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Ozone Oxidation of Pharmaceuticals and Personal Care Products

Kinetics and Transformation Products

Daniel Malnes

ABSTRACT

Ozone Oxidation of Pharmaceuticals and Personal Care Products: Kinetics and Transformation Products

Daniel Malnes

Pharmaceuticals and personal care product (PPCPs) substances has been detected in various water bodies in Sweden. A substantial part of these compounds are spread in nature due to insufficient removal in water treatment plants. Pharmaceutical products are developed to be chemically stable, and to achieve a therapeutic effect already in low concentrations. Aquatic and amphibian organisms exposed to these substances have displayed sublethal effects, due to the limited reduction capacity of the waste water treatment plants. One promising alternative for the reduction of PPCPs is ozone oxidation.

This thesis has focused on developing a method which could imitate a water treatment process, with respect to commonly used ozone doses and residence times as well as the requirement of a continuous process. The thesis also consisted of applying the developed method, to study the reduction kinetics and transformation products of some PPCPs with ozone oxidation.

Five compounds were selected for studying the reduction kinetics with ozone, and the identification of transformation products. The method was developed on principles with a broad support in the chemically technical literature, and modifications of already existing equipment was made to better simulate the turbulent conditions found in the water treatment plant. The developed method had however, from a mathematical point of view, problems of properly simulating the conditions found in water treatment plants with respect to typically applied ozone doses and flow regime. The method was however considered as sufficient to proceed to the experimental phase, and experiments of the ozone oxidation's effects on the PPCPs was investigated.

The results prove a reduction of all the investigated substances following the ozone oxidation - two out of five substances had kinetics similar to that found in the academic literature and the remaining substances were found to have increased kinetics. For one of the substances, carbamazepine, one major transformation product, BQM, was identified through comparison with earlier studies. Another, minor transformation product was also identified through the same process, and the concentration of the transformation product was semi-quantified. For fexofenadine, one earlier known transformation product, fexofenadine-N-oxide, was identified but not semi-quantified, since the concentration was below the level of quantification.

Keywords: advanced water treatment, water treatment techniques, PPCPs, pharmaceutical residues, ozone oxidation, transformation products

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REFERAT

Ozonoxidation av läkemedel och personvårdsprodukter: kinetik och transformationsprodukter
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Läkemedels- och personvårdsämnen har upptäckts i olika vattenkroppar i Sverige. En väsentlig del av dessa ämnen sprids i naturen på grund av otillräcklig borttagning i avloppsreningsverk. Läkemedelsprodukter är utformade för att vara kemiskt stabila och för att uppnå en terapeutisk effekt i biologiska varelser redan vid låga halter. Akvatiska och amfibiska organismer som exponeras för dessa ämnen har uppvisat subletala effekter, på grund av begränsad reduktionskapacitet i avloppsvattenverken. Ett lovande alternativ för reducering av läkemedels- och personvårdsämnen är ozonoxidation.

Det här examensarbetet har fokuserat på att utveckla en metod som kunde imitera en reningsprocess vid ett vattenreningsverk, med avseende på typiska ozondoser och uppehållstider samt krav på en kontinuerlig process. Examensarbetet bestod också av att applicera den utvecklade metoden, för att studera reduktionskinetiken och bildandet av transformationsprodukter från vissa läkemedel- och personvårdsprodukter med ozonoxidation.

Metoden som utvecklades byggdes på principer med brett underlag i den kemiskt tekniska litteraturen, och modifieringar till utrustningen genomfördes för att bättre simulera de turbulenta förhållanden som råder i vattenreningsverk. Den utvecklade metoden hade dock, matematiskt sett, svårigheter med att simulera de förhållanden som råder i vattenreningsverk med avseende på typiska ozondoser och flödesregim. Metoden bedömdes dock som tillräcklig för att fortgå till experimentstadiet, och undersökningar av ozonoxideringens effekt på läkemedels- och personvårdsämnena genomfördes.

Resultaten påvisar en minskning av samtliga ämnen till följd av ozonoxideringen - för två av fem ämnen är kinetiken jämförbar med den i den akademiska litteraturen och för övriga ämnen en förhöjd kinetik. För ett av ämnena, karbamazepin, identifierades en tidigare känd stor transformationsprodukt, BQM, genom jämförelse med tidigare studier. En annan, mindre transformationsprodukt identifierades också genom samma process, och koncentrationen av transformationsprodukten semi-kvantifierades. För fexofenadin kunde en tidigare känd transformationsprodukt, fexofenadin-N-oxid, identifieras men inte semi-kvantifieras, då halterna låg under kvantifikationsgränsen.

Nyckelord: avancerad rening, vattenreningsteknik, PPCPs, läkemedelsrester, ozonoxidering, transformationsprodukter

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PREFACE

This thesis has been performed to obtain the degree of Master of Science in Environmental and Water Engineering at Uppsala university and the Swedish University of Agricultural Sciences. The thesis corresponds to 30 credits, and has been performed during the fall semester of 2018 and part of the spring semester 2019.
The supervisor of this project has been Dr Oksana Golovko, at the Department of Aquatic Sciences and Assessment at the Swedish University of Agricultural Sciences.
The subject reviewer of this project has been Associate Professor Lutz Ahrens, at the Department of Aquatic Sciences and Assessment at the Swedish University of Agricultural Sciences.

I would like to thank the following people who have contributed in one way or another in the actualizing of this project:

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If you want to go fast, go alone. If you want to go far, go together. - African proverb.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Ozonoxidation av läkemedel och personvårdsprodukter: kinetik och transformationsprodukter

Daniel Malnes

Avloppsvattenrening i Sverige och i resten av världen bygger på principen att reducera ämnen som förekommer i sådana volymer att de inte bryts ned i tillräcklig grad innan de når naturen, där de kan påverka akvatiska och amfibiska organismer samt omkringliggande natur som direkt eller indirekt kan ge upphov till negativa effekter. Historiskt har övergödning och tungmetaller, till följd av direkta utsläpp av avloppsvatten från tätorter till sjöar och vattendrag, varit i fokus. Kring tidigt 2010-tal upptäcktes det att vissa läkemdelsrester och personvårdsprodukter inte reduceras tillräckligt i reningsverken i Sverige, utan upptäcks i ytvatten långt från avloppsvattenverken, och i vissa fall påträffas vissa av dessa ämnen - efter att ha passerat ännu en reningsprocess, denna gång i dricksvattenreningsverk - till och med i dricksvatten. Specifikt läkemedel har ett behov av att vara persistenta på grund av att klara av att passera den kemiskt aggressiva miljön i magsäcken i tillräcklig grad för att nå mag-tarmkanalen, där ämnena i läkemedlet kan tas upp och uppnå den effekt som läkemedlet är avsett för. En viss mängd läkemedel kommer dock inte att tas upp, utan kommer att komma ut vid ett toalettbesök.

Personvårdsprodukterna - kosmetika och parfymer, medel för att behandla akne, deodorant, insektavvisande medel, nagellack, hårfärg med flera - hamnar i avloppsreningsverket efter att vi tvättar händerna, eller efter bad eller dusch. Dessa produkter kan också hamna i ytvatten efter utomhusbad.

På grund av dessa ämnens persistenta egenskaper och direkta utsläpp i naturen har det spekulerats om vilka som drabbas av dessa ämnens utsläpp, bland annat vattenlevande organismer och de dricksvattenverk som använder sig av ytvatten för att rena till dricksvatten. I en svensk studie har en mängd olika läkemedelsprodukter studerats, och av dessa hittades 66 i ytvatten och i ett fall kunde 26 olika läkemdelsämnen upptäckas i dricksvattenprov.

På grund av läkemedlens karaktär - de är designade att uppnå en biologisk effekt vid en låg koncentration - är det möjligt att det klassiska tillvägagångssättet att utvärdera akut och kronisk toxicitet för akvatiska och amfibiska organismer inte är rätt synvinkel för att utvärdera dessa ämnens negativa effekter, då ett läkemedel som är akut eller kroniskt toxiskt sannolikt drar ner dess chanser att nå marknaden. Vissa studier har valt andra tillvägagångssätt för att utvärdera andra effekter dessa ämnen kan ha för utsatta organismer, bland annat stressnivåer (”förlorad” energi som skulle kunna gå till tillväxt), djärvhet (ökade chanser att bli uppäten av rovdjur), och minskad socialisering (minskade chanser för reproducering).

På grund av att informationen kring läkemedlens och personvårdsprodukternas fullständiga effekter i den akvatiska miljön fortfarande håller på att kartläggas, samt exempel på ämnen i läkemedelskategorins påverkan på miljön, kan Miljöbalken 2 kap. §3 - också mer känd som försiktighetsprincipen - tillämpas. Från lagstiftningen har olika metoder provats för att bryta ner läkemedlen och personvårdsprodukt-

terna i både dricks- och avloppsreningsverk, och ett av de mest lovande alternativen i dagsläget ser ut att vara en kombination av ozon och ett efterföljande kol- eller biologiskt filter.
Ozon kan användas som ett starkt oxidationsmedel, vilket innebär att det reagerar med ett stort antal ämnen genom att ta elektroner från det andra ämnet. Den kemiska processen betyder ofta att nya ämnen bildas. I kontexten för vad detta examensarbete kommer att behandla kommer dessa nya bildade ämnen att kallas för *transformationsprodukter*.

Det här examensarbetet har behandlat en nedskalning av en vattenbehandlingsprocess med ozonoxidation av läkemedelsämnen och personvårdsämnen till laborationsskala, där målet för nedskalningen har varit att försöka efterlikna ozondoser och kontakttider med ozon som vanligtvis används i vattenreningsverk.

I det här arbetet har fem ämnen - koffein, karbamazepin, fexofenadin, lamotrigin, och oxazepam - studerats med avseende på deras nedbrytning av ozon, hur snabbt reaktionen mellan ozonet och dessa ämnen har varit, och för vissa ämnen har även transformationsprodukter identifierats. Dessa experiment har genomförts med ”ultrarent” filtrerat vatten, MilliQ.

Resultaten för nedskalningen av ozonoxidationsprocessen till laborationsskala påvisar svårigheter att imitera de förhållanden som normalt sett används i vattenreningsverk, främst med avseende på typiska ozondoser och turbulent mixning.
Utformningen för att försöka efterlikna en typisk behandlingsprocess med ozon gjordes genom att

1. skapa ett sätt att, på förhand, lösa ozongasen i vätska och på så sätt styra ozondosen;
2. sammanföra två strömmar med olika vatten - ett innehållande det vattenlösta ozonet och det andra innehållande läkemedelsämnena/personvårdsprodukterna - i ett mixningskärl;
3. i ovan nämnda mixningskärl skapa så turbulent mixning som möjligt genom: aktiv blandning med en impeller, placering av inloppen av vattenströmmarna direkt ovanför impellatorn i mixningskärlet, att placera utloppet i mixningskärlet nära bottnen för ökad blandningstid, och konstruktionen av bafflar som bryter upp tvådimensionell mixning till tredimensionell mixning;
4. samla upp vattnet efter utloppet, för analys av innehållet.

Alla studerade ämnen reagerade med ozonoxidationen - halterna av ämnena hade minskat efter behandlingen. Två av fem ämnen reagerade ungefär lika snabbt som i andra studier, medan resten av ämnena hade högre reaktionshastigheter jämfört med andra vetenskapliga studier.
Försök för identifikation av transformationsprodukter för två ämnen - karbamazepin och fexofenadin - genomfördes, där det för karbamazepin identifierades en tidigare känd transformationsprodukt - BQM - och för fexofenadin identifierades den tidigare kända transformationsprodukten fexofenadin-N-oxid.

List of abbreviations

ACC	Azacyclonol.
BaQD	1-(2-benzoic acid)-(1H,3H)-quinazoline-2,4-dione.
BQD	1-(2-benzaldehyde)-(1H,3H)-quinazoline-2,4-dione.
BQM	1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one.
CEC	(Predicted) Critical effect concentration.
DWTP	Drinking water treatment plant.
FXF-N-oxide	Fexofenadine-N-oxide.
HDT	Hydraulic Detention Time, the assumed, mathematically determined time any one water molecule spends inside a specified vessel under idealized conditions.
IS	Isotopically labeled standard.
K_{OW}	Octanol-water partitioning coefficient.
MQ	MilliQ.
MS	Mass spectrometry.
NOM	Natural organic matter.
PFA	perfluoroalkoxy alkane.
PPCPs	Pharmaceuticals and personal care products.
PTFE	Polytetrafluoroethylene, a fluoroplastic material with one of the highest known chemical resistance of all known plastic materials.
PVC	Polyvinyl chloride, a synthetic plastic material, with varying numbers of carbon-chloride bonds.
PVDF	Polyvinylidene fluoride, a synthetic fluorinated polymer with a high chemical resistance.
RTD	Residence Time Distribution, the distribution of time any one water molecule spends inside a specified vessel, which is determined experimentally.

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UPLC	Ultra-high pressure liquid chromatography.
UV	Ultraviolet.
WWTP	Wastewater treatment plant.

WORDLIST

Exit age distribution	The distribution of time inside a vessel the components have spent, from the moment of entering the vessel until the exiting of the vessel.
Hydroxyl radicals	A product formed from the self-degradation process of ozone, which is a highly reactive oxidative.
Impeller	Overarching classification for mixing devices which includes: paddles, propellers, and turbines.
Transformation products	Here defined as the products from the reaction with ozone in specific, i.e. ozone transformation products.

CONTENTS

1 INTRODUCTION

Currently, there are more than 1,000 active pharmaceutical ingredients on the Swedish market. Although there are great benefits from the use of pharmaceuticals there are also some disadvantages - due to pharmaceuticals' chemical stability they degrade slowly in nature (Hedlund, 2018). Recent evidence shows that pharmaceuticals can be found in aquatic environments (Fick, Lindberg, Kaj, & Brorström-Lundén, 2011; Finnson, 2017; Hedlund, 2018). From a screening project in Sweden, summarized by Fick et al. (2011), it was discovered from 101 studied pharmaceuticals that:

- 92 pharmaceuticals could be found in the incoming waters to at least one waste water treatment plant;
- 66 pharmaceuticals were detected in measurable levels in surface waters, of which five were in concentrations estimated to have pharmaceutical effect in fish; and
- 26 pharmaceuticals could be found in drinking water samples.

Evidence has been put forward about the non-lethal effects pharmaceuticals and personal care products (PPCPs) can have on different aquatic species, for instance:

- Caffeine has been found to cause stress in California mussel (Del Rey, Granek, & Buckley, 2011);
- Carbamazepine has decreased the activity of Japanese medaka fish (Nassef et al., 2010);
- Oxazepam has lead to increased activity and other changes in European perch (Brodin, Fick, Jonsson, & Klaminder, 2013).

Furthermore, the so-called "cocktail effect" - the assumption that the combined effect of several chemical compounds with similar biochemical effects in low doses still can have an unwanted effect, even if found in concentrations below the level of effect of each individual chemical compound - has been found to have some evidence (Backhaus, 2014; Brian et al., 2005; Wallberg, Wallman, Thorén, Nilsson, & Christiansson, 2016).

It is important to protect water bodies - in Sweden surface waters account for 50% of the source for drinking water (Svenskt Vatten, 2016). The main consumer of this drinking water from surface waters are larger cities (Svenskt Vatten, 2016) which, from a public health perspective, can be considered especially important to protect, as any mishap will impact a comparably large part of the population.

As waste and drinking water treatment plants (WWTP and DWTP, respectively) are not originally designed to treat PPCPs, the possibilities to reduce them have been investigated (Björlenius, 2016; Finnson, 2017). One of the most promising techniques is the combination of ozone oxidation followed by either active carbon or a biological step (Baresel, Magnér, Magnusson, & Olshammar, 2017; Björlenius, 2016; Finnson, 2017; Wahlberg, Björlenius, & Paxéus, 2010).

For DWTPs, Snyder (2008) found that an ozone dose of 2.5 $mgO_3 \times L^{-1}$ was comparably effective for removal of a wide range of pharmaceuticals, which could be found at various geographical locations across the United States.
However, there are considerations to the ozone oxidation technique: by-products from the ozone oxidizing technique may form (Crittenden, Trussell, Hand, Howe, & Tchobanoglous, 2012a), the choice of materials in contact with ozone is of importance (Björlenius, 2016; Gottschalk, Libra, & Saupe, 2009), and the ozone gas has to be safely contained to ensure safe operation conditions (Björlenius, 2016).

Since ozone oxidation treats substances chemically some new, unknown products may form (Björlenius, 2016), products which are known as transformation products. The lack of knowledge about which products are formed and what properties these transformation products have are reasons of concern, because this promising, PPCP reducing technique might form even more stable and harmful products (Orhon, Orhon, Dilek, & Yetis, 2017).
Many studies have focused on the reduction potential of pharmaceuticals with ozone oxidation (Baresel et al., 2017; Broséus et al., 2009; Ternes et al., 2002) and exposure tests after ozone oxidation of pharmaceuticals (Altmann et al., 2012; Sehlén et al., 2015; Wahlberg et al., 2010), while others have had a more direct aim to try to identify the transformation products of ozone oxidation of one or a few pharmaceuticals (McDowell, Huber, Wagner, von Gunten, & Ternes, 2005; Orhon et al., 2017; Rosal et al., 2009). With a knowledge of which transformation products are formed it is possible to do a more careful risk assessment (Orhon et al., 2017), as individual compounds can be investigated more thoroughly with respect to factors concerning for instance bioaccumulation, persistence in the environment and toxicity.

1.1 OBJECTIVE

The main aims of this work were:
the down-scaling of an ozone oxidizing treatment to lab-scale, mainly regarding the ratio between water flow and ozone dose; and
the identification of the main transformation products by ozone oxidation.
To achieve these goals, the following questions were investigated:

- How can sufficiently high dosing of ozone be achieved, with an ozone generator which has a constant ozone production rate and static gas flow rate?
- Which pumping rate is needed to reach a certain desirable hydraulic retention time, such that the lab-scale setup can be said to properly mimic the continuous-flow conditions which can be found in a water treatment plant?
- Which equipment is needed to
    1. Maximize the likelihood that the reaction between ozone and pharmaceuticals is taking place, such that transformation products form;
    2. Minimize any contamination?

1.2 LIMITATIONS

To maintain the main aims of the project, the following limitations have been set:

- Focus will be on constructing a functional setup, i.e. any optimization, other than those absolutely vital regarding the experiment setup, will not be investigated;
- Physical and chemical parameters which could affect the effectiveness of the ozone oxidizing treatment will not be investigated, i.e. water samples will not be investigated with respect to their similarities or differences in the water matrix.
- Only the few, chosen chemicals will be experimented with, as data analysis can be time-consuming.
- Heat transfer from mass transfer processes will not be investigated, i.e. any aspects regarding temperature differences in the liquid phase due to introducing gaseous ozone into water will not be taken into consideration.

2 BACKGROUND

2.1 PPCPS

PPCPs is an umbrella term, which includes substances found in pharmaceuticals and personal care products. The term pharmaceutical covers a wide-ranging class of compounds with substantial variability in structures, function, behavior, and activity. Developed to elicit a biological effect, they are used in both humans and animals to cure diseases, fight infections, and/or reduce symptoms. Many drugs are not fully metabolized in the body and so may be excreted to the sewer system. According to US Food & Drug Administration (2016), personal care products are a a class of items which are commonly found in "the health and beauty sections of drug and department stores", however a legal definition of it does not exist. To get an idea of what products are refered to, table 1 presents a non-overlapping compilation from two different sources.

Table 1: A selection of products included in the category of "personal care products" from two independent sources.

Crittenden et al. (2012a)	**US Food & Drug Administration (2016)**
cosmetics and fragrances	toothpaste
acne medication	deodorants
insect repelants	fingernail polishes
lotions	eye and facial makeup preparations
detergents	hair colors

2.2 OCCURENCE OF PPCPS IN NATURE

PPCPs have been detected in various water bodies in Sweden (Fick et al., 2011; Glimstedt, Ahrens, & Wiberg, 2016). For instance, 92 out of 101 studied pharmaceuticals could be found in waste water, concentrations varying between low $ng \times L^{-1}$ to $\sim 500\ \mu g \times L^{-1}$, and in surface waters 66 out of the 101 pharmaceuticals could be found in concentrations of low $ng \times L^{-1}$ to $\sim 2\ \mu g \times L^{-1}$ (Fick et al., 2011). It is important to remember that, while mostly not acutely toxic, "Many drugs [...] are designed to affect specific biological pathways in target organisms at relatively low doses and exposure concentrations" (Ankley, Brooks, Huggett, Sumpter, & P, 2007). It has been shown that environmentally relevant concentrations of PPCPs are causing effects on aquatic species and amphibians (Brian et al., 2005; Säfholm, Ribbenstedt, Fick, & Berg, 2014). It is not straightforward how these substances interact with diverse aquatic lifeforms - different species might exhibit different responses by the same substance, as exemplified by propranolol and sertraline in the report by Brodin et al. (2014). In other cases, the same responses might be exhibited by different species, as exemplified by diazepam and fluoxetine in the report by Brodin et al. (2014).
It has been proposed that active pharmaceutical ingredients with "a similar mode of action" should be evaluated together (Ågerstrand et al., 2015). This could be based on the cause that similar responses can be achieved by different substances within

the same group of compounds, for instance anticholinesterasic drugs and psychiatric drugs (Brodin et al., 2014)
PPCPs are included in a group called "emerging substances" - substances which can be found in nature but their ecological effects are not fully understood and it is suspected that the use of substances in this group is only going to increase in the future (Chapman, 2006). Therefore, it is reasonable to assume that the concentration of substances in this group will increase, unless action to reverse this trend is taken.

2.3 Overview of Selected PPCPs

In the following section, the PPCPs used in the experiments will be described more in-depth, with regards to important factors for the experiments in which they will be studied. The physical and chemical properties which are presented are briefly explained as to why they are of importance.

Chemical formula: A basic overview of which atoms a molecule/compound consists of.

Chemical structure: A representation of how a molecule is spatially arranged. Can be useful to evaluate where the ozone oxidation treatment will affect the molecule.

Molecular weight: Calculated from the basis of a compound's chemical formula. Commonly used in mass spectrometry (MS), together with an ionized molecule's mass of fragmented parts and their respective frequency, to identify the original, unidentified (unionized) compound (Simonsen, 2005).

Water solubility: An important factor for determining where in nature - air, water or octanol - a compound could be found (Gulliver, 2012). If available together with solubility in octanol, it can be used to calculate the partition coefficient K_{OW}.

log(P): The n-octanol/water partition coefficient, which can also be known as log K_{OW} (Fick, Lindberg, Tysklind, & Larsson, 2010), is a model of how chemically hydrophobic a compound is (European Chemicals Agency, 2017). It can be used as a screening tool to evaluate if there is a risk for bioaccumulation of a compound (Schäfer et al., 2015), through the analogy that n-octanol acts as lipid-rich tissue which absorbs the compound through passive diffusion, for example through the gills (European Chemicals Agency, 2017). For human pharmaceuticals, a value of $\log(K_{OW})$ greater than 4.5 is a threshold for investigation of a compound's persistence, bioaccumulation and toxicity, due to the potential risk the compound may pose to the environment (European Medicines Agency, 2006).

CEC: "(Predicted) Critical effect concentration", a concentration at which the compound is predicted to have the same effect in fish as it has for a therapeutical dose for humans (Fick et al., 2010).

k_{O_3}: Reaction rate of the substance with ozone. PPCPs appear to degrade according

to second-order rates, with constants varying depending on the substance (Snyder, Westerhoff, Yoon, & Sedlak, 2003).

2.3.1 Caffeine

Caffeine (fig. 1) is a stimulant acting on the central nervous system (National Center for Biotechnology Information, 2018a), perhaps most notably known by being the stimulant in coffee. It is an interesting compound to study as it is a compound of anthropogenic origin, its presence in water bodies a clear indicator of contact with anthropogenic sources (Seiler, Zaugg, Thomas, & Howcroft, 1999).
The following physical and chemical information about caffeine has been retrieved from National Center for Biotechnology Information (2018a), unless stated otherwise.

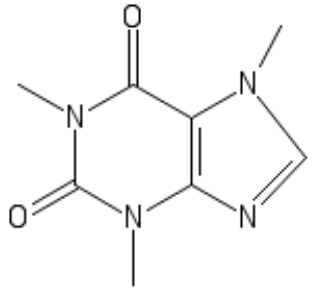
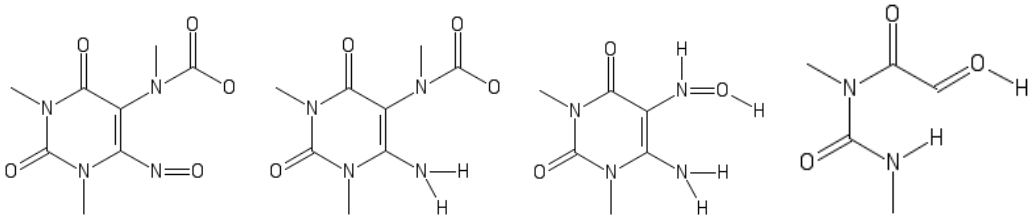


Figure 1: Chemical structure of caffeine.

Chemical formula: $C_8H_{10}N_4O_2$
Molecular weight: 194 $g \times mol^{-1}$
Water solubility: 22 $g \times L^{-1}$ at 25 °C
log(P): -0.07
k_{O_3}: 0.25 - 1.1 $M^{-1}s^{-1}$ (Rosal et al., 2009)

Caffeine has been detected in levels varying between 27-400 $ng \times L^{-1}$ in Swedish water supplies, with the average concentration being 170 $ng \times L^{-1}$ (Glimstedt et al., 2016). Caffeine has been placed on the NORMAN list of "emerging substances", meaning it has been found in the environment but is neither monitored nor is there sufficient knowledge about its impact on the environment (NORMAN, 2016).
Caffeine has been proven to reduce health for crab (*Carcinus maenas*), inducing oxidative stress and was part in the damaging of DNA (Aguirre-Martínez, Del Valls, & Martín-Díaz, 2013). In a different study, with the test organism California mussel (*Mytilus californianus*), it was found that when exposed to caffeine, levels of Hsp70 (Heat Shock Proteins, sizes between 68-78 *kDa*) - a family of proteins which, when many of these proteins are expressed, indicate that the organism is under the influence of environmental stress (Tavaria, Gabriele, Kola, & Anderson, 1996) - followed a concentration-dependent response at environmentally relevant concentrations (Del Rey et al., 2011).



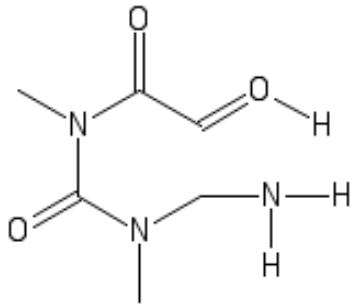
(a) Chemical structure of $C_8H_{11}N_4O_5$.

(b) Chemical structure of $C_8H_{12}N_4O_4Na$.

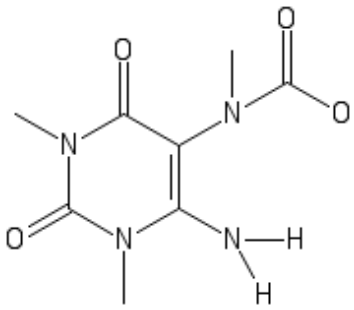
(c) Chemical structure of $C_7H_{11}N_4O_3$.

(d) Chemical structure of $C_5H_8N_2O_3Na$.

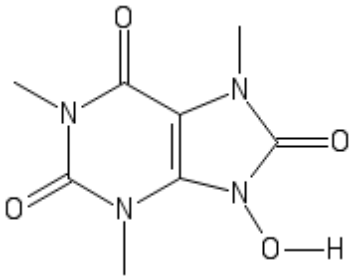
Figure 2: Chemical structure of caffeine's ozone oxidation products at pH 3 (Rosal et al., 2009).



(a) Chemical structure of $C_6H_9N_3O_4Na$.



(b) Chemical structure of $C_8H_{12}N_4O_4Na$.



(c) Chemical structure of $C_8H_{11}N_4O_4$.

Figure 3: Chemical structure of caffeine's ozone oxidation products at pH 8 (Rosal et al., 2009).

Known Transformation Products. Some ozone oxidation transformation products for caffeine have been identified by Rosal et al. (2009) at two different pHs, see figures 2 and 3. Ozone concentrations was varied, with ozone molar to caffeine concentration ratio ranging from 0.6 to 8. It was found that the oxidation products were:

- pH 3
  - $C_8H_{11}N_4O_5$
  - $C_8H_{12}N_4O_4Na$
  - $C_7H_{11}N_4O_3$
  - $C_5H_8N_2O_3Na$
- pH 8
  - $C_6H_9N_3O_4Na$
  - $C_8H_{12}N_4O_4Na$
  - $C_8H_{11}N_4O_4$

2.3.2 Carbamazepine

Carbamazapine (fig. 4) is an anticonvulsant, which is used to treat epilepsy (National Center for Biotechnology Information, 2018b). The following physical and chemical information about carbamazepine has been retrieved from National Center for Biotechnology Information (2018b), unless stated otherwise.

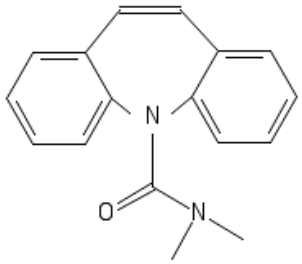
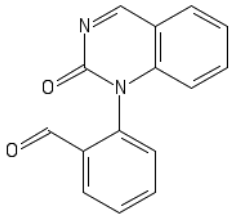


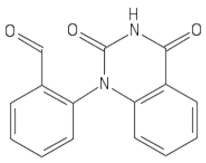
Figure 4: Chemical structure of carbamazepine.

Chemical formula: $C_{15}H_{12}N_2O$
Molecular weight: 236 $g \times mol^{-1}$
Water solubility: 18 $mg \times L^{-1}$ at 25 °C
log(P): 2.2 (Fick et al., 2010)
CEC: 347 $\mu g \times L^{-1}$ (Fick et al., 2010)
k_{O_3}: $\sim 3 \times 10^5$ $M^{-1}s^{-1}$ (Huber, Canonica, Park, & Von Gunten, 2003)

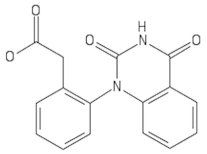
Carbamazepine is, similarly to caffeine, also an " emerging substance" (NORMAN, 2016). According to Fick et al. (2011), carbamazepine could be found in Swedish surface waters, concentrations ranging from 4.9-760 $ng \times L^{-1}$.
Carbamazepine has been shown to decrease the activity and feeding rate of Japanese medaka fish (*Oryzias latipes*) (Nassef et al., 2010).



(a) Chemical structure of BQM.



(b) Chemical structure of BQD.



(c) Chemical structure of BaQD.

Figure 5: Chemical structures of previously identified major transformation products of carbamazepine by ozone oxidation (McDowell et al., 2005).

Known Transformation Products. Trials identifying major oxidation products has been performed by McDowell et al. (2005), see figure 5. It was discovered that, with an ozone dose of approximately 400 μM and a contact time of 20 min, the following three major transformation products were produced:

- 1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one (BQM),
- 1-(2-benzaldehyde)-(1H,3H)-quinazoline-2,4-dione (BQD),
- 1-(2-benzoic acid)-(1H,3H)-quinazoline-2,4-dione (BaQD).

Additional minor transformation products were identified by Hübner, Seiwert, Reemtsma, and Jekel (2014), whom also proposed the degradation pathway of carbamazepine by ozone and hydroxyl radicals.

2.3.3 Fexofenadine

Fexofenadine (fig. 6) is an antihistamine, used to treat seasonal allergies (National Center for Biotechnology Information, 2018c).
The following physical and chemical information about fexofenadine has been retrieved from National Center for Biotechnology Information (2018c), unless stated otherwise.

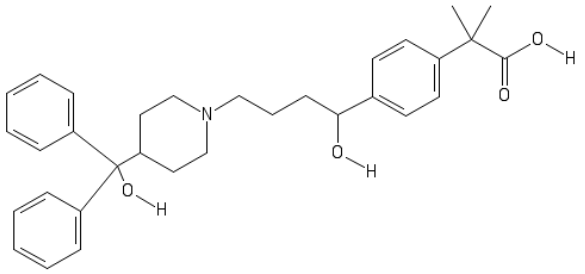
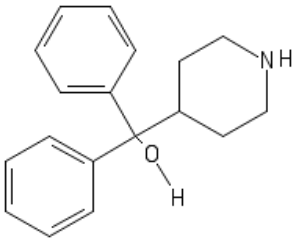


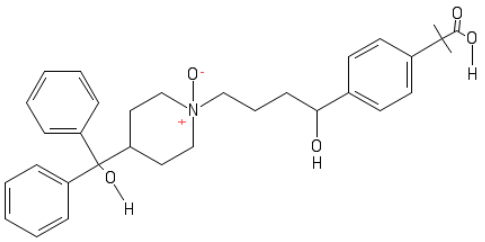
Figure 6: Chemical structure of fexofenadine.

Chemical formula: $C_{32}H_{39}NO_4$
Molecular weight: 502 $g \times mol^{-1}$
Water solubility: 0.024 $mg \times L^{-1}$ at 25 °C
log(P): 2.8 (Fick et al., 2010)
CEC: 20 $\mu g \times L^{-1}$ (Fick et al., 2010)
k_{O_3}: 9.0×10^3 $M^{-1}s^{-1}$ (Borowska et al., 2016)

Fexofenadine has been determined to have "finding of no significant impact" when assessed for environmental impact (Bloom, 2010). In a study by Jonsson, Fick, Klaminder, and Brodin (2014), it was found that fexofenadine could increase the boldness in damselfly larvae (*Zygoptera*), something which could lead to an increased chance of being eaten by a predator.
Fick et al. (2011) reported that fexofenadine could be found in Swedish surface waters, in concentrations from below a level of quantification (5.0 $ng \times L^{-1}$) up to 150 $ng \times L^{-1}$.



(a) Chemical structure of ACC.



(b) Chemical structure of FXF-N-oxide.

Figure 7: Chemical structure of fexofenadine's ozone oxidation products found by Borowska et al. (2016).

Known Transformation Products. Similarly to caffeine and carbamazepine, experiments have been made to try to identify the main transformation products of ozone oxidation (Borowska et al., 2016), see figure 7. The experiment was performed with waste water, and with varying ozone doses - 4-400 μM. It was found that the major transformation product was fexofenadine N-oxide (FXF-N-oxide). Small amounts of other transformation products were also found, for which available commercial standards azacyclonol (ACC) was found (Borowska et al., 2016).

2.3.4 Lamotrigine

Lamotrigine (fig. 8) is an anticonvulsant, mostly used in treatment of seizures (National Center for Biotechnology Information, 2018d). The following physical and chemical information about lamotrigine has been retrieved from National Center for Biotechnology Information (2018d), unless stated otherwise.

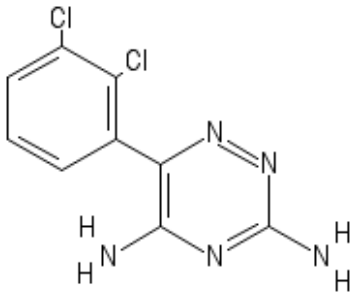
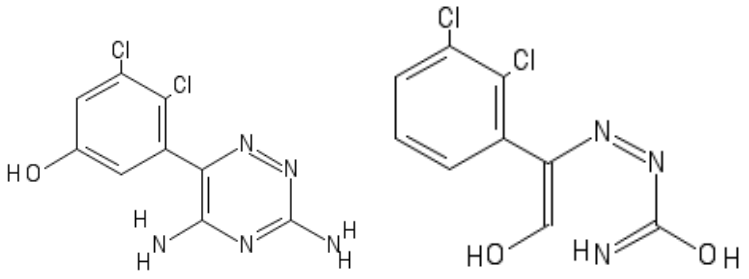


Figure 8: Chemical structure of lamotrigine.

Chemical formula: $C_9H_7Cl_2N_5$
Molecular weight: 256 $g \times mol^{-1}$
Water solubility: 170 $mg \times L^{-1}$ at 25 °C
log(P): 1.0 (Fick et al., 2010)
CEC: 1.4 $mg \times L^{-1}$ (Fick et al., 2010)
k_{O_3}: $\sim 4\ M^{-1}s^{-1}$ (Keen, Ferrer, Thurman, & Linden, 2014)

Lamotrigine has been considered to have "finding of no significant impact" in its environmental impact when assessed at three different aquatic trophic levels (Bloom, 2006). It has however been marked as potentially persistent (FASS, 2018), which is a reason to investigate the compound further. It is also included in the list of "emerging substances" by NORMAN (2016).



(a) Chemical structure of $C_9H_8Cl_2N_5O^+$.

(b) Chemical structure of $C_9H_8Cl_2N_3O_2^+$.

Figure 9: Chemical structure of lamotrigine's ozone oxidation products, as suggested by Keen et al. (2014).

Known Transformation Products. Keen et al. (2014) have investigated the products of ozone reacting with lamotrigine, using an ozone dose of 100 μM and a contact time of 30 min - see figure 9 - and finding the following products:

- $C_9H_8Cl_2N_5O^+$
- $C_9H_8Cl_2N_3O_2^+$

2.3.5 Oxazepam

Oxazepam (fig. 10) is classified as an antianxiety agent and as a benzodiazepine, which is used to treat anxiety and symptoms which arises from alcohol withdrawal (National Center for Biotechnology Information, 2018e).
The following physical and chemical information about oxazepam has been retrieved from National Center for Biotechnology Information (2018e).

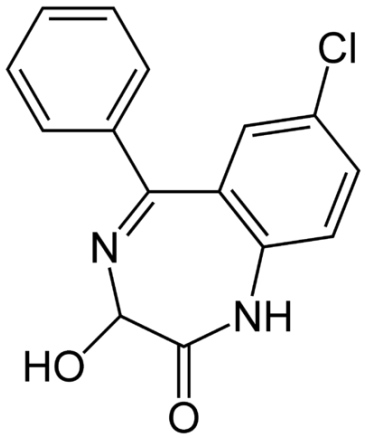


Figure 10: Chemical structure of oxazepam.

Chemical formula: $C_{15}H_{11}ClN_2O_2$
Molecular weight: 287 $g \times mol^{-1}$
Water solubility: 179 $mg \times L^{-1}$ at 25 °C
log(P): 2.3 (Fick et al., 2010)
CEC: 31 $\mu g \times L^{-1}$ (Fick et al., 2010)
k_{O_3}: $\sim 1\ M^{-1}s^{-1}$ (Lee, Kovalova, McArdell, & von Gunten, 2014)

In the national screening programme in Sweden, Fick et al. (2011) measured concentrations of oxazepam in surface water below level of quantification (5.0 $ng \times L^{-1}$) up to 580 $ng \times L^{-1}$. It is included in the list of "emerging substances" by NORMAN (2016). It has been found that oxazepam is very persistent, still in its potent, therapeutical state even after spending decades in sediments in a freshwater lake (Klaminder et al., 2015).
Recent findings suggest that oxazepam can transfer between species in the food web and that it seems like oxazepam can alter pike (*Esox lucius*) behaviour by reducing their instinct to hunt for food (Lagesson, 2018). Furthermore, in a study by Brodin et al. (2013), it was proven that oxazepam altered the behaviour of European perch (*Perca fluviatilis*) by increasing their activity, reducing their social interactions, and increasing their feeding rate.

Transformation products: It appears that at the present time, transformation products for oxazepam is an unexplored field. It could however be due to the cause that oxazepam is known to be resistant to ozone oxidation (Sehlén et al., 2015), due to its lack of ozone-reactive sites which is investigated more in section 2.4 Ozone and Its Use in Water Treatment.

2.4 Ozone and Its Use in Water Treatment

Ozone oxidation is the process of oxidation through the use of ozone. The use of ozone in water treatment is not a new idea, having been used in France as a disinfectant as early as 1906 (Crittenden et al., 2012a), and is, out of the most common chemical disinfectants, the strongest oxidant (Crittenden et al., 2012a). When dissolved in water, ozone starts a decaying process with final products being hydroxyl radicals, which themselves can react with contaminants and pathogens (Crittenden et al., 2012a).

Ozone is known to attack trace organic compounds at a minimum of four sites - olefins, amines, aromatics, and sulfur-containing products - transforming the organic compounds in predictable ways (Hübner, von Gunten, & Jekel, 2015).

2.4.1 Producing the Ozone

Ozone is an unstable and short-lived substance which cannot be stored in tanks due to being explosive in high concentrations (Crittenden et al., 2012a). Due to the reasons above, it has to be produced on-site (Björlenius, 2016; Crittenden et al., 2012a). The source material for ozone production can come by separating oxygen from the air, pure oxygen gas, or producing it from water (Gottschalk et al., 2009). The most common method of producing ozone, for bench- and full-scale applications, is by separating it from air or from pure oxygen gas (Gottschalk et al., 2009). The ozone production is achieved by running an electrical current through oxygen gas, O_2 (Crittenden et al., 2012a; Gottschalk et al., 2009), which for every three oxygen gas molecules, produces two ozone molecules (Gottschalk et al., 2009)
$3O_2 \longrightarrow 2O_3$.

2.4.2 Mixing Ozone with Water

The process of transporting molecules, often from one phase to another, from a place with higher concentration to a place with lower concentration is called "mass transfer" (American Institute of Chemical Engineers, 2016a; Crittenden et al., 2012a). For the mass transfer across a gas-liquid interface, for instance the absorption of a gas to the liquid phase, Crittenden et al. (2012a) refers to equation 1 to represent the mass flux.

$$J_A = K_L(C_b - \frac{y_b}{H}) \tag{1}$$

where
J_A: mass flux of ozone across the air-water interface $[mg \times m^{-2} \times s^{-1}]$
K_L: overall mass transfer coefficient $[m \times s^{-1}]$
C_b: liquid-phase concentration of ozone in bulk solution $[mg \times L^{-1}]$
y_b: gas-phase concentration of ozone in bulk solution $[mg \times L^{-1}]$
H: Henry's law constant, L of water/L of air [$dim.less$].

The mass transfer for a specific system can however be hard to predict, as Gottschalk et al. (2009) cites numerous parameters which could affect the mass transfer such as:

reactor geometry, kinematic viscosity, surface tension, density, Henry's law constant, diffusion coefficient, and coalescence behaviour of bubbles.
There are however some technical aspects which will affect how efficiently ozone will be transferred to the aqueous phase. In the report by Wahlberg et al. (2010), it is mentioned that a high area between the gas and the water is desirable, which is also verified by Paul, Atiemo-Obeng, and Kresta (2004). Furthermore, for an increased stability of ozone in water Crittenden et al. (2012a) recommends that: the pH is low, the alkalinity is high, the water's content of TOC is low, and that the temperature is low (close to 2°C). Putting some of these technical aspects into use, a steady-state dose of 40 $mgO_3 \times L^{-1}$ has been achieved through continuously bubbling ozone into distilled water chilled to 2°C by using a gas-washing bottle (Bader & Hoigné, 1981).

The literature, mainly Paul et al. (2004), suggests that there are a wide variety of ways in which a mixing process can be achieved depending on the process requirements. One common method is mechanically stirred vessels (Paul et al., 2004), which is used for purposes such as blending of liquids for neutralization reactions, and gas dispersion in liquid for ozonation. More on mechanically stirred vessels will be presented in 2.5 Mechanically Stirred Vessels.

2.4.3 Dosage

It has been suggested that a dosage of 5 $mgO_3 \times L^{-1}$ should not be exceeded for WWTPs, although higher doses results in a higher removal of pharmaceutical residue (Wahlberg et al., 2010). The limit is set due to the higher ecotoxicity at higher doses (Wahlberg et al., 2010).
Snyder (2008) proved that a dose of 2.5 $mgO_3 \times L^{-1}$ was, compared with UV-dosing at 40 $mJ \times cm^{-2}$ and free chlorine at 3.5 $mg \times L^{-1}$, very efficient in reducing PPCPs in DWTPs.

2.4.4 Chemical Considerations

Studies have noted that harmful by-products of ozone oxidation may be formed by naturally occurring constituents in water, most notably natural organic matter (NOM) and bromide (Crittenden et al., 2012a). Crittenden et al. (2012a) lists the following as known by-products of ozone oxidation in drinking water treatment, with class of compounds listed first and specific by-product listed afterwards:

- Trihalomethane
  - Bromoform
- Aldehydes
  - Formaldehyde
  - Acetaldehyde
  - Glyoxal
  - Methyl glyoxal

- Carboxylic acids
  - Formate
  - Acetate
  - Oxalate
- Ketoacids
  - Glyoxylic acid
  - Pyruvic acid
  - Ketomalonic acid
- Oxyhalides
  - Bromate

Control of the levels of by-products can be taken, such as removal of NOM before ozone oxidation and adsorption of produced by-products by activated carbon (Crittenden et al., 2012a).

2.4.5 Materials Withstanding Ozone Oxidation

Due to ozone's highly reactive nature, materials of the equipment which are used in process of ozone oxidation - reactors, tubing, valves, seals, and gas contactors - all have to be resistant towards the highly corrosive effects of ozone (Gottschalk et al., 2009). For full-scale implementations, material choice is paramount to withstand the long-term effects of such an aggressive oxidation ozone exerts, while at a lab-scale factors concerning investment costs can be considered (Gottschalk et al., 2009). However, for the study of treatment of trace contaminants in a lab-scale Gottschalk et al. (2009) recommends only letting stainless steel and glass come in contact with the ozonated water, as to avoid any adsorption of chemical products or leaching of contaminants. Some other materials mentioned by Gottschalk et al. (2009) as being ozone resistant in variable degrees are: PTFE, PVC, PVDF, Viton.

2.5 Mechanically Stirred Vessels

Due to its practicality for continuous, batch, and fed-batch mode operations, mechanically stirred vessels are used globally for a range of different applications (Paul et al., 2004). Depending on the need of the process, certain pieces of equipment must be chosen with care. Paul et al. (2004) investigates the subject thoroughly, and therefore only factors of most importance for this experiment are presented below.

2.5.1 Pumping

To simulate the conditions at a water treatment plant, a constant pumping of water into the reactor vessel is needed such that it can be said that it is a continuous-flow system. Depending on how big the reactor vessel and the water flow is, an idealized time the water spends inside the reactor vessel, called Hydraulic Detention Time

(HDT), can be calculated (Crittenden et al., 2012a) with equation 2.

$$\tau = \frac{V}{Q} \tag{2}$$

where
τ: hydraulic detention time [s]
V: volume of the reactor vessel [m^3]
Q: water flow through the reactor vessel [$m^3 \times s^{-1}$].

Since a mixing process rarely exhibits perfect flow patterns, an important part for understanding the hydraulics of the system is to evaluate its flow behavior and residence time distribution (RTD) (American Institute of Chemical Engineers, 2016b; Crittenden et al., 2012a). One way of determining the RTD is by performing a tracer test.
A *tracer test* can be performed with at least two methods - a step-input test and a pulse test - and with two different conservative constituents - a dye or a salt solution (Crittenden et al., 2012a). A pulse test with a dye entails that a colored, conservative constituent is introduced at the inlet to the (mixing) system, and samples are collected at the outlet, analysis with a spectrophotometer of the samples revealing the RTD (Crittenden et al., 2012a). This will reveal the mean residence time, $\bar{t}$, for the system, which is always less than τ, and is calculated with equation 3 (Crittenden et al., 2012a)

$$\bar{t} = \frac{\int_0^\infty Ctdt}{\int_0^\infty Cdt} \tag{3}$$

where
$\bar{t}$: mean residence time of tracer in reactor vessel [min]
C: concentration exiting reactor at time t [$mg \times L^{-1}$]
t: time since addition of tracer pulse to reactor vessel's entrance [min].

Short circuiting is a problem which often occurs in a continuous-flow mixing system, which is where part of the flow has a significantly shorter HDT than the mean (American Institute of Chemical Engineers, 2016b; Crittenden et al., 2012a). The problem is common for a continuous-flow, mechanically stirred systems, and can have at least two causes: (1) due to circulation patterns occuring, and (2) due to poor fluid mechanics caused by placement of inlet and outlet (American Institute of Chemical Engineers, 2016b; Crittenden et al., 2012a). Paul et al. (2004) suggests that the inlet and outlet are located far from each other to prevent this very phenomena. Additionally, the inlet should optimally be placed in a turbulent region of the vessel to achieve a quick dispersion, and the outlet should be placed on the side, close to the bottom of the vessel (Paul et al., 2004).

If no significant short circuiting can be observed, the tracer data is normalized with respect to (1) residence time - where the normalized data is referred to as normalized time θ - and (2) output concentration - where the normalized data is referred to as exit

age distribution E(θ) - to standardize the data analysis of the tracer data (Crittenden et al., 2012a).

To calculate the normalized time, equation 4 is used (Crittenden et al., 2012a).

$$\theta = \frac{t}{\bar{t}} \tag{4}$$

where
θ: normalized time [*dimensionless*]
t: time since addition of tracer pulse to reactor vessel's entrance [*min*]
$\bar{t}$: mean residence time of tracer in reactor vessel [*min*].

With the normalized time readily available, the normalized concentration can be calculated using equation 5

$$C_N = \int_0^\infty C_t d(\theta) \tag{5}$$

where
C_N: total mass concentration of tracer recovered [$mg \times L^{-1}$]
C_t: concentration exiting reactor at time t [$mg \times L^{-1}$]
θ: normalized time [*dimensionless*].

The normalized concentration will always be less than the input of tracer mass, and the tracer test can be considered successful if more than 95% of the tracer mass is recovered (Crittenden et al., 2012a).

The exit age distribution can then be calculated with equation 6 (Crittenden et al., 2012a)

$$E(\theta) = \frac{C_t}{C_N} \tag{6}$$

where
E(θ): exit age distribution [*dimensionless*]
C_t: concentration exiting reactor at time t [$mg \times L^{-1}$]
C_N: total mass concentration of tracer recovered [$mg \times L^{-1}$].

E(θ) vs θ can then be plotted.

To determine the spread of the data, the variance can be calculated with respect to, for instance, time (Crittenden et al., 2012a). Using equation 7 (Crittenden et al., 2012a):

$$\sigma_t^2 = \frac{\int_0^\infty (t - \bar{t})^2 C dt}{\int_0^\infty C dt} \tag{7}$$

where
σ_t^2: variance with respect to t [min^2]
C: concentration exiting reactor at time t [$mg \times L^{-1}$]
t: time since addition of tracer pulse to reactor vessel's entrance [min]
$\bar{t}$: mean residence time of tracer in reactor vessel [min].

2.5.2 Impeller

Crittenden et al. (2012a) states that "Because of their large size, virtually all water treatment processes takes place in turbulent flow.". To evaluate which regime the flow is in, the Reynolds number is used. An equation to approximate the Reynolds number for vertical turbines, which could serve as an approximation to the coming experiment, is given in Crittenden et al. (2012a):

$$Re = \frac{D^2 N \rho}{\mu} \tag{8}$$

where
Re: Reynolds number [$dimensionless$]
D: diameter of impeller [m]
N: impeller speed [s^{-1}]
ρ: density of water [$kg \times m^{-3}$]
μ: dynamic viscosity of water [$N \times s \times m^{-2}$].

From equation 8, it can be calculated whether the flow is in the turbulent regime (Re$>$ 10^4), in the transitional regime (10^4 $>$Re$>$ 10^2), or in the laminar regime (10^2 $>$Re) (Paul et al., 2004).

For the application of mixing in the transitional and turbulent flow regimes for low viscosity fluids, impellers are chosen on basis of which direction the fluid flow is wished to be pumped in - radial or axial - and which level of shear force the impellers exerts on the fluid (Paul et al., 2004).
Axial flow impellers are commonly used in processes such as blending and gas inducement (Paul et al., 2004). Depending on application and impeller design, such an impeller can have angled blades varying between 10 and 90° from the horizontal with 45° being the most common (Paul et al., 2004). For gas dispersion applications, the less common upwards pumping action from the axial impeller can be preferred (Paul et al., 2004).
Radial flow impellers' most effective application is for gas-liquid and liquid-liquid dispersion (Paul et al., 2004). The advantage, as compared with axial flow impellers, is that a higher turbulence and higher shear can be achieved with lower pumping (Paul et al., 2004). The pumping action from this kind of impeller is radially outwards towards the wall of the vessel (Paul et al., 2004). This pumping action, coupled with suitable baffles, can lead to a good mixing quality in the entire volume (see Figure 11) (Paul et al., 2004).

2.5.3 Blending

Blending is mixing at least two liquid components to a certain level of homogeneity (Crittenden et al., 2012a). Blending can be further divided into two categories, blending of *miscible* and *immiscible* liquids (Paul et al., 2004), where *miscible* liquid blending is the most interesting for the upcoming application (Crittenden et al., 2012a).

In water treatment applications, some processes require dosing of a chemical to the water stream to be treated (Crittenden et al., 2012a). Oftentimes, data of the water stream's flow rate and the dosing chemical's concentration is readily available (Crittenden et al., 2012a), and as such the flow rate of the dosing chemical can be calculated to achieve the proper dose by equation 9 (Crittenden et al., 2012a)

$$Q_A C_A = Q_W C_{dose} \tag{9}$$

where
Q_A: flow rate of feed stream for chemical A [$L \times min^{-1}$]
C_A: concentration of chemical A in feed stream [$mg \times L^{-1}$]
Q_W: flow rate of water stream to be treated [$L \times min^{-1}$]
C_{dose}: dose of chemical A to be applied to the water stream [$mg \times L^{-1}$].

Since the flow in real reactors is nonideal (Crittenden et al., 2012a), calculation 10 can be used to evaluate how large the unblended fraction of the feed stream and the water stream is (Crittenden et al., 2012a).

$$\overline{X}_A = \frac{C_{dose}}{C_A + C_{dose}} \tag{10}$$

where
$\overline{X}_A$: volume fraction of stream containing chemical A in unblended condition [*dimensionless*]
C_{dose}: dose of chemical A to be applied to the water stream [$mg \times L^{-1}$]
C_A: concentration of chemical A in feed stream [$mg \times L^{-1}$].

As was presented at the beginning of the former section, "[...] virtually all water treatment processes take place in turbulent flow.", an understanding of turbulence is a good starting point for understanding blending in turbulent flow.
Turbulence is the momentum created in a liquid due to a force inducing kinetic energy in the fluid (Crittenden et al., 2012a), a momentum which gradually shrinks smaller throughout the liquid because of energy loss called "eddy transfer of momentum" (Crittenden et al., 2012a). These "eddies" reach a point where they cannot become any smaller, and the energy contained in this motion will dissipate into the fluid - a point which is known as "Kolmogorov eddy size" (Crittenden et al., 2012a). This Kolmogorov eddy size is the dividing line between macroscale mixing - where the mass transfer is limited by molecular diffusion but also more dominantly by turbulent dif-

fusion (dispersion) - and the microscale mixing - where only molecular diffusion is taking place - which can be estimated with equation 11: (Crittenden et al., 2012a)

$$\eta = (\frac{v}{\varepsilon})^{\frac{1}{4}} \tag{11}$$

where
η: diameter of the smallest eddy $[m]$
v: kinematic viscosity $[m^2 \times s^{-1}]$
ε: energy dissipation rate at point of interest $[J \times kg^{-1} \times s^{-1}]$.

Since the energy dissipation rate is not uniform throughout the liquid being mixed, and the fact that the rate of dissipation inside the vessel is equal to the input energy to the system, an average can be used using equation 12 (Crittenden et al., 2012a)

$$\bar{\varepsilon} = \frac{P}{M} \tag{12}$$

where
$\bar{\varepsilon}$: average energy dissipation rate per unit mass for mixing vessel $[J \times kg^{-1} \times s^{-1}]$
P: power of mixing input to the entire vessel $[J \times s^{-1}]$
M: mass of water in mixing vessel $[kg]$.

As can be interpreted from equations 11 and 12 combined - the higher the power input, the smaller the diameter of the smallest eddy will become and thus the more the macroscale mixing will affect the total mixing (Crittenden et al., 2012a).

Dispersion is the mixing process which is caused by the turbulent shearing forces between fluid layers or by eddies formed by turbulent momentum in the fluid (Crittenden et al., 2012a). Dispersion coefficients are usually much larger than molecular diffusion coefficients - a majority of the time a factor 10^6 or higher, with the exception of groundwater flow (Crittenden et al., 2012a) - and the coefficients are identical for all constituents in the fluid (Crittenden et al., 2012a). The dispersion can be estimated with the dispersion number d which, for an ideal continuously mechanically stirred vessel, approaches infinity (Crittenden et al., 2012a). The dispersion number can be calculated from the Peclet number Pe, which is achieved by inversing the Peclet number (Crittenden et al., 2012a). The Peclet number in turn can be estimated from the tracer curve, by using equation 13 (Crittenden et al., 2012a)

$$\sigma_\theta^2 = \frac{\sigma_t^2}{\bar{t}^2} = \left(\frac{2}{Pe}\right) - \left[2\left(\frac{1}{Pe}\right)^2 (1 - e^{-Pe})\right] \tag{13}$$

Molecular diffusion occurs independently of the water flow regime, and is the result of the Brownian motion of the particles in the water (Crittenden et al., 2012a). To try to

quantify the time for mass transfer to occur by molecular diffusion, equation 14 can be used (Crittenden et al., 2012a)

$$t_d = \frac{3R^2}{4D_l} \tag{14}$$

where
t_d: time for molecules to diffuse in or out of an eddy $[s]$
R: radius of eddy $[m]$
D_l: liquid diffusivity of chemical molecule $[10^{-9} m^2 \times s^{-1}]$.

Here, R is calculated with the results from equation 11 by equation 15 (Crittenden et al., 2012a)

$$R_{avg} = \frac{1}{2}\eta \tag{15}$$

where
R_{avg}: radius of smallest eddy $[m]$
η: diameter of the smallest eddy $[m]$

The ozone liquid diffusivity is a value which varies depending on temperature, which is in the interval between 1.3 to 1.9×10^{-9} $m^2 \times s^{-1}$ for temperatures between 10 to 25°C (Johnson & Davis, 1996).

2.5.4 Blending Quality

How well a blending of components is can be investigated with respect to different aspects, however the most common method is to evaluate the variation in time (Crittenden et al., 2012a).

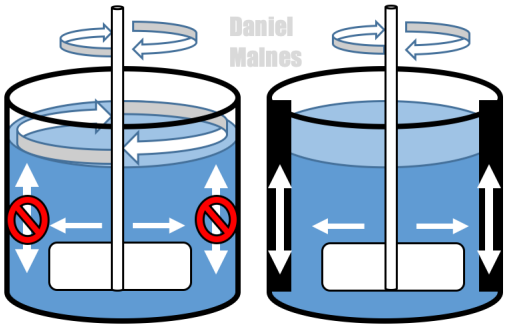


Figure 11: A sketch of two systems: (Left) Unbaffled system with solid body rotation, caused by the combination of vessel geometry and the impeller forces on the fluid, with poor top-to-bottom mixing, and (Right) Baffled system, which breaks up the fluid's two-dimensional rotation.

From these results, conclusions of the *uniformity of the blending* can be made (Crittenden et al., 2012a).

Improvement of a system's mixing quality may be needed, and should be met depending on the challenge. Depending on the tank geometry, the impeller can create a two-dimensional flow called "solid-body rotation" with poor top-to-bottom mixing as a result (Crittenden et al., 2012a; Paul et al., 2004; ProQuip Tank Agitators, 2017), which can be solved by installing baffles along the tank's walls (Crittenden et al., 2012a; Paul et al., 2004; ProQuip Tank Agitators, 2017). Another way of increasing the mixing quality in mechanically stirred vessels with continuous-flow is to put additional stirred vessels in series (Crittenden et al., 2012a).

3 MATERIALS

3.1 EXPERIMENTAL EQUIPMENT

The ozone generator used was a Q-005 (ANDS Trade s.r.o., Slovak republic) with a constant gas flow of 15 $L \times min^{-1}$ and a constant ozone production capacity of 5 $gO_3 \times h^{-1}$.

The pump used was a Cole Parmer MasterFlex peristaltic pump, model number 7520-57, 1-100 [rpm] (USA).
The pumping heads were Cole Parmer model 7519-50 (large tubes) and 7519-60 (small tubes) (USA).

Different sorts of tubing was purchased, chosen on their specific purpose in the experiment.
Tygon® S3 E-LFL tubing (Ismatec, Germany) compatible with the peristaltic pump, of varying inner - and outer diameters, were purchased, presented in table 2.

Table 2: Tygon® S3 E-LFL tubing used in experiment.

Inner diameter [mm]	**Outer diameter [mm]**
1.6	4.8
3.2	6.4
4.8	8.0

PTFE tubing (BOLA, Germany) with inner diameter 9 [mm] and outer diameter 11 [mm] was purchased, with the primary focus to direct the ozone-containing gas flow from the ozone generator.

Y-connectors to connect or divide gas flow were purchased, which was made of PVDF plastic (Bürkle, Germany).
Straight, universal connectors, to connect tubes of varying sizes, were purchased. The connectors were made of PVDF plastic (Bürkle, Germany).
Flangeless fittings to connect tubes to the mixing vessel caps were purchased, which

were made of PFA plastic (IDEX Health & Science, USA).

Hose clamps for tubings with outer diameters 8-10 mm, 10-12 mm, and 12-14 mm - made of acid-resistant stainless steel (Clas Ohlson, Sweden) - were purchased.

A BELL-CO glass ball spinner mixing vessel (fig. 12) (USA) with a volume of 1 L was used. The inner diameter of the vessel was approximately 123 mm, and the height to the 1 L mark was approximately 80 mm from the bottom of the vessel. Included with the mixing vessel was:

- A top lid with space to install the included two-bladed flat Teflon radial flow impeller;
- Two side lids, including two valves for directing liquid, connected to Teflon tubing, and one gas valve with open/close operation.

Figure 12: The mixing/reaction vessel.

From the materials, an experiment setup - with measurable levels of aqueous ozone, see section 3.2.3 Dissolved Ozone - was constructed.

3.2 Sample Analysis Devices

3.2.1 Temperature

A handheld device from Clean Instruments (China), model DOZ30, was used to measure the temperature. It has a measuring range of 0-100°C (Clean Instruments, n.d.).

3.2.2 pH-meter

A pH-meter was used to measure the pH.

3.2.3 Dissolved Ozone

A Hach Lange DR 1900 portable spectrophotometer (Germany) was used for measuring the aqueous ozone dose. It has a wave length accuracy of $\pm$ 2 nm in the 340-800 nm range (Hach Lange, 2014). The wave length for evaluating the dissolved ozone dose was 552 nm.
A test kit, consisting of Hach Lange LCK 310 Chlorine/Ozone/Chlorine dioxide cuvette test (Germany) with a measuring range of 0.05-2.0 $mgO_3 \times L^{-1}$ (Hach Lange, ND), was used.

3.2.4 Retention Time Distribution

A spectrophotometric method was used for analyzing the residence time distribution, with the machine Avantes Avalight-DH-S-Bal (Netherlands) with a cuvette size of 1cm. Methylene blue was purchased from Sigma-Aldrich (Sweden).

3.2.5 Chemical Analysis of Selected Compounds in Water Samples

Water samples of different characteristics were available for the experiment, more precisely MilliQ-water and tap water. The MilliQ-water was generated by a MilliQ (MQ) Advantage Ultrapure Water purification system which was filtered through a 0.22 μm Millipak Express membrane and an LC-Pak polishing unit (Merk Millipore, Billercia, MA).

Methanol, acetonitrile, ammonium acetate, formic acid, ammonia and ethyl acetate of high analytical grade were acquired from Sigma-Aldrich (Sweden). All analytical standards used for analysis were of high purity grade (>95%). Native standards (caffeine, carbamazepine, fexofenadine, lamotrigine, oxazepam) originate from Sigma-Aldrich (Sweden). Isotopically labeled standards (IS) (carbamazepin-d10, caffeine-c13, oxazepam-d10) for the target compounds were obtained from Wellington Laboratories (Canada), Teknolab AB (Kungsbacka, Sweden), Sigma-Aldrich and Toronto Research Chemicals (Toronto, Canada). Detailed information about internal and native standards can be found elsewhere (Rostvall et al., 2018).

A DIONEX UltiMate 3000 ultra-high pressure liquid chromatography (UPLC) system (Thermo Scientific, Waltham, MA, USA) coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ QUANTIVA, Thermo SCIENTIFIC, Waltham, MA, USA) was used for the analysis of the aqueous compounds. An Acquity UPLC BEH-C18 column (Waters, 100 $mm\times$ 2.1 i.d., 1.7 μm particle size from Waters Corporation, Manchester, UK) was used as an analytical column. The injection volume was 10 μL for all samples. A heated electrospray ionization (H-ESI) was used to ionize the target compounds. The spray voltage was set to static: positive ion V 3500. Nitrogen (purity >99.999%) was used as a sheath gas (50 arbitrary units), auxiliary gas (15 arbitrary units) and sweep gas (2 arbitrary units). The vaporizer was heated to 400°C and the capillary to 325°C. Two selected reaction monitoring (SRM) transitions were monitored for all analytes. The mobile phase consisted of MQ with 5 mM ammonium acetate and 2 % of acetonitrile. The flow rate was 0.5 $mL \times min^{-1}$ and run time was 15 min. The chromatography data acquisition mode was performed in a positive and negative mode using selected-reaction monitoring.

Xcalibur software (Thermo Fisher Scientific, San Jose, CA, USA) software was used for optimizing the instrument methods and running of samples. The obtained data were evaluated using TraceFinderTM 3.3. software (Thermo Fisher).

4 Methods

4.1 Measuring the Temperature

The cap of the Clean Instruments DOZ30 was removed, and put into the sample. Slight mixing during a one or two minute period for the instrument to converge to a value, depending on whether the instrument displayed a stable value, was allowed before the temperature was noted.

4.2 Measuring the pH

The pH-meter was calibrated using liquids with known pH-values - pH 4, pH 7, and pH 10 - using MilliQ-water to rinse the glass rod between each calibration liquid step. The glass rod was then directly placed into the sample volume, which was stirred by a magnetic bar, and the instrument was allowed approximately one minute to converge to a value.

4.3 Measuring the Aqueous Ozone Dose

A blank sample was run in the Hach Lange DR 1900 spectrophotometer. A glass vial containing the solid reagent was prepared with an addition of the liquid reagent. 70 mL samples of the aqueous ozone were extracted with an auto-pipette and put into the glass vial. The cap of the vial was put on, and the vial was turned up-side-down three times. The sample was allowed 2 minutes to react before being put in the spectrophotometer with the protection cap for analysis of the ozone concentration.

4.4 Determining the Residence Time Distribution

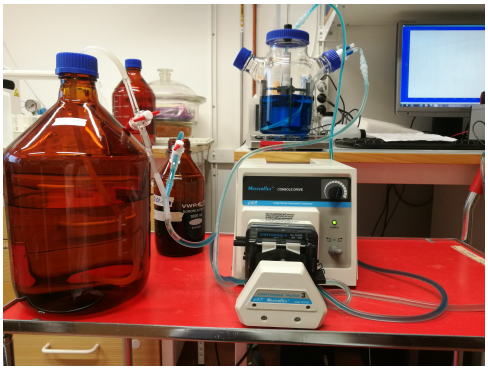


Figure 13: The setup for determining the RTD with methylene blue.

The determination of the RTD was performed by tuning in the experiment equipment.
The mixing vessel's in- and outflow were set equal by adjusting the pumping heads. The outlet was located close to the mixing vessel's wall and close to the bottom - leading through the spectrophotometer and into waste collection - and the inlet just beneath the water surface and directly above the impeller - the inlet located $\frac{1}{4}$ of a turn clockwise from the outlet, due to the impeller turning clockwise. The impeller rate was set to 140 rpm, the highest rate possible for the equipment to run in a stable manner. MilliQ-water was filled into the mixing vessel up until the 1 L marking. MilliQ water was then pumped into the tubes until the tubes were completely filled with MilliQ-water. The water level in the mixing vessel was adjusted by adding more MilliQ-water until the 1 L mark.
The spectrophotometer was calibrated by running a dark blank without the cuvette and running a bright blank with the cuvette filled with air.

18 mg of methylene blue was diluted into 1 L MilliQ. A tube filled with MilliQ-water was placed into the bottle containing the diluted methylene blue. The spectrophotometer was set to record absorption before the tracer dye was started to pump the dye into the mixing vessel, a timer starting as the first volume of dye entered the mixing vessel. Approximately 3 L of MilliQ-water was subsequently pumped into the mixing vessel. A snapshot of the performed experiment is displayed in figure 13.

Calibration curves were analyzed, to find out which concentration corresponded to which absorbance.

4.5 Determining Degradation and Transformation Products

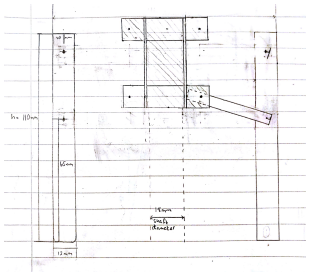
Individual standards of five selected compounds were spiked into a 2 L bottle of MilliQ, to obtain a concentration of 100 $\mu g \times L^{-1}$. Blank samples from the mixing chamber and the sample collection vessel were collected by mixing MilliQ inside the vessels. Control samples were collected from the spiked MilliQ-vessel, after having been mixed thoroughly. Ozone oxidized samples were collected in the sample collection vessel, after letting the first 2.5 to 3τ go to waste collection. The samples from the sample collection vessel was not mixed. All samples were collected in triplicates. Before any analysis, all samples were dosed with 10 ng of an isotopically labeled standard per sample. In the present study, blank samples were collected to check any pre-existing contamination.
The calibration curves were prepared in 1 mL by adding 10 ng of an isotopically labeled standard and varying doses - 0.5, 1, 5, 10, 25, 50, and 100 ng - of native standards.

5 Results

5.1 Construction of Baffles

The mixing vessel was not equipped with baffles, and neither was there any readily available. A process of outlining the mixing vessel's and the experiment's specific requirements was undertaken, and the following requirements were identified:

- The baffles must be expandable, small enough to fit through bottle neck and big enough to touch walls in the broader part of the vessel;
- The material of the baffle system should ideally withstand ozone oxidation;
- The material of the baffle system should ideally not adsorp chemicals of interest;
- There must be space to fit the mixing shaft;
- The baffle system must be stable enough to stop a solid-body rotation to develop.
- The baffle system should not be of a material which can be magnetized, due to the current setup utilizing magnetism to induce motion of the impeller.



(a) Part of the rough sketch of the baffle system to fit the requirements.

(b) A prototype, in cardboard, of the foldable baffle system.

(c) Finished product, in PVC, produced by constructor.

Figure 14: The process of developing the foldable baffle system, from sketch to finished product.

From the requirements stated above, a process of developing a baffle system which could fulfill these requirements was undertaken. The process is visualized in figure 14.
The produced baffle system fit inside the mixing vessel, it had space for the mixing shaft, it was stable enough to stop solid-body rotation to develop, and it was made of PVC - which was not magnetized, and has been said in the literature to have some ozone resistance. However, the baffle system's adsorption of the chemicals of interest was not known.

5.2 Aqueous Ozone

An iterative process of finding a way of dissolve ozone, and at the same time achieving different ozone doses, was taken. The placement of this step in the experiment setup is visualized in figure 15.

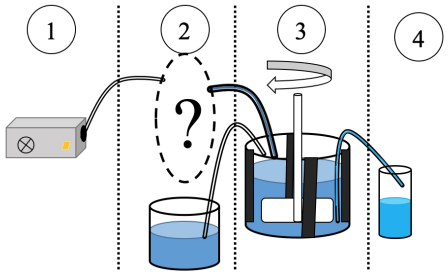


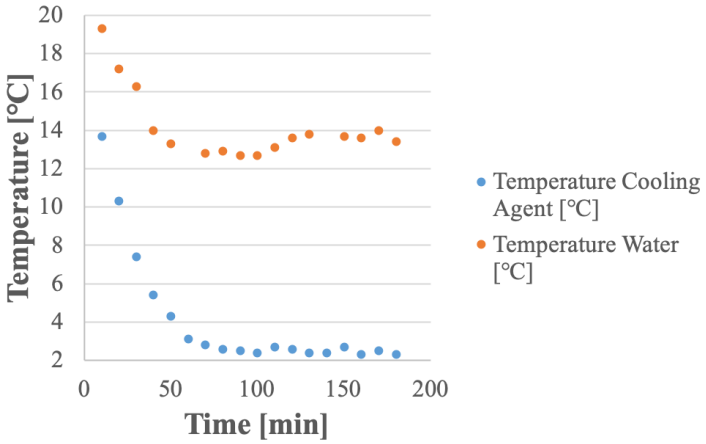
Figure 15: A sketch of the experiment setup. ①: Ozone generator. ②: "?" is representing the missing step for dissolving the gaseous ozone into the water, and the vessel in front contains the PPCP-spiked water. ③: The mixing chamber, where the aqueous ozone and the PPCP-spiked water is being mixed. ④: Collection of the ozone oxidized PPCPs.

The different approaches are presented in the chronological order of which they were tested.

5.2.1 Gas-washing Bottle

It has been described by Bader and Hoigné (1981) that a steady-state aqueous ozone dose of 40 $mgO_3 \times L^{-1}$ can be achieved by using a gas-washing bottle and distilled water chilled to 2°C. A similar approach was taken, however with different water matrices and temperatures, in an attempt to achieve different aqueous ozone doses. The setup for achieving a cooler temperature of the water-to-be-ozonated is pictured in figure 16a, however missing its cooling agent of regular tap water. The temperature of both the cooling agent and the water inside the gas-washing bottle are presented in figure 16b and values are presented in table B.1 in Appendix B.1.

(a) Setup for increasing the stability of aqueous ozone.



(b) Temperatures from the measurements of the setup in figure 16a, values in table B.1.

Figure 16: The setup for an attempted increased ozone dose through cooling (16a), and resulting temperatures (16b). NOTE: The setup in figure 16a was not in action at the time of the picture.

The results of the tested water matrices for dissolving gaseous ozone into water are presented in figure 17 and values for the concentrations are found in table B.2 in Appendix B.2.
It is shown that the temperature is an important factor for the aqueous ozone dose. Another important observation is the relatively quick rise to steady-state the chilled MilliQ exhibits, which generally also exhibits a higher ozone dose than that of tap water. Concentrations are not near concentrations of 40 $mgO_3 \times L^{-1}$, which has been reported by Bader and Hoigné (1981). Due to the gas-washing bottle's small volume (V=125 mL), this approach was abandoned.

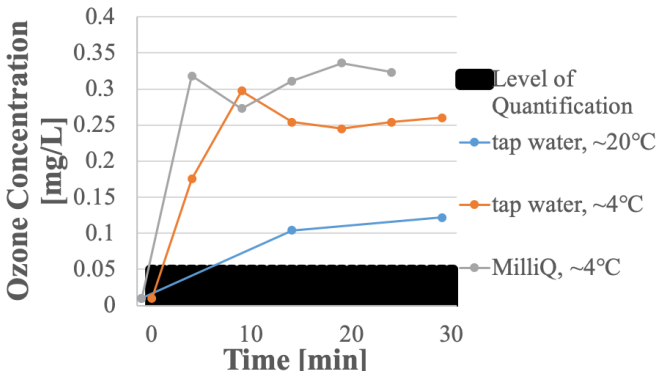


Figure 17: Dissolved ozone concentrations achieved using a gas-washing bottle, values in table B.2.

5.2.2 Aquarium Air Diffuser Stone

The second approach for dissolving ozone into water was by means of connecting six air diffuser stones (fig. 18), originally designed for aquarium use, to try to increase the area over which the ozone-containing gas can be dissolved. Measurements every 5 minutes over a 15 minute period of time was sampled.

Figure 18: Aquarium air diffuser stones, connected to a tube supplying ozone-containing gas. NOTE: The setup is not in operative state.

All samples of aqueous ozone concentration was below the level of detection for the instrument. The experiment was terminated after this 15 minute period.

5.2.3 Bubble Column

A bubble column was tested (fig. 19), as it was suspected that the similarities to the gas-washing bottle ratio could be a factor influencing gas dissolving. A back valve was installed at the bottom to the gas-feeding tube to prevent backflow of water. The gas flow was set to create as small bubbles as possible. Samples were collected every 5 minutes for 25 minutes directly from the bubble column.
All samples displayed values below the level of detection for the instrument.

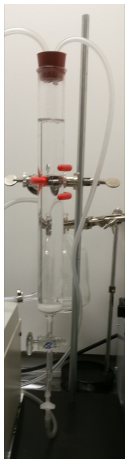


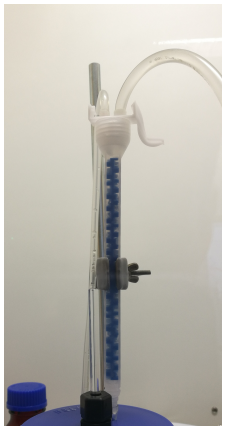
Figure 19: Bubble column setup, connected with one tube for gas flow and one tube for liquid flow.

5.2.4 Static Mixer

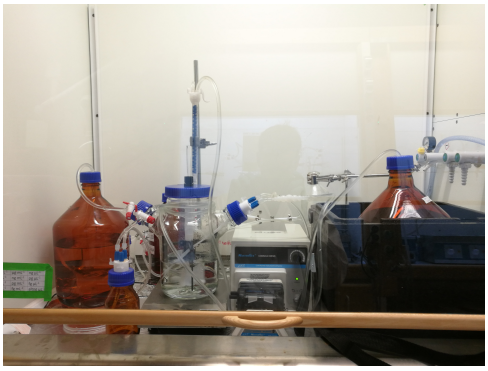
A static mixer was tested (fig. 20b). Noteworthy is that the setup for this approach includes *all* other steps of the experiment setup, as it was an integrated part of the setup (fig. 20c). With other words, no separate step to mix the gas into liquid is required, since the water-to-be-treated stream comes in contact

and mixes with the ozone-containing gas directly before entering the reactor vessel. The water-to-be-treated was cooled to better dissolve the ozone-containing gas (fig. 20a). Sampling was performed every 10 minutes for 40 minutes, and a final reading was performed 47 minutes after the experiment started due to the supplying MilliQ-water bottle was emptied.

(a) Setup similar to that presented in 5.2.1 Gas-washing Bottle, but larger in scale.



(b) The static mixer used in the experiments.



(c) The static mixer setup in full scale. Note that the static mixer is on top of the reactor vessel.

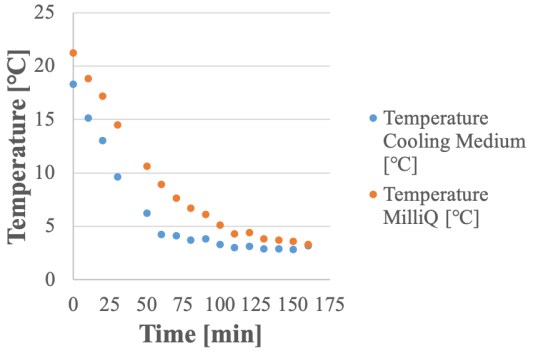
Figure 20: The setup for the static mixer approach, with emphasis on a few key parts of the equipment.

All samples were below the level of detection for the measurement method.

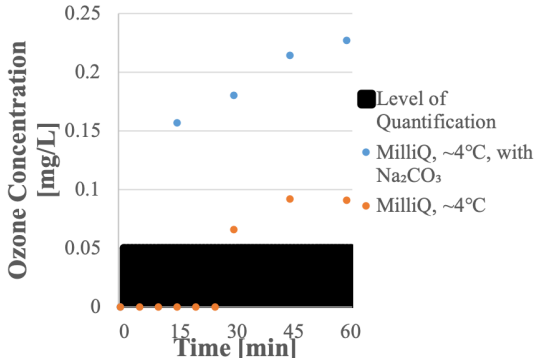
5.2.5 Aquarium Air Diffuser Stone - Revisited

The setup from 5.2.2 Aquarium Air Diffuser Stone was slightly altered - connecting the gas tubes leading to the diffuser stones by the means of Y-connectors (fig. 21) instead of the ring-shaped setup previously presented in figure 18 - and the ozone gas was allowed a longer time to enter the liquid phase. Temperature was adjusted to cooler temperatures (fig. 22a, values in table B.3 in Appendix B.3) as this parameter has been proven to increase the aqueous ozone doses in the previous setups, see 5.2.1 Gas-washing Bottle and figure 17. pH and alkalinity were other parameters which were adjusted, the results presented in figure 22b and values in table B.4 in Appendix B.4.
The addition of Na_2CO_3 to the chilled MilliQ increased the aqueous ozone concentration, the concentration more than double that compared to only chilled MilliQ.

Figure 21: The adjusted aquarium air diffuser stone setup, with gas inlet at the top and a gas outlet with a back valve installed on the left side.



(a) Temperature of the cooling medium and the MilliQ inside the ozone diffuser reactor. Values for the temperature are presented in table B.3.



(b) Effects of the aqueous ozone concentration after addition of Na_2CO_3, both waters chilled to steady-state temperature for MilliQ in figure 22a. Values in table B.4.

Figure 22: Temperatures of the cooling agent and the MilliQ inside the ozone diffuser reactor, as well as the resulting aqueous ozone concentrations of two water matrices differing in pH and alkalinity simultaneously.

5.3 Residence Time Distribution

The baffled mixing/reaction vessel - with its included but width-adjusted 60 mm Teflon (PTFE) impeller - was used for the experiment. The impeller speed was set to 140 rpm, the highest for the impeller to run in a stable manner. The pumping rate was set to approximately $1.\bar{6} \times 10^{-6}\ m^3 \times s^{-1}$ ($100\ mL \times min^{-1} \pm 4\ mL$), with the volume in the mixing vessel being 0.001 m^3 (1 L) to approximate a residence time of 10 minutes in the mixing/reactor vessel according to equation 2.
The data from the experiment is presented in is presented in figure 23.

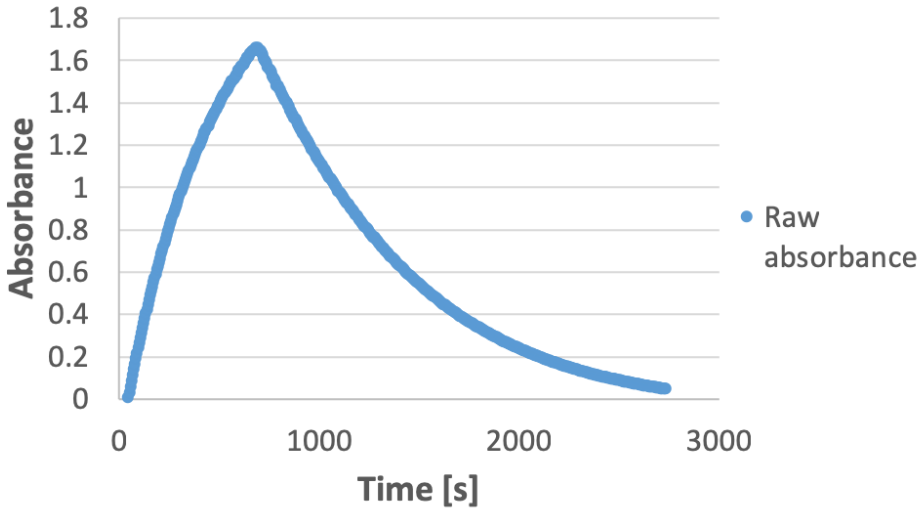


Figure 23: The non-normalized data from the residence time distribution experiment.

The starting volume was approximated to 1 L, and the volume at the end of the experiment was approximated to 0.95 L.

The absorbance data was correlated to the concentration of the methylene blue by the creation of a calibration curve. The calibration curve and the values associated with it is presented in Appendix B.5 Calibration Curve for RTD.

The mean residence time, which is used to calculate the normalized time below, was calculated with equation 3:

$$\bar{t} = \frac{\int_0^\infty Ctdt}{\int_0^\infty Cdt} \approx \frac{\sum \overline{C}t\Delta t}{\sum \overline{C}\Delta t} = \frac{1.1 \times 10^7}{12 \times 10^3} \approx 923\,s \approx 15\,min.$$

C_N, the value to normalize the concentration - and also determine the recovered tracer mass concentration - was calculated with equation 5:

$$C_N = \int_0^\infty Cd(\frac{t}{\bar{t}}) = \frac{\int_0^\infty Cdt}{\bar{t}} \approx \frac{\sum \overline{C}\Delta t}{\bar{t}} = \frac{12 \times 10^3}{923} \approx 13\,mg \times L^{-1}.$$

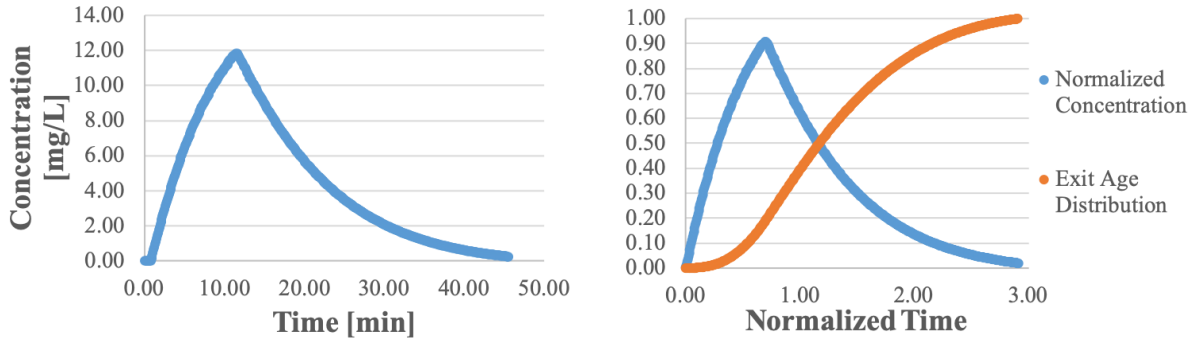
Equation 4 was used to calculate the normalized time:

$$\theta = \frac{t}{\bar{t}}$$

and equation 6 was used to calculate the normalized concentration:

$$E(\theta) = \frac{C_t}{C_N}.$$

The normalized concentration and the normalized time could then be plotted against each other (fig. 24b).



(a) The residence time distribution with respect to concentration.

(b) The concentration- and time-normalized residence time distribution.

Figure 24: The mean detention time (fig. 24a) and the normalized (fig. 24b) data from the residence time distribution experiment.

The variance with respect to time could then be calculated with equation 7:

$$\sigma_t^2 = \frac{\int_0^\infty (t-\bar{t})^2 C dt}{\int_0^\infty C dt} \approx \frac{\sum \overline{(t-\bar{t})^2 C} \Delta t}{\sum \overline{C} \Delta t} = \frac{39 \times 10^3}{200} = 193\, min^2,$$

meaning that the standard deviation is:

$$\sigma_t = \sqrt{\sigma_t^2} = 14\, min.$$

$$\bar{t} \pm \sigma_t = 15 \pm 14\, min.$$

5.4 Impeller, Blending, and Blending Quality

The impeller was cut down to a width of 60 mm (0.060 m), the impeller speed was displayed to be 140 rpm ($2.\overline{3}\ s^{-1}$), and the density and the dynamic viscosity of the water at 4°C was estimated with a table by Crittenden, Trussell, Hand, Howe, and Tchobanoglous (2012b) to be $10^3\ kg \times m^{-3}$ and $1.5 \times 10^{-3}\ N \times s \times m^{-2}$ respectively. With equation 8 it yielded:

$$Re = \frac{D^2 N \rho}{\mu} = \frac{(0.060[m])^2 \times 2.\overline{3}[s^{-1}] \times 10^3[kg \times m^{-3}]}{1.5 \times 10^{-3}[N \times s \times m^{-2}]} \approx 5.5 \times 10^3,$$

which means that from the impeller's kinetically induced motion in the liquid alone, the flow can be approximated to be in the transitional regime ($10^4 > Re > 10^2$).

The average dissipation rate per unit mass for the mixing vessel - which is used to determine the diameter of the smallest eddy below, and also where the dividing line between the macro- and microscale mixing was - had to be calculated with equation 12:

$$\bar{\varepsilon} = \frac{P}{M},$$

however P - the power of mixing input to the entire vessel - first had to be determined.

The moment of inertia was calculated by dividing the mixing shaft into its three main components - the flat blade, which was approximated with the equation for a thin plate; the magnetic stirrer bar, which was approximated with the equation for a cylinder; and the hollow shaft, which was approximated with the equation for a thick-walled cylindrical tube with open ends.

$$
\begin{cases}
①P = \vec{\tau} \cdot \vec{\omega} \Leftrightarrow ②, ③ \Leftrightarrow P = (-5.0 \times 10^{-4}\,[Nm]\hat{z}) \cdot (-15\,[rad \times s^{-1}]\hat{z}) = 7.4\,[mW] \\
②\vec{\omega} = 2\pi \cdot \nu = 2\pi \cdot -2.\overline{3}\,[s^{-1}]\hat{z} \approx -15\,[rad \times s^{-1}]\hat{z} \\
③\vec{\tau} = \dfrac{d\vec{L}}{dt} \Leftrightarrow \vec{\tau} \int_{t_0=0}^{t_1=1} dt = \int d\vec{L} \Leftrightarrow ④ \Leftrightarrow \\
\quad \vec{\tau} \times 1\,[s] = -5.0 \times 10^{-4}\,[kg \times m^2 \times s^{-1}]\hat{z} \Leftrightarrow \vec{\tau} = -5.0 \times 10^{-4}\,[Nm]\hat{z} \\
④\vec{L} = I\vec{\omega} = \Big(\sum \dfrac{1}{12} m_1 a^2 + \dfrac{1}{12} m_2 (h^2 + 3r^2) + \dfrac{1}{2} m_3 (r_1^2 + r_2^2)\Big)\vec{\omega} \Leftrightarrow ② \Leftrightarrow \\
\quad \Leftrightarrow I\vec{\omega} = \Big(\sum \dfrac{1}{12} 4.1 \times 10^{-3}\,[kg] \times 2 \times (25 \times 10^{-3}\,[m])^2 \\
\quad + \dfrac{1}{12} 37 \times 10^{-3}\,[kg]\big((76 \times 10^{-3}\,[m])^2 + 3(\dfrac{11}{2} \times 10^{-3}\,[m])^2\big) \\
\quad + \dfrac{1}{2} 83 \times 10^{-3}\,[kg]\big((8 \times 10^{-3}\,[m])^2 + (18 \times 10^{-3}\,[m])^2\big)\Big)(-15\,[rad \times s^{-1}]\hat{z}) = \\
\quad = (4.1 \times 10^{-7}\,[kg \times m^2] + 1.8 \times 10^{-5}\,[kg \times m^2] + 1.6 \times 10^{-5}\,[kg \times m^2])(-15\,[rad \times s^{-1}]\hat{z}) \\
\quad = (3.4 \times 10^{-5}\,[kg \times m^2])(-15\,[rad \times s^{-1}]\hat{z}) = -5.0 \times 10^{-4}\,[kg \times m^2 \times s^{-1}]\hat{z},
\end{cases}
$$

where the xy-axis was positive anticlockwise and the z-axis was pointed upwards. Returning to equation 12:

$$\bar{\varepsilon} = \frac{P}{M} = \frac{7.4 \times 10^{-3}\,[W]}{10^{-3}\,[m^3] \times 10^3\,[kg \times m^{-3}]} \approx 7.4 \times 10^{-3}\,J \times kg^{-1} \times s^{-1}.$$

From the above result, equation 11 could be used to calculate the diameter of the smallest eddy:

$$\eta = \left(\frac{v}{\bar{\varepsilon}}\right)^{\frac{1}{4}} = \left(\frac{1.5 \times 10^{-3}\,[N \times s \times m^{-2}]}{7.4 \times 10^{-3}\,[J \times kg^{-1} \times s^{-1}]}\right)^{\frac{1}{4}} = 0.67\,m.$$

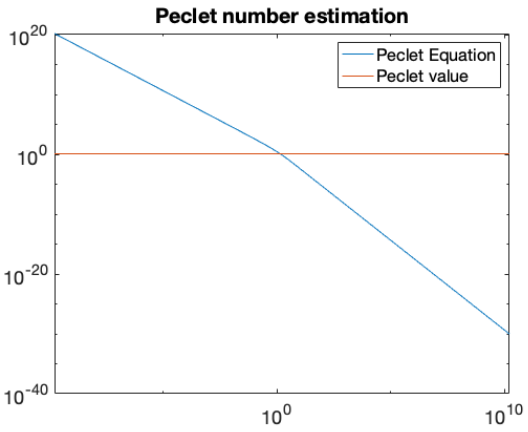
The radius of the smallest eddy was calculated with equation 15 - which is half of the diameter - and the result was put into equation 14 to calculate the time for the molecules to diffuse out of the eddy. The ozone liquid diffusivity was approximated by extrapolating data from Johnson and Davis (1996) for 277 K to $1.07 \times 10^{-9}\,m^2 \times s^{-1}$:

$$t_d = \frac{3R^2}{4D_l} = \frac{3(0.34\,[m])^2}{4(1.1 \times 10^{-9}\,[m^2 \times s^{-1}])} \approx 7.9 \times 10^7\,s.$$

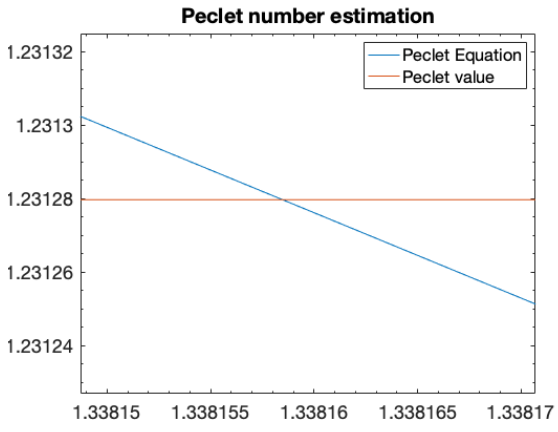
The dispersion in the vessel was determined by using equation 13 - using values of σ_t and $\bar{t}$ from the previous section, 5.3 Residence Time Distribution.

$$\frac{\sigma_t^2}{\bar{t}^2} = \left(\frac{2}{Pe}\right) - \left[2\left(\frac{1}{Pe}\right)^2 (1 - e^{-Pe})\right]$$

The value was approximated with a self-written MATLAB code, which can be found in Appendix C Matlab-Code for Determining the Peclet Number, the results presented in figure 25.
$Pe \approx 1.3$.



(a) Theoretical Peclet numbers (blue), and experimental value (orange).



(b) Figure 25a zoomed in to where the theoretical and experimental values meet.

Figure 25: The determination of the Peclet number (read on the x-axis) from experimental values.

The dispersion number could be calculated determined by inverting the Peclet number:

$$d = \frac{1}{Pe} = \frac{1}{1.3} \approx 0.75.$$

5.5 Kinetics and Transformation Products

The experiment setup included the step for dissolving the gaseous ozone from section 5.2.5 Aquarium Air Diffuser Stones - Revisited - a step which from now on will be referred to as the ”ozonation chamber”.
Calculations for the applied ozone dose is based on equation 9, which are presented in table B.6 in Appendix B.6 Applied Ozone Doses and Unblended Fractions. The calculations for the second-order reaction rate constants are presented in table B.7 in Appendix B.7 Reaction Rate Calculations.

5.5.1 Caffeine - Degradation

The initial concentration of the caffeine was approximately 100 $\mu g \times L^{-1}$. The ozone dose in the ozonation chamber was measured to 0.31 $mgO_3 \times L^{-1}$. The applied ozone dose was calculated to 0.25 $mgO_3 \times L^{-1}$.
The degradation of caffeine by ozone is displayed in figure 26. The concentration was reduced by approximately 50% as compared with the initial concentration. The second-order reaction rate constant was calculated to 3.0×10^3 $M^{-1}s^{-1}$.

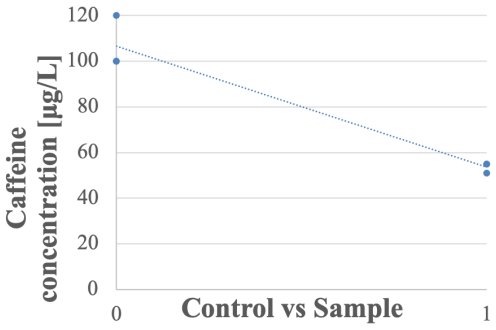


Figure 26: Degradation of caffeine of the ozone oxidation treatment.

Transformation products for caffeine could not be identified, as the underlying data for the identification of the transformation products (i.e. ionization fragments of the ozone transformation products) were not available in the literature.

5.5.2 Carbamazepine - Degradation and Transformation Products

The initial concentration of the carbamazepine was approximately 100 $\mu g \times L^{-1}$. The ozone dose in the ozonation chamber was measured to 0.38 $mgO_3 \times L^{-1}$. The applied ozone dose was calculated to 0.31 $mgO_3 \times L^{-1}$.
The degradation of carbamazepine by the ozone oxidation treatment is displayed in figure 27, and was determined to have reduced the concentration by 97%. The second-order reaction rate constant was calculated to 1.5×10^5 $M^{-1}s^{-1}$.

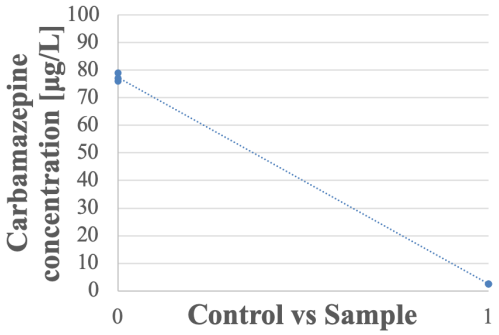
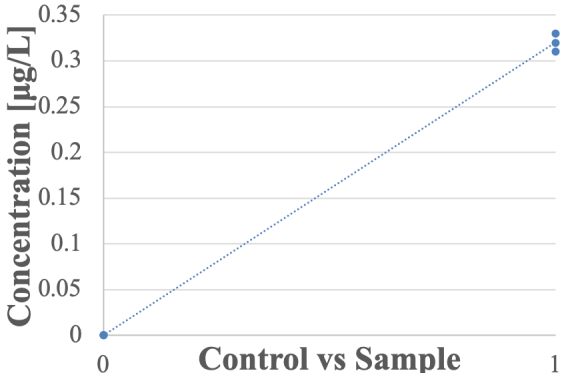
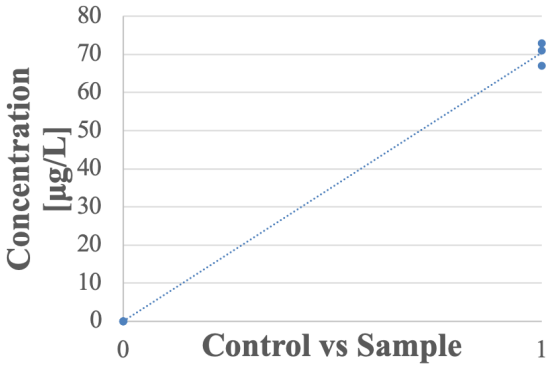


Figure 27: Degradation of carbamazepine of the ozone oxidation treatment.

A comparison was made of the findings of transformation products identified by Hübner et al. (2014), and analysis of the peaks in the LC-MS, identified two different transformation products. A semi-quantitative approach of the identified transformation products are presented in figure 28.



(a) Semi-quantitative concentrations of carbamazepine's minor transformation products, carbamazepine V.



(b) Semi-quantitative concentrations of carbamazepine's major transformation products, BQM.

Figure 28: Semi-quantitative concentration of carbamazepine's ozone oxidation transformation products.

The main identified transformation product was found to be 1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one (BQM), and the minor identified transformation product was carbamazepine V.

5.5.3 Fexofenadine - Degradation and Transformation Products

The initial concentration of the fexofenadine was measured to be approximately 100 $\mu g \times L^{-1}$.
The ozone dose in the ozonation chamber was measured to 0.57 $mgO_3 \times L^{-1}$. The applied ozone dose was calculated to 0.47 $mgO_3 \times L^{-1}$.
The degradation of fexofenadine is displayed in figure 29. The ozone oxidation treatment reduced the fexofenadine concentration by approximately 52%. The second-order reaction rate constant was calculated to 9.1×10^3 $M^{-1}s^{-1}$.

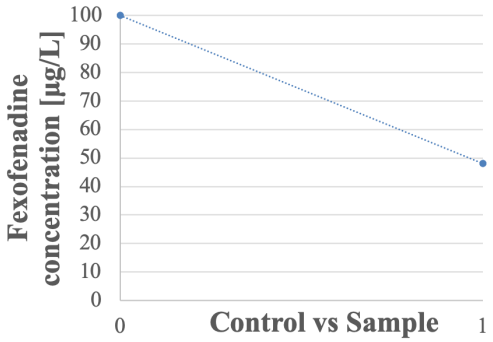


Figure 29: Degradation of fexofenadine of the ozone oxidation treatment.

For the identification of transformation products, the results were compared to the findings of Borowska et al. (2016). One transformation product was detected in small yields, however in concentrations below the level of quantification. The transformation product which was detected was fexofenadine N-oxide.

5.5.4 Lamotrigine - Degradation and Transformation Products

The initial concentration of lamotrigine was approximately 100 $\mu g \times L^{-1}$.
The measured ozone dose in the ozonation chamber was measured to 0.23 $mgO_3 \times L^{-1}$. The applied ozone dose was calculated to 0.19 $mgO_3 \times L^{-1}$.
The degradation of lamotrigine is displayed in figure 30, and the ozone oxidation treatment reduced the lamotrigine concentration by approximately 28%. The second-order reaction rate constant was calculated to 2.5×10^3 $M^{-1}s^{-1}$.
The transformation products for lamotrigine were not investigated.

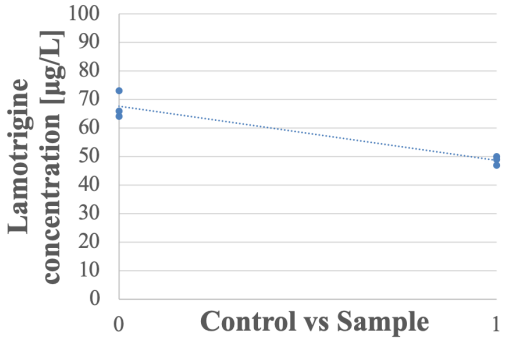


Figure 30: Degradation of lamotrigine of the ozone oxidation treatment.

5.5.5 Oxazepam - Degradation

A solution with an oxazepam concentration of approximately 100 $\mu g \times L^{-1}$ was prepared.
The ozone dose in the ozonation chamber was measured to 0.35 $mgO_3 \times L^{-1}$. The applied ozone dose was calculated to 0.28 $mgO_3 \times L^{-1}$.
The reduction of oxazepam is displayed in figure 31. The degradation of oxazepam by the ozone oxidation treatment was approximately 42%. The second-order reaction rate constant was calculated to $4.0 \times 10^3\ M^{-1}s^{-1}$.
The water level in the mixing chamber - where oxazepam and the aqueous ozone were mixed - fell from 1 L to approximately 0.5 L during the experiment period. It was noted that the water level in ozonation chamber - one of the inlet sources - was higher than usual, possibly being the cause of the water level decrease.
The ozone transformation products of oxazepam were not investigated.

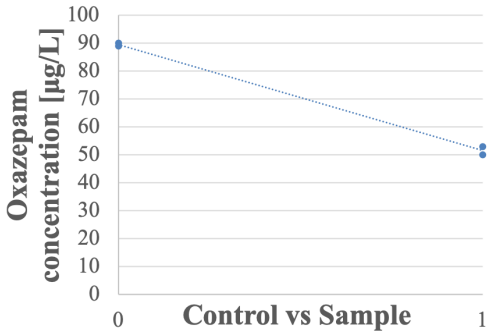


Figure 31: Degradation of oxazepam of the ozone oxidation treatment.

6 Discussion

The baffles were - due to the material they were constructed of - not stable over time and may have had an influence on the concentration of the reactants, possibly increasing adsorption and leaching over time due to increased brittleness of the material.
Alternate materials for the baffles were thought of (see subsection A.3 Stainless Steel Baffles in Appendix) however these ideas could not be realized within the project's time frame. Stainless steel could also have been affected of the magnetism from the magnetic stirrer plate from the current setup, which could have compromised the stability of the baffles.

Reduction of contamination of the samples was achieved by operating in closed systems, with most components being constructed of strong C-F bonds, e.g. Teflon, or inorganic compounds, i.e. glass. The peristaltic pump reduced contamination from the surroundings, the only contact the chemicals and the aqueous ozone having either in tubes or in the glass vessels. Any influence of gas entering the mixing vessel or the ozonation chamber was minimized by using back valves with Viton ® packings.

The mean residence time for the constituents in the mixing vessel, 15 min, exceeded that of the calculated hydraulic detention time, 10 min, which is contradicting the literature (Crittenden et al., 2012a). Furthermore, the residence time distribution data revealed that approximately 13 $mg \times L^{-1}$ of the injected 18 $mg \times L^{-1}$ was recovered, which is approximately 72% of the concentration mass. The recovered concentration is below the level of an acceptable tracer test (>95%), and a redo of the experiment could yield more reliable data. Another experiment might also reveal which pumping rate is needed to reach the desirable mean residence time of 10 min. One reason as to why such a relatively low amount of tracer mass concentration was recovered could be that

the measurements and the calibration curves were measured on different occasions. The Peclet number - and subsequently the dispersion number - were based on the results from the tracer test, and therefore unreliable. However, the calculated values could be considered to be a rough indicator of the resulting dispersion number.

The mixing was calculated to be in the transitional regime, which means the mixing vessel could not solely simulate turbulent conditions. The impacts of any increase in turbulent mixing due to the implementation of the baffles were not measured, however it was observed that a centralized vortex - which was developed when mixing without the baffles - did not develop. With support from the theory (see section 2.5.3 Blending Quality) it could be argued that the mixing with the baffles installed contributed to a break up of the two-dimensional flow, and increasing the top-to-bottom mixing inside the mixing vessel.

The rotational speed of the impeller was fairly low, which greatly affects how small eddies could be formed. The diameter of the smallest eddy formed by the mixing exceeded the size of the mixing vessel, creating difficulties drawing any conclusions. Furthermore, the calculations for the time for the ozone to diffuse out of an eddy of the formerly calculated size was based upon extrapolated values for the ozone diffusivity, creating even more uncertainties.

The tested methods of dissolving ozone into water was not exhaustive, as there exist more methods for this purpose (see for instance A.1 Ozone Gas Directly Into Mixing Vessel, A.2 Rushton Impeller, and Björlenius (2016); Gottschalk et al. (2009); Paul et al. (2004)). A different experiment setup might have have differing ozone mass transfer rates over the gas-liquid phase, and therefore deliver more consistent, and higher, aqueous ozone concentrations.

The difference between the method for dissolving gaseous ozone in section 5.2.5 Aquarium Air Diffuser Stone - Revisited and section 5.2.2 Aquarium Air Diffuser Stone could be dependent on several factors. In the former experiments, the gaseous ozone was allowed a longer time to enter the liquid phase, which is suspected to be the most important factor to the observed higher aqueous ozone doses. Another factor which could have contributed is the use of y-connectors instead of an o-ring for distributing the gas to the diffuser stones, possibly distributing the gas more evenly. A third factor could be the implementation of a back valve for the off-gas just outside of the ozone diffuser reactor, possibly influencing the gaseous concentration of ozone in the ozonation chamber and thus leading to a faster equilibrium between the gaseous phase and the aqueous phase inside the ozonation chamber.

The results from 5.2 Aqueous Ozone prove that there are several physio-chemical parameters which affect the aqueous ozone dose. The water matrix - more specifically TOC, temperature, pH, and alkalinity - did have an impact on which final concentrations could be achieved. Due to using the alkali Na_2CO_3 as a basic pH-adjusting agent, it is possible that the increased alkalinity contributed to the observed higher ozone doses in 5.2.5 Aquarim Air Diffuser Stone - Revisisted, as a higher pH lower the

stability of aqueous ozone (Crittenden et al., 2012a). A decision was however made *not* to add Na_2CO_3 to the water which was to be ozonated, due to possible pH-effects on the PPCPs when the aqueous ozone and the PPCP-spiked water were to be mixed.

For all the studied substances, the experiments were performed with ultra pure water. More advanced water matrices - for instance raw water, filtered raw water, or purified waste water - would likely yield different results, due to more advanced water matrices. The ozone could have to oxidize other substances in the more advanced water matrix than for ultra pure water and reach a steady-state later, as exemplified in figure 17 with tap water, which could lead to a lower degradation of PPCPs.

The aqueous ozone concentrations in the experiments with the PPCP substances were higher than during the investigation of a functioning setup, at times even higher than the concentrations achieved with added Na_2CO_3 (see fig. 22). Also, no adjustments of the sample preparation method for the determination of the aqueous ozone dose was done. It was however noted that small amounts of reagent was stuck inside the cap of the testing kit, and therefore not reacting with the aqueous ozone. This likely contributed to the higher observed aqueous ozone doses, if comparing the ozone doses measured in figure 22b and the ozone doses measured in the experiments with the PPCPs.

During the analysis of the degradation of caffeine, trace levels of caffeine was found in all blank samples ($\sim 3\ \mu g \times L^{-1}$). In comparison with the control sample (100 $\mu g \times L^{-1}$) and the ozone oxidized samples (55 $\mu g \times L^{-1}$), it did not have a big impact on the results. The degradation kinetics of caffeine during the experiments are higher than that reported by Rosal et al. (2009), $3.0 \times 10^3\ M^{-1}s^{-1}$ as compared to 0.25-1.1 $M^{-1}s^{-1}$. The deviation from reported values could be due to a range of factors, for instance: initial concentration of caffeine, ozone dose, contact time etc.

The degradation of carbamazepine was comparable to the, by Huber et al. (2003), reported kinetics, $1.5 \times 10^5\ M^{-1}s^{-1}$ and $3 \times 10^5\ M^{-1}s^{-1}$ respectively. The major transformation product from the experiments, BQM, is also the major transformation product found by Hübner et al. (2014). The other major transformation products found by Hübner et al. (2014) - BaQM, BQD, and BaQD - are formed from either the degradation of BQM or by an alternate, hydroxyl radical-dependent route. Since BQM has a low reaction rate with ozone but a rather high reaction rate with hydroxyl radicals (Hübner et al., 2014), and the fact that other transformation products were not detected, it is assumed that the oxidation of the carbamazepine was to a large extent controlled by molecular ozone.

The ozone dose measured at the ozone chamber for the experiments for fexofenadine was unusually high compared to the experiments with other substances - 65% higher, if a mean is taken over the aqueous ozone doses for caffeine, carbamazepine, and oxazepam. This could have been due to an error in the sample preparation, and since no extra measurement was made the sample preparation error cannot be ruled out. The kinetic reduction rate for fexofenadine is similar to those found by Borowska et

al. (2016), $9.1 \times 10^3\ M^{-1}s^{-1}$ and $9.0 \times 10^3\ M^{-1}s^{-1}$ respectively. The transformation products of fexofenadine was detected only in small quantities, and only fexofenadine N-oxide was detected. There is a possibility that, due to the ozone not being quenched at the end of the experiment, part of the transformation products further reacted with the ozone, and therefore also degraded.

The ozone dose was lower than those in the other experiments - 45% lower, if a mean is taken over the aqueous ozone doses for caffeine, carbamazepine, and oxazepam. Possible causes could be errors in the ozone sample measurements, which could be ruled out if duplicates of the ozone dose had been taken. The kinetic rate for the degradation of lamotrigine is higher than those reported by Keen et al. (2014), $2.5 \times 10^3\ M^{-1}s^{-1}$ and $\sim 4\ M^{-1}s^{-1}$ respectively. Possible explanations for this could be differing pH to that in the literature, and not having quenched the ozone after the experiment was performed.

The apparent second-order kinetic rate for the degradation of oxazepam was experimentally higher than the values found in the literature, $4.0 \times 10^3\ M^{-1}s^{-1}$ and $\sim 1\ M^{-1}s^{-1}$ respectively. Possible explanations for this could be the lack of ozone quenching at the end of the experiment. The water level in the mixing chamber was observed to have decreased during the time of the experiment, however it is assumed that this is not the cause of the higher calculated kinetic rate due to the fact that the water level inside the ozonation chamber appeared to be higher than in earlier experiments.

7 CONCLUSIONS

A baffle system made of PVC was constructed, to minimize solid-body rotation and to work with the experiment setup's requirements. Reduction of contamination was achieved by using experiment equipment made of ozone-resistant materials as well as performing the experiment in a closed system. An experiment setup to study the reduction kinetics of PPCPs with ozone oxidation was investigated, which resulted in an intermediate step to dissolve gaseous ozone into water, which concentration was measurable. The concentrations of aqueous ozone was in the interval of 0.19 and 0.47 $mgO_3 \times L^{-1}$ when used to oxidize substances.

A mechanically stirred vessel was used to mix aqueous ozone and selected PPCPs, where the Reynolds number of the system was calculated to be in the transitional regime. This meant that the goal of turbulent mixing was not achieved, however the contribution of the installed baffles to a more turbulent mixing was not taken into account but it is suspected to have contributed to an increased top-to-bottom mixing. A tracer study with methylene blue was performed, but the concentration mass of the tracer was to low to lead to any definitive conclusions. Based on the results of the tracer study, the mechanically stirred vessel was calculated to have a dispersion number of d=0.75 and the ozone liquid diffusivity in the experiments was approximated to be $7.9 \times 10^7\ s$.

Temperature and alkalinity appears to have had significant impacts on which aqueous ozone concentrations could be achieved. There appears to be a minor, but significant, difference between MilliQ and tap water for the steady-state concentration of aqueous ozone.

The second-order reaction rate of the studied compounds were in the order $k_{CBZ} >> k_{FXF} > k_{OXA} \approx k_{CAF} \approx k_{LAM}$. Carbamazepine's transformation products were identified by comparison with other experiments, with the main transformation product from the experiments presented in the results is BQM. Fexofenadine's transformation product, fexofenadine-N-oxide, was identified by comparison with other experiments, however not quantified.

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APPENDIX

A ALTERNATE IDEAS

In this section, ideas which were thought of will be presented, along with the reason why these ideas were not implemented into this project.
This section can partly be thought of as possibilities for improvement, and partly as valuable information to know what to avoid.

A.1 OZONE GAS DIRECTLY INTO MIXING VESSEL

An initial idea to introduce the ozone gas directly into the mixing vessel was thought of. However, due to the ozone generator only having an on/off-operation and not a variable ozone concentration, such a setup would have resulted in a strong dependence between the HRT and the ozone dose.
It is perhaps a possibility that a separate device to control the gas flow – possibly a manometer – could have been implemented, to achieve control of the gas pressure, but an uncertainty of gas pressure build-up in the current ozone generator's silicon tubing - possibly leading to the silicon tube breaking due to high internal pressure - it was deemed that such a solution was not suitable for this setup.

A.2 RUSHTON IMPELLER

After the decision of having a mixing reactor was made, an investigating process of improving the mixing through the impeller itself was undertaken. Rushton impellers, and its derivatives such as the Smith impeller, are cited in numerous publications in gas-liquid dispersion, e. g. Crittenden et al. (2012a); Paul et al. (2004); Scargiali (2007). This device can be mounted at the bottom of an overhead mixer which can add a more precise knowledge about the actual impeller speed, provided that the overhead mixer can display such information. It also increases the complexity of the setup, given that impeller speed needs to be at a certain rate to properly distribute the gas in the mixing vessel (Scargiali, 2007). This impeller speed could be close to the impeller shaft's natural frequency, something which, if not taken into consideration, ultimately could lead to the impeller shaft's breakdown (Paul et al., 2004).

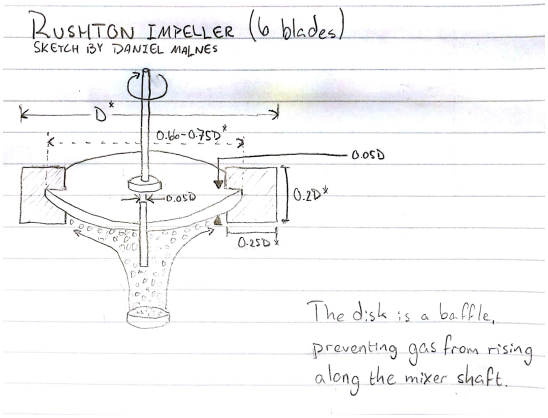

Figure A.1: A sketch of a Rushton impeller, and typical dimensions for such a device.

A.3 Stainless Steel Baffles

To improve the mixing, a baffle system made out of stainless steel was thought of. Due to the material's resistance towards ozone oxidation, together with the minimal adsorption of test substances to its surface, it was thought of as a good choice for this purpose. However, due to the setup relying on a magnetic stirrer, the metal construction would have been affected by the magnetic forces and most probably would have collapsed.
Another baffle system could have been used, which is the already-included baffles in the mixing jar. This would have circumvented the entire need of constructing a separate baffle device. Such a decision would have required a knowledge of how the setup would have been constructed in advance, and as such was not a viable option when the project was started.

B TABLES

In this section, tables from the experiments are presented, as to back up the figures displayed in 5 Results.

B.1 TEMPERATURES FOR GAS-WASHING BOTTLE SETUP

Table B.1: Measured temperatures in the cooling medium/agent surrounding the gas-washing bottle and the tap water inside the gas-washing bottle in figure 16b.

Time [min]	**Temperature Cooling Medium [°C]**	**Temperature Tap Water [°C]**
0	20	N.A.*
10	14	19
20	10	17
30	7.4	16
40	5.4	14
50	4.3	13
60	3.1	14
70	2.8	13
80	2.6	13
90	2.5	13
100	2.4	13
110	2.7	13
120	2.6	14
130	2.4	14
140	N.A.	N.A.
150	2.7	14
160	2.3	14
170	2.5	14
180	2.3	13

*N.A.: not available.
Additional note: Another reading, with approximately 10 times the volume compared to the test volume in the experiment, was performed. The water was transferred to a beaker where the temperature measurement device could fit, revealing the temperature to be 7.7 °C.

B.2 Concentrations for Gas-washing Bottle Setup

Table B.2: Measured concentrations of aqueous ozone, samples extracted directly from the gas-washing bottle. Values for figure 17.

Character of water: room temperature tap water.	
Time [min]	**Aqueous Ozone Concentration [mg/L]**
0	0.01
15	0.10
30	0.12
Character of water: chilled tap water.	
Time [min]	**Aqueous Ozone Concentration [mg/L]**
1	0.01
5	0.18
10	0.30
15	0.25
20	0.25
25	0.25
30	0.26
Character of water: chilled MilliQ.	
Time [min]	**Aqueous Ozone Concentration [mg/L]**
0	0.01
5	0.32
10	0.27
15	0.31
20	0.34
25	0.32

B.3 Temperatures for Air Diffuser Stones Setup

Table B.3: Measured temperatures in the cooling medium/agent surrounding the air diffusor reactor and the MilliQ inside the air diffusor reactor. Values for figure 22a.

Time [min]	**Temperature Cooling Medium [°C]**	**Temperature MilliQ [°C]**
0	18	21
10	15	19
20	13	17
30	9.6	15
40	N.A.	N.A.
50	6.2	11
60	4.2	8.9
70	4.1	7.6
80	3.7	6.7
90	3.8	6.1
100	3.3	5.1
110	3	4.3
120	3.1	4.4
130	2.9	3.8
140	2.9	3.7
150	2.8	3.6
160	3.2	3.3

N.A.: not available

B.4 Concentrations for the Air Diffuser Stones Setup

Table B.4: Measured concentrations of aqueous ozone, samples extracted directly from the gas-washing bottle. Values for figure 22b.

Character of water: chilled MilliQ.	
Time [min]	**Aqueous Ozone Concentration [mg/L]**
0	0
5	0
10	0
15	0
20	0
25	0
30	0.066
45	0.092
60	0.091
Character of water: chilled MilliQ with Na_2CO_3.	
Time [min]	**Aqueous Ozone Concentration [mg/L]**
0	0
15	0.16
30	0.18
45	0.21
60	0.23

B.5 Calibration Curve for RTD

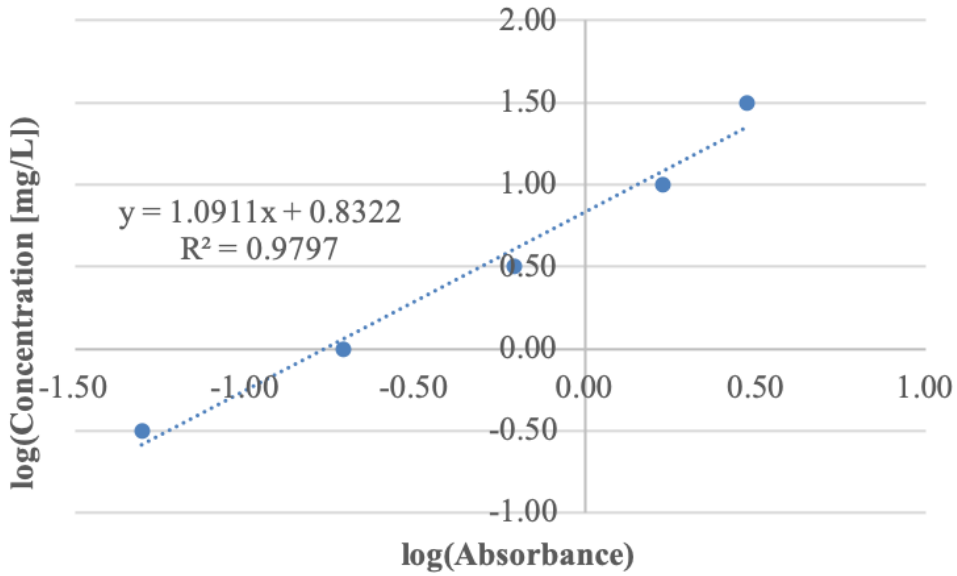

Figure B.2: The log-log transformed calibration curve, for correlating the absorbance and the concentration. Values presented in table B.5.

Table B.5: Dosed concentrations of methylene blue and the resulting absorbance response from the spectrophotometer - used to determine the calibration curve in figure B.2.

Concentration [$mg \times L^{-1}$]	0.32	1	3.2	10	32
log(Concentration)	-0.5	0	0.5	1	1.5
Absorbance [*unitless*]	0.050	0.19	0.62	1.7	3.0
log(Absorbance)	-1.3	-0.71	-0.21	0.23	0.47

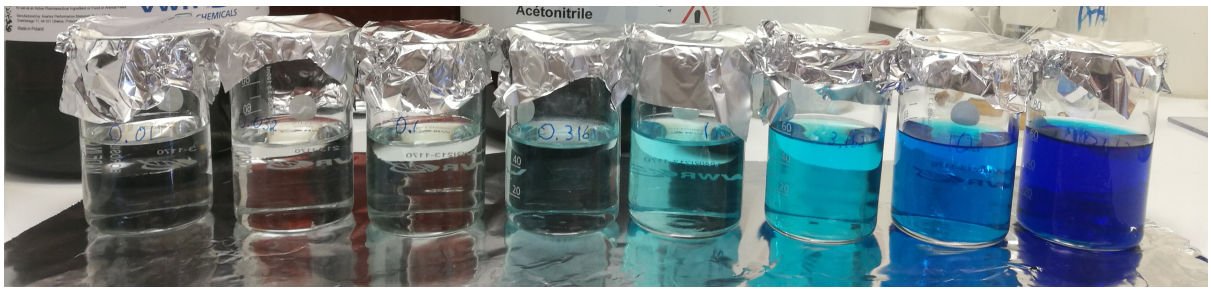

Figure B.3: The increasing concentration of methylene blue, used to determine the calibration curve in figure B.2. The two left-most concentrations could not be used due to negative absorbance values, and the third concentration from the left was excluded as it was an outlier. Remaining values are presented in table B.5.

B.6 Applied Ozone Doses and Unblended Fractions

Table B.6: Calculations based on equation 9 for evaluating the applied ozone dose based on the concentration in the feed stream and the flow rate of the to-be-treated stream, and equation 10 for approximating the unblended fraction.

Substance	Q_A $[mL \times min^{-1}]$	Q_W $[mL \times min^{-1}]$	C_A $[mgO_3 \times L^{-1}]$	$C_{dose} (= \frac{Q_A \times C_A}{Q_W})$ $[mgO_3 \times L^{-1}]$	$\overline{X}_A (= \frac{C_{dose}}{C_A + C_{dose}})$ $[unitless]$
CAF			0.31	0.25	0.45
CBZ			0.38	0.31	0.45
FXF	46	56	0.57	0.47	0.45
LAM			0.23	0.19	0.45
OXA			0.35	0.28	0.45

Q_A: Feed stream flow rate.
C_A: Concentration of ozone in the feed stream.
Q_W: Flow rate of the to-be-treated water stream.
C_{dose}: Applied ozone dose.
$\overline{X}_A$: volume fraction of stream containing ozone in unblended condition.
CAF: caffeine, CBZ: carbamazepine, FXF: fexofenadine, LAM: lamotrigine, OXA: oxazepam.

B.7 Reaction Rate Calculations

For the calculation of the reaction rate, an average was taken over the measured concentrations of the collected samples ($\overline{C}$) of the control and the ozone oxidized samples which was divided by the molar mass (M)

$$[X] = \frac{\overline{C}}{M}$$

$\frac{1}{[X]}$ is plotted against t, and k is read as the slope between the value for the control and the value for the sample.

Table B.7: Calculations of the second-order rate kinetic constants for the investigated substances, based on values from the performed experiments.

	Caffeine	
	Control	Samples
$\overline{C}$ $[\frac{g}{L}]$	110×10^{-6}	54×10^{-6}
M $[\frac{g}{mol}]$	194	
$[CAF]$ $[\frac{mol}{L}]$	5.5×10^{-7}	2.8×10^{-7}
$\frac{1}{[CAF]}$	1.8×10^{6}	3.6×10^{6}
t [s]	600	
k $[M^{-1}s^{-1}]$	3.0×10^{3}	

	Carbamazepine	
	Control	Samples
$\overline{C}$ $[\frac{g}{L}]$	77×10^{-6}	2.5×10^{-6}
M $[\frac{g}{mol}]$	236	
$[CBZ]$ $[\frac{mol}{L}]$	3.3×10^{-7}	1.1×10^{-8}
$\frac{1}{[CBZ]}$	3.1×10^{6}	9.3×10^{7}
t [s]	600	

k $[M^{-1}s^{-1}]$	1.5×10^5

	Fexofenadine	
	Control	Samples
$\overline{C}$ $[\frac{g}{L}]$	100×10^{-6}	48×10^{-6}
M $[\frac{g}{mol}]$	502	
$[FXF]$ $[\frac{mol}{L}]$	2.0×10^{-7}	9.6×10^{-7}
$\frac{1}{[FXF]}$	5.0×10^6	1.1×10^7
t [s]	600	
k $[M^{-1}s^{-1}]$	9.1×10^3	

	Lamotrigine	
	Control	Samples
$\overline{C}$ $[\frac{g}{L}]$	68×10^{-6}	49×10^{-6}
M $[\frac{g}{mol}]$	256	
$[LAM]$ $[\frac{mol}{L}]$	2.6×10^{-7}	1.9×10^{-7}
$\frac{1}{[LAM]}$	3.8×10^6	5.3×10^6
t [s]	600	
k $[M^{-1}s^{-1}]$	2.5×10^3	

	Oxazepam	
	Control	Samples
$\overline{C}$ $[\frac{g}{L}]$	90×10^{-6}	52×10^{-6}
M $[\frac{g}{mol}]$	287	

$[OXA]$ $[\frac{mol}{L}]$	3.1×10^{-7}	1.8×10^{-7}
$\frac{1}{[OXA]}$	3.2×10^{6}	5.6×10^{6}
t [s]	600	
k $[M^{-1}s^{-1}]$	4.0×10^{3}	

C MATLAB-CODE FOR DETERMINING THE PECLET NUMBER

```
clear; close all; clc;
%% Calculations for determining the Peclet number

check=(15.3834^2)/192.1976; % Value to check against when calculating Pe

check_low=log(check)-10;
check_high=log(check)+10;

p=logspace(check_low,check_high,1000)'; % Creating a vector with 1000 values between 10^check_low and 10^check_high
p_e=zeros(size(p)); % Creating a storage vector for input of calculated values in for-loop below

% for-loop to calculate Pe-values
for i=1:size(p)
x=p(i); % value is whatever is in position i in the vector p
p_e(i)=(2/x)*((2*(1/x)^(2))*(1-exp(-x))); % the value is calculated with the equation, and stored in the i:th position in vector p_e
end

check_vector=zeros(size(p));

for i=1:size(p)
check_vector(i)=check;
end

plot1=loglog(p,p_e,'-');
title('Peclet number estimation')
xlim([p(1) p(end)])
hold on
plot2=loglog(p,check_vector,'-');
hold off
legend([plot1,plot2],'Peclet Equation','Peclet value')
```