109	10.7	0.1
Venlafaxine	HESI	96.2	7.8	0.5