



**REMOVAL OF PHARMACEUTICALS FROM WASTEWATER/ LIQUID WASTE  
BY SONOCAVITATION**

Lappeenranta–Lahti University of Technology LUT

Master's Programme in Chemical Engineering

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## ABSTRACT

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### **Removal of Pharmaceuticals From Wastewater/ Liquid Waste by Sonocavitation**

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Examiner(s): Professor, Amit Bhatnagar and Professor, Susana Rodríguez Couto

Keywords: sonocavitation, pharmaceutical wastewater, membrane filtration, activated carbon, hydroxyl radical, advanced oxidation process

Water treatment technologies based on cavitation enable the purification of wastewater in an energy-efficient manner and with no or less use of oxidizing chemicals. The aim of this work is to find out the suitability of ultrasonic cavitation for the treatment of pharmaceutical factory wastewater/liquid waste, focusing especially on the oxidation of organic substances and the formation of possible harmful by-products.

In the theory part of the diploma thesis, the necessity of pharmaceutical compounds, the principle of pharmaceutical production and the environmental effects arising from the production of active pharmaceutical compounds, especially in terms of the aquatic environment, are reviewed. Different treatment methods for pharmaceutical industry waste are presented, as well as the composition of liquid waste from the pharmaceutical industry based on literature sources. In the theory part, various wastewater treatment methods of the pharmaceutical industry are presented, such as advanced oxidation processes, different forms of cavitation and the theory related to cavitation, especially in terms of ultrasound cavitation.

Based on the explanations of the theory part, a sampling and research plan was drawn up, and pilot-scale test equipment was assembled, which was used for test runs. In the work, it was noticed that in the ultrasonic cavitation treatment, pharmaceutical substances were broken down and volatile organic compounds were well removed from the treated water, but due to the formation of solid matter and the high organic load, the method needs a catalyst to enhance oxidation, an optimal pH to work effectively and the removal of solid matter in order to use the method to reach concentrations in which the treated water does not have environmental impacts.

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### **Lääkeaineiden poisto lääketehtaan jätevedestä/ nestemäisestä jätteestä ultraäänikavitaatiolla**

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Kavitaatioon perustuvat vedenkäsittelytekniikat mahdollistavat jäteveden puhdistuksen energiatehokkaasti ja ilman tai vähemmällä hapetuskemikaalien käytöllä. Työn aiheena on selvittää ultraäänikavitaation soveltuvuus lääketehtaan jäteveden/ nestemäisen jätteen käsittelyyn keskittyen erityisesti orgaanisten aineiden hapettamiseen ja mahdollisten haitallisten sivutuotteiden muodostumisen selvittämiseen.

Diplomityön teoriaosuudessa käydään läpi lääkeaineiden tarpeellisuus, lääkeaineiden tuotannon periaate sekä lääkeaineiden tuotannossa syntyvät ympäristövaikutukset erityisesti vesiympäristön kannalta. Lääketeollisuuden jätteiden eri käsittelymenetelmät esitellään sekä lääketeollisuuden nestemäisen jätteen koostumus kirjallisuuslähteisiin perustuen. Teoriaosuudessa esitellään eri lääketeollisuuden jäteveden käsittelymenetelmät, kuten kehittyneet hapetusprosessit, kavitaation eri muodot ja kavitaatioon liittyvä teoria erityisesti ultraäänikavitaation kannalta.

Teoriaosuuden selvitysten perusteella laadittiin näytteenotto- ja tutkimusohjelma sekä koottiin pilot-mittakaavan koelaitteisto, jolla tehtiin testiajoja. Työssä huomattiin, että ultraäänikavitaatiokäsittelyssä lääkeaineiden hajoamista tapahtuu ja haihtuvat orgaaniset yhdisteet poistuvat käsiteltävästä vedestä hyvin, mutta kiintoaineen muodostumisen ja korkean orgaanisen kuormituksen vuoksi menetelmä tarvitsee katalyyttia hapettumisen tehostamiseksi, optimaalisen pH:n toimiakseen tehokkaasti ja kiintoaineen poiston, jotta menetelmän avulla päästään pitoisuuksiin, joissa käsitelty vesi on ympäristöön johtamiskelpoista.

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In Tampere 2 April 2024

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## SYMBOLS AND ABBREVIATIONS

$c$	conductivity	[mS/m]
$c$	speed of sound	[m/s]
$f$	frequency	[1/ $T_a$ ]
$p$	pressure	[bar, Pa]
$I$	acoustic intensity	[W/m <sup>2</sup> ]
kDa	unit of molecular weight	
redox	redox potential	[mV]
$T$	temperature	[°C, K]
$U$	voltage	[V]
$\lambda$	wavelength	[ $\mu\text{m}$ ]
$p_a$	acoustic pressure amplitude	[N/m <sup>2</sup> , Pa]
$\rho_0$	density	[kg/m <sup>3</sup> ]
$T_a$	acoustic period	[1/s]

AC	Sonocavitation or Acoustic Cavitation
AOP	Advanced Oxidation Process
AOX	Adsorbable organic halides
API	Active Pharmaceutical Ingredient
BOD	Biological Oxygen Demand
COD	Chemical Oxygen Demand
FNU	Formazine Nephelometric Units
HAA	Haloacetic Acids
LEL	Lower Explosion Limit
TDS	Total Dissolved Solids
THM	Trihalomethanes
TKN	Total Kjeldahl Nitrogen
TOC	Total Organic Carbon
TOX	Total Organic Halides
TSS	Total Suspended Solids
US	Ultrasound
ZVI	Zero Valent Iron
VOC	Volatile Organic Compounds

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# 1 Introduction

## 1.1 Background

The presence of pharmaceuticals in waterways is one of the emerging concerns related to wastewater, waterways and the aquatic ecosystem biodiversity. Pharmaceutical compounds affect water ecosystems as they affect humans and animals when consumed in higher concentrations; and when they break down, they can be even more hazardous to the environment than their original formulation due to the formation of toxic by-products or metabolites. When exposed to the environment, the natural functioning of organisms is affected and puts them at risk. Studies show that active pharmaceutical compound toxicity level increases when they occur in mixtures as a result of a synergistic effect (Verlicchi et al. 2017).

In addition, the pharmaceutical industry uses large amounts of solvents, salts, nitrogen and fluorine compounds, as well as acids and bases, which end up in waterways along with wastewater. The analytical tools to analyze pharmaceutical compounds have developed enormously in recent years and new methods have been developed to remove pharmaceutical compounds from wastewater. (Luo et al. 2019)

In this work, the Advanced Oxidation Process (AOP) technique, ultrasonic cavitation, and its effectiveness in the treatment of pharmaceutical wastewater is investigated.

The work presents the generation of wastewater containing pharmaceutical compounds, simulating the composition of wastewater from the pharmaceutical industry. This study simulates the amount of wastewater produced and what harmful substances it contains in addition to active pharmaceutical ingredients (APIs). In addition, the study briefly explains how wastewater containing pharmaceutical compounds is currently treated. The operating principle and the chemical reactions ultrasonic cavitation create are presented.

The quality and properties of the treated wastewater are presented based on literature sources and analysis results for the following parameters: Chemical oxygen demand (COD), water content, biological oxygen demand (BOD), total organic carbon (TOC), evaporation residue, hardness, fluoride, chloride, sulfate, total solids, total nitrogen, ammonium nitrogen and pH.

## 1.2 Research Problem

Wastewater from the pharmaceutical industry is different in composition with regard to different factories, production processes and pharmaceutical compounds in production. In this work, the aim was to find out the concentration levels for process washing and rinsing waters and to test the ultrasonic cavitation method in a practical application for these waters.

In this study, the first goal was to test the efficiency of different cavitation intensities/frequencies for water treatment. For this purpose, the effect of temperature, pH and feed water concentration on the efficiency of the method was evaluated. In addition, the physicochemical composition of the water were analysed in relation to the efficiency of the method.

There are no clear studies in the literature on the effectiveness of the cavitation method for removing pharmaceutical compounds from pharma production facility wastewater, nor there are clear research results on the effect of cavitation in the physicochemical properties of water, such as the effect of cavitation on the concentrations of various substances, including nitrogen, phosphorus, COD, pH, fluoride, chloride, sulfate and heavy metals. (Zeng et al. 2015)

In this study, another goal was to present the concentration levels of the physicochemical parameters of the pharmaceutical factory's wastewater. The literature suggests that various substances can be present in the pharmaceutical factory's wastewater, but there are very few, if any, research results on similar waters in the literature regarding the concentration levels of different compounds.

The third goal of the work was to find out whether harmful by-products are produced in API water treatment using the ultrasonic cavitation method.

The results of the work are presented by comparing the concentration of the original sample water with the concentration after the ultrasonic cavitation treatment. If necessary, the pH or concentration of the feed water was adjusted. These changes were recorded and presented in the work. The purpose was to achieve the greatest possible reductions with respect to the feed water by enhancing the necessary unit processes. (Thanekar et al. 2018)

### 1.3 Materials and methods

The pharmaceutical compounds-containing wastewater samples were collected from a load of liquid waste coming to one of Fortum Waste Solutions' processing facilities on the 13<sup>th</sup> of November 2023. Immediately after sampling, the test water was stored in a refrigerator at a temperature of about 6 °C and the laboratory samples were delivered to the analyzing laboratories in insulated cold packs. Laboratory samples were analysed for pharmaceutical compounds in accordance with the EPA 1694 method in a third-party accredited laboratory (EPA, 2007). The physicochemical analyses of the samples were made in one of the accredited laboratories of Fortum Waste Solutions.

Once the physicochemical analyses were made and the concentration levels were known, the necessary pretreatment methods were selected (for example, filtration or pH adjustment with acid or base), after which the sample was treated with ultrasonic cavitation. Processing can be done as a batch process or through flow using a separate flow chamber. Method testing was carried out with separate equipment assembled for this test processing.

We used UIP2000hdT-230 ultrasonic equipment (Hielscher Ultrasonics GmbH, Germany) for conducting the sonocavitation experiments. The device was equipped with a flow chamber and the maximum supply pressure was 5 bar. The equipment was supplemented with the necessary pumps and tanks/containers, so that the adjustment of the process was successful. During the pilot tests, necessary measurements were made with handheld devices (for example, conductivity, redox, pH, temperature, and for gases, for example, lower explosion limit (LEL) and oxygen measurements).

The results were written down in the protocol and at the end of the test run. The same samples as the baseline untreated sample water were taken and analysed in the same laboratories.

After the results were completed, the process effectiveness was assessed and further development actions are presented to improve the process.

## 2 Production and use of pharmaceuticals

People have used medicines or believed healing substances for over 3,000 years. At that time, diseases were cured with substances found in nature. The industrial production of pharmaceuticals like today started at the end of the 19th century. Determining medicinal substances according to their chemical, physical, biological or structural properties is difficult, as they can be all of the above. Medicinal substances are all substances that are used to treat people and living creatures like animals. (Taylor, D. 2016)

Medicines are used to treat thousands of different diseases and ailments that people suffer from. Medicines are essential for functioning health care. However, the use of medicines causes direct and indirect effects on the environment, which must be solved and managed responsibly. (WHO, 2023)

### 2.1 Pharmaceutical manufacturing, production and waste quantities

In general, the preparation of pharmaceuticals takes place in two stages. In the first stage, a mass of pharmaceutical compounds is synthesized from the raw materials, and in the second stage, the actual product is made in the form of tablets, solutions or creams. (Figure 1) Alkalis, acids, organic solvents and salts in various forms are used as raw materials for drug synthesis. In the same factory, dozens of different pharmaceuticals may be produced, in which case, the process equipment must be washed at the end of each product batch, and process washing waste is generated from this. (Velageti et al. 2002)

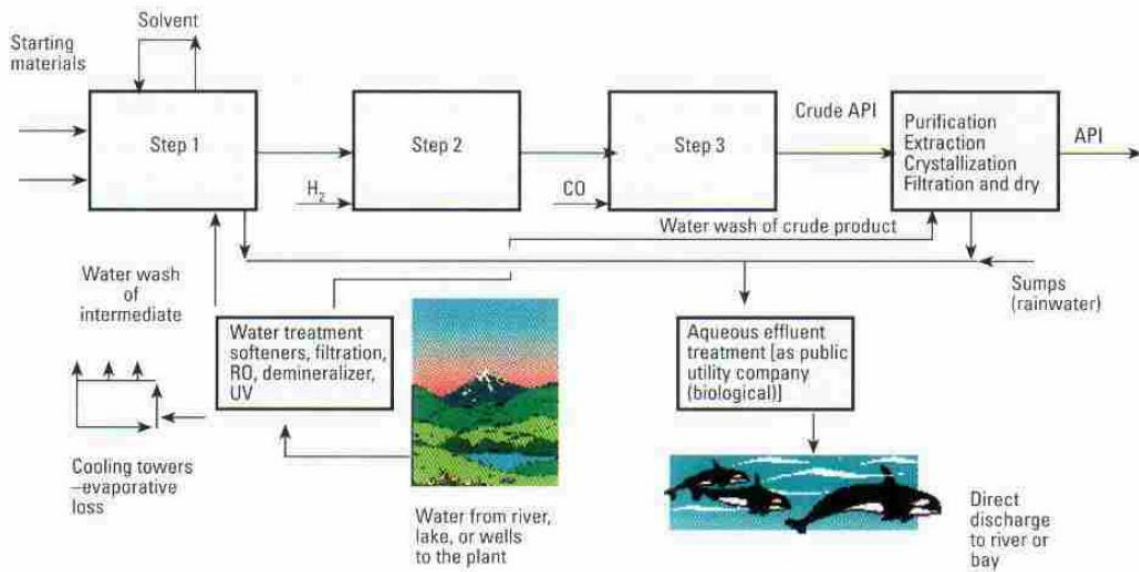


Figure 1. Flow chart of a typical API manufacturing facility (Velageti et al. 2002)

## 2.2 The use of medicinal substances and ending up in waterbodies

Medicinal substances can end up directly in the waterways from the production of medicinal substances or indirectly by passing through the wastewater treatment and purification process. In accordance with good manufacturing practices, wastewater discharge must be monitored and also rainwater falling on the factory area and all process water in contact with pharmaceuticals must be directed to the cleaning process. (Velageti et al. 2002)

Medicinal products end up in municipal wastewater treatment plants as a result of human activity when medicines are used. The largest concentrations come, for example, from wastewater from hospitals and treatment facilities. In an urban environment, wastewater is typically treated with a biological cleaning process, which is an ineffective cleaning method for many medicinal substances or only partially breaks down the medicinal substances into intermediate products of the active pharmaceutical ingredients. These intermediates can be more toxic to the environment than the original drugs. (Verlicchi, P. 2018)

Most of the active pharmaceutical compounds end up in the environment after the wastewater treatment process. This means that the current wastewater treatment processing is deficient in this respect. Some pharma substances can also end up in soil and agricultural cycles. This can happen, for example, from the spreading of sewage sludge on fields, the use of contaminated water for irrigation, the reuse of dredged masses or sediments from the

vicinity of wastewater treatment plant discharge pipes as a soil conditioner or in earthworks, the use of polluted groundwater, along with landfill leachate, or from medicines used for animal care. (Okeke et al. 2022)

### 2.3 Effects of pharmaceuticals on water bodies and the environment

Active pharmaceutical ingredients act in the environment in the same way as their original purpose of use, in which case, for example, sedative pharma substances calm the species in the aquatic environment and prevent their natural way of functioning.

Research has found that, for example, pharmaceutical hormones ending up in water bodies can cause a distortion of the natural gender distribution in fish, which manifests itself to a large extent as a higher proportion of female fish. Antimicrobial resistance is a risk to the aquatic environment that manifests itself as the spread of antimicrobials that have entered the environment and bacteria resistant to them and the emergence of new resistance genes under suitable conditions. New antimicrobial-resistant bacteria from nature can find their way back to humans and cause diseases for which there are no treatments. (Garcia et al. 2020). Antibiotic resistance is a recognized risk (UNEP 2022), and in order to control it, the World Health Organization (WHO) has issued guidelines for the use of antibiotics and created a separate monitoring system AWaRe (Access, Watch and Reserve) to support the countries of the world to understand, guide and monitor the matter. (WHO 2023)

Drug synthesis is often multi-step, and the intermediate stages of active pharmaceutical compounds can be more toxic than the finished drugs (final product). When entering the water, the drugs may break down into intermediate substances, in which case the damage to the aquatic life can be devastating.

Active pharma substances can affect the environment in many ways. They can hinder plant growth and reduce yields. On the other hand, plants can be used to break down active pharmaceutical compounds through phytoremediation.

Some active pharmaceutical compounds, such as psychoactive pharmaceutical compounds, accumulate/enrich in the food chain and have been found, for example, in the brain, liver and kidneys of predatory fish (brown trout). Psychoactive pharma substances accumulate in the fattiest tissues of fish. (Grabicova et al. 2017).

### 3 Composition and current treatment methods of wastewater generated in API production

In API production, active pharmaceutical ingredients are synthesized from inorganic and organic raw materials, which are used as medicines for humans and animals. The physicochemical composition of one of the wastewaters produced in API production has been clarified in a study (Changotra et al. 2020), from which the table shown below (Table 1.) has been created.

Table 1. Physicochemical composition of one API production wastewater (Changotra et al. 2020)

Parameter	Concentration
pH	7.12 ± 0.35
Color	Dark brown
BOD <sub>5</sub>	25650 ± 245
COD	52856 ± 365
BOD <sub>5</sub> /COD	0.48 ± 0.06
TOC	12440 ± 146
TSS	10560 ± 278
TDS	39890 ± 580
TKN	3450 ± 140
Nitrate	23 ± 1.10
Nitrite	69 ± 3.2
Sulfates	10254 ± 275
Chloride	9020 ± 260
Phosphate	1.9 ± 0.32

*Note:* In the table, the values are presented in milligrams per liter (mg/ L), except for the BOD<sub>5</sub>/COD ratio, color and pH.

#### 3.1 Properties of pharmaceutical wastewater

The wastewater generated in API production is synthesized from chemical raw materials in several different steps. They contain high COD concentrations, while BOD concentrations are clearly lower. A low BOD/COD ratio is a sign of weak biodegradability, which improves with treatment, when strongly stable APIs gradually break down closer to the raw materials.



Regarding biotoxicity, raw API wastewater with a high COD concentration is fundamentally more biotoxic than water with a lower COD concentration. (Liu et al. 2016)

### 3.2 Treatment of medicinal wastewater and liquid waste

Nowadays API wastewater is treated with conventional methods. The structure of API substances is often very complex and they are synthesized in several steps, in which case there can be several media/phases. Typically, the wastewater generated in API production is treated with a biological wastewater treatment process. The advantages of this process are that the treatment works well for waters containing easily degradable organic matter. However, due to the complexity of the API substances, the end result may be partially decomposed active substances, in which case the cleaning result will be insufficient and the dangerous properties of API compounds will remain. (Vieno et al. 2007)

A large amount of API wastewater is also treated by chemical oxidation with the so-called Fenton process, where the pH of the water is lowered using sulfuric acid and the organic substances are broken down by chemical oxidation with hydrogen peroxide (Liu et al. 2016). Oxidation is often enhanced with ultraviolet light. Even with this method, the efficiency of the process might be low due to the nature of the API substances. (Blum et al. 2017)

Reverse osmosis and nano- and ultrafiltration are also typical treatment methods for API waters. The result of these methods is often good, especially with reverse osmosis, but the amount of rejects generated during the treatment is significant, so the functionality, especially for large amounts of water, is not cost-effective. In addition, API waters may contain high concentrations of organic solvents, which shorten the service life of the membranes. (Kodamatani et al. 2023)

Adsorption using activated carbon filtration is widely used. The advantage of activated carbon filtration is that it works well for compounds in ionic form and hydrophobic substances, but for hydrophilic and molecular substances it shows modest adsorption capacity. (Oesterle et al. 2020)

Distillation is also used considerably in the pharmaceutical industry, and often wastewater with a high organic load has already gone through the distillation process. How much API

water is directed to the distillation, washing process or wastewater tank is often balanced in the way the process is run. (Gadipelly et al. 2014)

Evaporation is also a common treatment method for API waters. In this method, the quality of the feed must be known particularly well in order to avoid feeding azeotropic substances to the evaporation, if this happens, the efficiency will be low. (Periyannan et al. 2022)

The treatment of API water with a high organic load requires a lot of energy. The environmentally safe way to treat API containing water is to destroy API substances in high-temperature incineration and take care of proper slag and ash handling. Carbon dioxide emissions are also produced in this way, so there is not yet a completely sustainable method. (Sapkota et al. 2023)

### 3.3 Advanced Oxidation Processes

Advanced oxidation processes (AOPs) are based on in situ generation of strong oxidants, which can be used to oxidize target organic compounds. Sulfate or chlorine radicals can be used as oxidants, but most AOP techniques are based on the generation and use of OH radicals. The efficiency and mechanisms of the oxidation reactions always depend on the process parameters and the water matrix to be treated. The efficiency of OH radicals to destroy organic compounds is disturbed by the occurrence of other competing reactions in the treated water. Such reactions include, for example, the consumption of radicals to oxidize carbonate, nitrite, bicarbonate and organic matter, in which case the target organic compound does not react with OH-radicals. The reactions can be influenced by changing the process parameters, for example pH, to make the properties of the selected AOP more suitable. A study found that TOC reduction and ibuprofen degradation were at a better level when the water pH was lower (around pH 4) and zero valent iron (ZVI) was added to the treated water. The reaction can also be enhanced by adding hydrogen peroxide, in which case more OH radicals are available for reactions (Yavas-Ziylan et al. 2018). Figure 2 shows the classification of different AOP technologies. AOPs can be based on ozone, UV, electrochemical (eAOP), catalytic (cAOP) and physical (pAOP). Ultrasound and sonocavitation are classified as pAOPs. (Mikos et al. 2018)

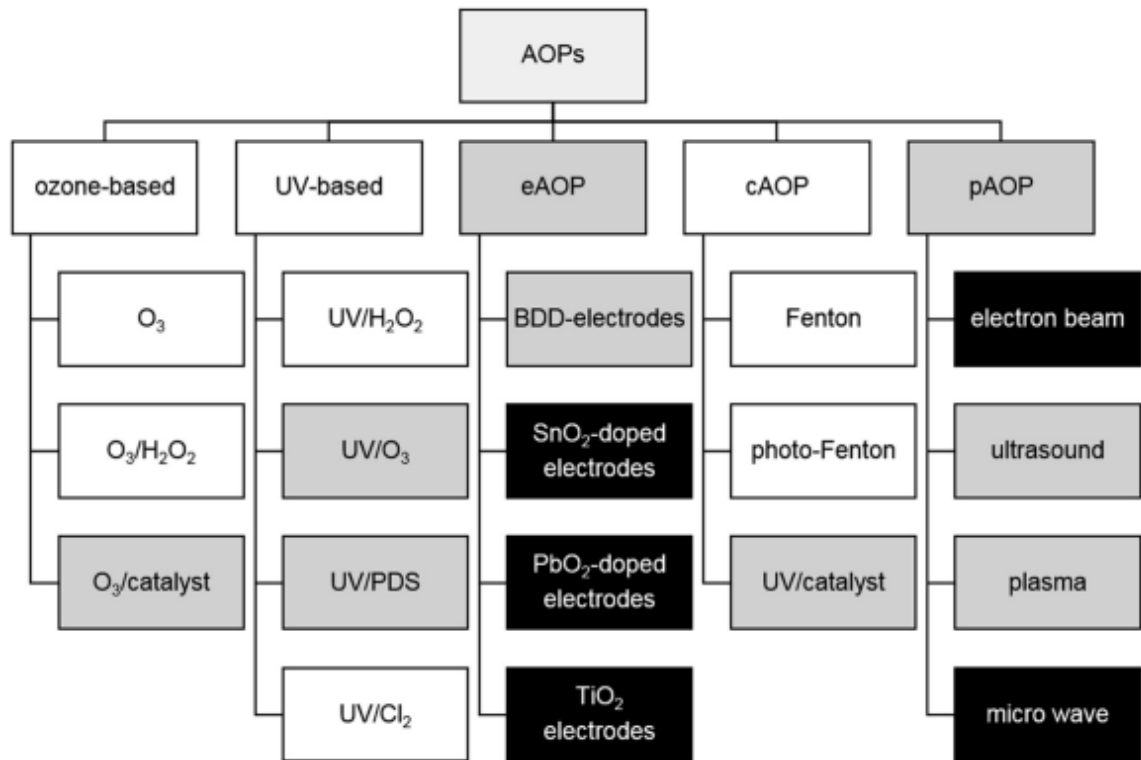


Figure 2. Classification of AOP technologies (Mikos et al. 2018)

### 3.4 Oxidation by-products

Hazardous chemicals can be produced as byproducts of oxidation, such as bromate when bromine is oxidized (Myllykangas et al. 2000), chlorate and perchlorate when chlorine is oxidized, and various organic halo compounds, such as total organic halides (TOX), haloacetic acids (HAA) and trihalomethanes (THM). The formation of oxidation by-products is diverse and depends on the type of radical and the composition of the water. Inorganic compounds such as chlorite, chlorate, perchlorate and bromate need a reaction with the OH radical to form, but in water with high organic load, OH radicals first react with organic compounds under neutral conditions. If there are a lot of oxidizing chlorine compounds in the water, a sequential reaction with the OH radical can occur, resulting in the formation of chlorate and perchlorate. Bromate is formed in very pure water and in direct reaction with the OH radical. When reacting with organic compounds, OH radicals have not been found to cause significant oxidation by-products in common water applications. However, it has been observed that at high pH and chlorine concentration (above 1 g/L)

halogenated organic compounds and adsorbable organic halides (AOX) can form. (Miklos et al. 2018)

## 4 Cavitation and its classification

Cavitation is a phenomenon where water molecules are moved at high speed in different directions, causing nucleation, growth and finally implosion of steam or gas in the water in a very short time. The cavitation phenomenon lasts a few milliseconds, during which the gas bubbles implode. As a result of the implosion, energy is released from the gas-vapor mixture, which manifests itself as high temperature (500- 15000 K) and pressure (100- 5000 atmospheres). (Wang et al. 2021). The phenomenon of acoustic cavitation is shown in Figure 3.

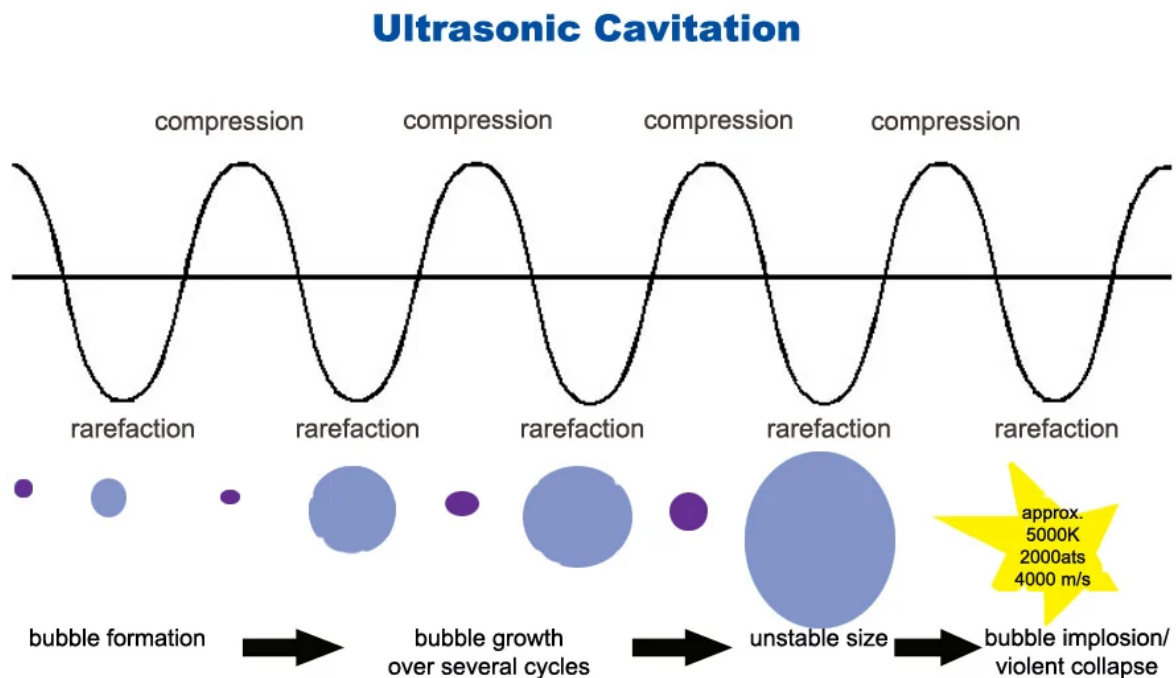


Figure 3. Principle of acoustic cavitation: bubble formation, growth and collapse generated by ultrasound (Hielscher Ultrasonics, 2024)

Scientific research has shown that cavitation is capable of breaking down very complex organic compounds (Liu et al. 2020, Braeutigam et al. 2012). The challenge for the development of the technology has been that the control of cavitation reactions is very difficult, when handling large amounts of liquid, the energy consumed in the reactions is

high, and because of the improper control of the reaction, the results have been poorly repeatable. (Camargo-Perea et al. 2020)

Cavitation can be classified into four different categories: Hydrodynamic cavitation (HC), optical cavitation (OC), particle cavitation (PC) and acoustic cavitation (AC). Of these, optical cavitation and particle cavitation are so weak in their effect that they are not of significant benefit for industrial applications in water treatment (Gogate, R. 2011). Ultrasonic cavitation and hydrodynamic cavitation have been found to be effective treatment methods for wastewater with a high COD concentration (Wu et al. 2018).

#### 4.1 Hydrodynamic cavitation (HC)

In hydrodynamic cavitation (HC), cavitation is generated by varying the pressure and flow in a pipe, nozzle or rotor and stator. As the turbulence increases, pressure and kinetic energy increase in the liquid and it begins to cavitate and vaporize. The gas bubbles grow until they explode, which causes the temperature and pressure to rise and the molecules to break up and jet streams to form in the liquid. There are several different reactors for hydrodynamic cavitation. Figure 4 shows different reactor types. (Wang et al. 2021).

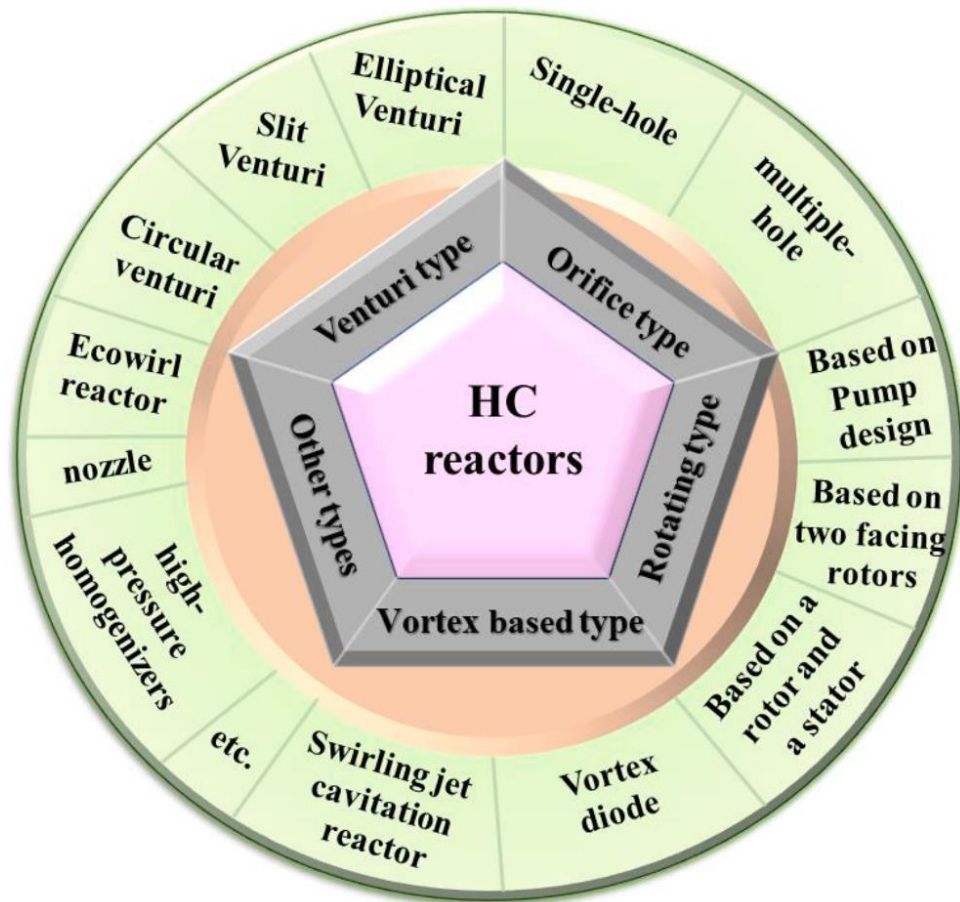


Figure 4. Different types of hydrodynamic cavitation reactors. (Wang et al. 2021)

#### 4.2 Ultrasonic/ acoustic cavitation

Sonocavitation or acoustic cavitation (AC) is a method that is widely used in the chemical industry, wastewater treatment, biotechnology, polymer technology, petrochemical industry and food technology. (Wang et al. 2021). Ultrasonic cavitation is produced by resonating piezoelectric material. In water treatment, ultrasound is implemented with the help of electric current by oscillating an ultrasound sensor or probe in water. Another option is to connect the ultrasonic oscillator directly to a container of water and make a so-called ultrasonic bath. (Yasui, K. 2018).

Ultrasonic cavitation produced by ultrasound (US) is a method in which water is sonicated at a high frequency (20-500 kHz), whereby cavitation bubbles are created in the water and when they reach a critical resonance size, when they collapse, they produce really high

temperature and pressure. If there are organic compounds in the water, they are destroyed by temperature and pressure and become mineralized. (Mikos et al. 2018)

Ultrasonic cavitation is a water treatment method in which the electric current is converted into ultrasonic vibrations with the help of a separate electromechanical converter. The vibration is transmitted to the water using an ultrasonic horn, which amplifies the vibration to the water/liquid being treated. Water/liquid processing can be done in batches in an open vessel or continuously in a flow cell. (Peshkovsky et al. 2010).

Sonocavitation is a method in which water molecules collide (and of course also other molecules in the liquid) until some of the molecules break up due to cavitation. The phenomenon of a single bubble collapse is shown in Figure 5. When breaking down, the molecules can generate a temperature of up to 4300 °C and a pressure of 500 atmospheres, which creates jet streams, where the reactions continue and it is possible, for example, to break down pharmaceutical/organic compounds and in general to speed up various reactions. (Gagol et al. 2018).

#### 4.3 Types of reactions and operating principles

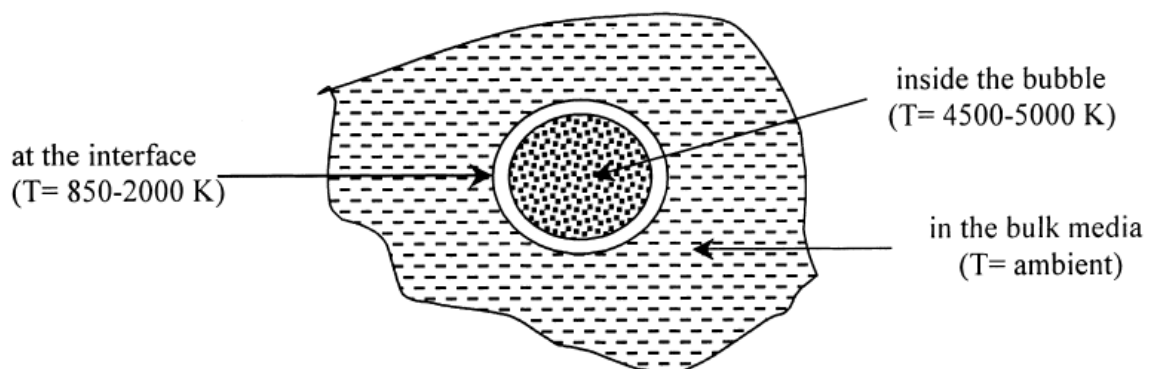
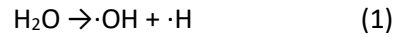


Figure 5. Chemical reaction zones and temperatures in cavitation phenomenon. (Ince et al. 2001)

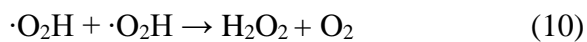
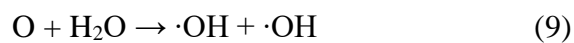


When the bubble collapses, pyrolysis of water starts to produce OH radicals and hydrogen atoms according to the reaction shown below (reaction 1) (Okitsu et al. 2018)



#### 4.3.1 Gaseous cavitation inside the cavitation bubble (pyrolysis of the highly volatile compounds)

When the bubble collapses, the water molecule breaks up and OH radicals, hydrogen and oxygen atoms, superoxide radicals, hydroperoxyl radicals, hydrogen peroxide and ozone are formed, and these oxidants diffuse into the surrounding liquid and react with the oxidizing compounds and ions in the liquid. The temperature in the cavitation bubble can reach up to 5000 K and a pressure of 300 bar (Yasui et al. 2004). The cavitation phenomenon occurs randomly in the treated water and the collapsing cavitation bubbles form hot spots in the water, shockwaves and jet streams into the surrounding water mass. (Yasui, K. 2018). Reactions inside the cavitation bubble are shown below (Ince et al. 2001). Re-formation of water and hydrogen peroxide can occur at the interface between the gas bubble and the bulk solution (reactions 2 to 10).



#### 4.3.2 The bubble/water interface (pyrolysis of the highly volatile compounds, or chemical reaction with OH<sup>-</sup>)

The reaction temperature at the bubble-water interface was already dropped to a temperature of 850-2000 K. Pyrolysis of highly volatile compounds can still occur and chemically the reactions are produced by OH radicals. Superoxide radicals and hydroperoxyl radicals are involved in the reactions. Among organic compounds, the degradation of hydrophobic compounds is enhanced at the interface due to their hydrophobic nature. For example, butanol breaks down more easily than ethanol, which is a completely water-soluble and hydrophilic substance. (Okitsu et al. 2018)

#### 4.3.3 Bulk solution (only by OH radicals)

Acoustic cavitation or so called vibrational cavitation in the water surrounding the hot spot areas takes place at the same temperature as before the treatment. The reaction conditions are better than without any treatment, due to the vibration caused by ultrasonic cavitation and thus better mixing conditions, giving more opportunities for reactions to occur. There may still be free OH radicals in the water, which cause reactions with oxidation potential at 2.8 V. (Okitsu et al. 2018)

### 4.4 Energy input and the power of the ultrasonic process

The length of one pressure oscillation is defined as the wavelength of the acoustic wave ( $\lambda$ ) and the acoustic period ( $T_a$ ) is determined as the time elapsed for one pressure oscillation. The number of pressure oscillations that occurred in one second is defined as frequency ( $f=1/T_a$ ). Sound as the unit of speed is defined as ( $c$ ), which is the progression of a pressure disturbance that occurred in a unit of time ( $c=f\lambda$ ). The amplitude of the pressure oscillation is defined as the amplitude of the acoustic pressure ( $p_a$ ).

The properties of water include its density and its ability to transmit sound change as the temperature changes. This should be taken into account in the different stages of the sonocavitation method.

Acoustic intensity ( $I$ ) can be defined as the energy flow through a unit area. The unit of acoustic intensity is  $\text{W/m}^2$ .

$$I = \frac{p_a^2}{2\rho_0 c}$$

(12)

where  $p_a$  is the acoustic pressure amplitude,  $\rho_0$  is the density of a medium (water) and  $c$  is the speed of sound in the medium (water). (Yasui, K. 2018)

## 5 Composition of the API wastewater

Currently, the wastewater generated in the production of pharmaceuticals is treated by evaporation or high-temperature incineration at Fortum Waste Solutions' treatment facilities. The treatment plant is located far from the source of the wastewater, so the wastewater must first be filled in a tanker truck and then transported to the treatment plant by road before the final treatment.

### 5.1 The composition of the investigated API wastewater

The sample water from the treatment tests arrived at the Fortum Waste Solutions treatment plant on the 13<sup>th</sup> of November 2023 and samples were taken as follows:

- Test water for sonocavitation experiments 2 x 120 L barrel
- 1 x 20 L canister as a spare (if there are challenges in analyzing the initial samples)
- Samples for analyzing starting concentrations 6 x 1000 mL glass bottle

In addition to physicochemical properties, the sample water was analyzed for pharmaceutical residues. One pharmaceutical compound was found in the sample. The results are presented in Table 2.

Table 2. Physicochemical composition of the investigated API production wastewater

Parameter	Unit	Concentration
pH		6.2 ± 0.2
Color		Dark brown
BOD <sub>7</sub>	mg/ L	21000 ± 4200
COD	mg/ L	38000 ± 7600
BOD <sub>7</sub> /COD		0.55
TOC	mg/ L	11000 ± 1650
TSS	mg/ L	13 ± 2.21
TDS	mg/ L	4000 ± 0.05
TKN	mg/ L	560 ± 84
Ammonia	mg/ L	13 ± 1.95
Chloride	mg/ L	370 ± 37
Sulfate	mg/ L	16 ± 1.6
Isopropanol	mg/ L	14000 ± 4760
Ethanol	mg/ L	160 ± 59.2
Methanol	mg/ L	190 ± 66.5
Acetone	mg/ L	150 ± 40.5
AOX	mg/ L	5.2 ± 1,04
Toluene	mg/ L	2.4 ± 0.65
Dichloromethane	mg/ L	3.2 ± 0.992
Tetrahydrofurane	mg/ L	3.3 ± 1.5
Acrylonitrile	µg/ L	<0.5 ± 0.2
Benzene	µg/ L	<0.1 ± 0.024
Ethylbenzene	µg/ L	0.2 ± 0.064
m,p-Xylene	µg/ L	0.1 ± 0.026
o-Xylene	µg/ L	<0.1 ± 0.026
Bromide	mg/ L	1.9 ± *
Heptane	µg/ L	20 ± 6.8
1-butanol	mg/ L	7.5 ± 2.78
Tert-butanol	mg/ L	0.26 ± 0.091
1,2,3,5-tetramethylbenzene	µg/ L	0.8 ± 0.24
1,2,3-Trimethylbenzene	µg/ L	0.7 ± 0.189
1,2,4,5-Tetramethylbenzene	µg/ L	0.3 ± 0.093
1,2,4,-Trimethylbenzene	µg/ L	0.6 ± 0.204
Chlorobenzene	µg/ L	0.3 ± 0.105
Naphthalene	µg/ L	5.0 ± 1.55
DIPE (Di-isopropyl ether)	µg/ L	3.6 ± 0.9
ETBE (ethyl tert-butyl ether)	µg/ L	3.1 ± 0.713
Ethyl acetate	mg/ L	3.8 ± 1.178
Methyl acetate	mg/ L	0.19 ± 0.076
Chloromethane	µg/ L	18 ± 7.74
Total hardness (Ca + Mg)	mmol/ L	0.41 ± 0,005
Perchlorate	µg/ L	49.8 ± *
Conductivity	mS/ m	160 ± 8

Water content	%	>97 ± *
API compound	mg/ L	4900 ± 2450

Table 2 shows the compounds whose laboratory analysis detection limit was exceeded. For example, 145 different APIs were examined in the samples and concentrations exceeding the detection limit were found for only one pharmaceutical compound. \*The laboratory that performed the analysis did not provide measurement uncertainty information.

## 6 Description of the test system

There were two trial runs for API water. A trial batch of 120 L of API water was reserved for both. The first test run consisted of sonocavitation, ceramic ultrafiltration and activated carbon filtration.

In the second test run, the API water was first treated with ceramic ultrafiltration and then with sonocavitation and in the last step with activated carbon filtration.

The water left over from the second test run was tested with sonocavitation, where the pH of the water was lowered to pH 3 with Kemira PIX-105 ferric sulfate.

### 6.1 Ultrasonic cavitation equipment

The test waters were treated with a test system consisting of a test water tank, a circulation pump, a solids filter and a sonocavitation device, as well as the necessary hoses, valves and flow meters. The description of the system is presented in Figure 6.

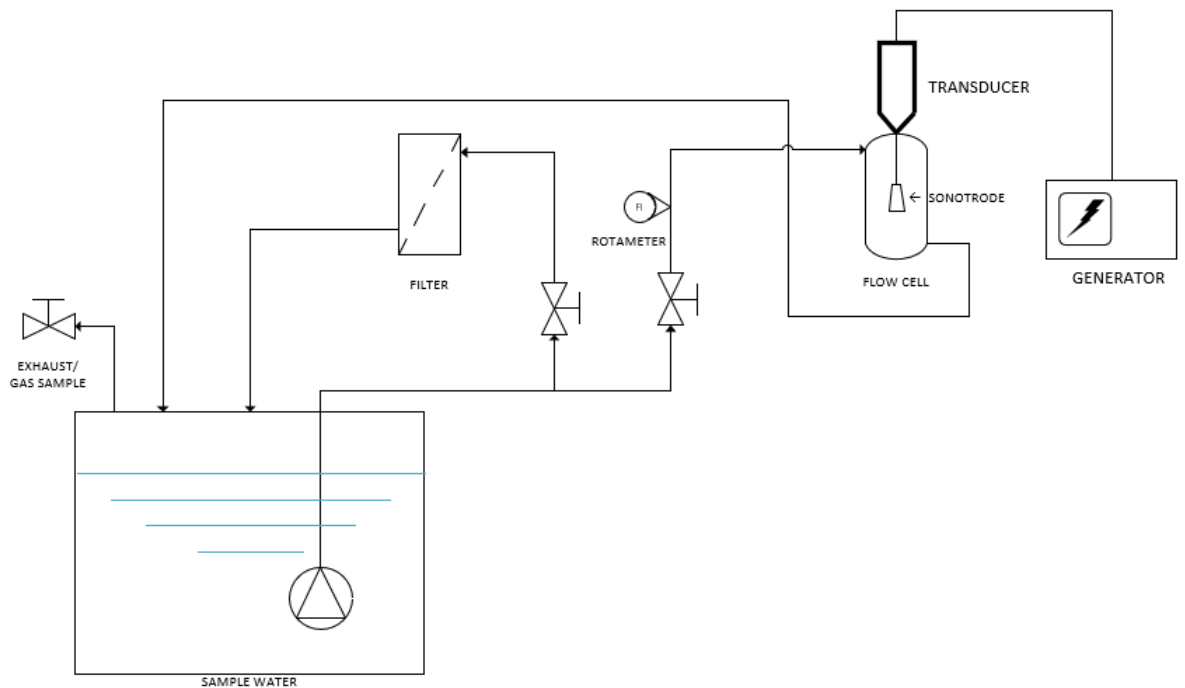


Figure 6. Flow diagram of the test system

Grundfos Unilift AP12 submersible pump was used as the feed pump of the system. The feed flow was divided between the solids filter (approx. 1200 L/h) and the sonocavitation equipment (approx. 240 L/h). The flow rates were adjusted with a rotameter. The degree of filtration of the solids filter was 50  $\mu\text{m}$  in the first test run and 10  $\mu\text{m}$  in subsequent runs. A Hielscher Ultrasonics UIP2000hdT device with a CS4d40L2 sonotrode and a B4-1.4 booster was used as the sonocavitation device.

Gases released from processing were measured with a Honeywell BW Ultra, Portable Multigas Detector. The gases measured were oxygen (% vol.), lower explosive limit concentration (LEL, %), hydrogen sulfide ( $\text{H}_2\text{S}$ ,  $\mu\text{g}/\text{L}$ ), volatile organic compounds (VOC,  $\mu\text{g}/\text{L}$ ) and chlorine ( $\text{Cl}_2$ ,  $\mu\text{g}/\text{L}$ ).

During the test run, pH, conductivity ( $\mu\text{S}/\text{cm}$ ), temperature ( $^{\circ}\text{C}$ ), turbidity (FNU) and redox potential (mV) were measured with hand meters. The results and comments from the test run were written down in the field measurement protocol.



## 6.2 Ultrafiltration equipment with ceramic membrane

The operating principle of ultrafiltration equipment with a ceramic membrane is cross-flow filtration, where water is fed to the membrane at a flow rate from 4.0 m/s to 6.0 m/s and a maximum pressure of 10 bar. Atech Innovations GmbH's ceramic membrane elements were used for membrane filtration. One membrane element has a length of 1200 mm and a diameter of 25.4 mm, which is divided into 19 pieces of 3.3 mm flow channels. The filtering area of the membrane element is 0.24 m<sup>2</sup>. A Lowara 3SV centrifugal pump was used as the feed pump of the equipment.

### 6.2.1 Ceramic ultrafiltration of the sonocavitation treated API water

The first test run for the sonocavitation treated API water was operated until the quality of the permeate leveled off and field measurements were made: Ceramic membrane filtration was first run with a 25 kDa resolution membrane. The supply pressure was 10 bar and the supply flow was 3200 L/ h. The temperature of the permeate was 22.6 °C, turbidity 2.05 FNU, conductivity 1491 µS/cm and redox potential 173.3 mV.

When operating with a 5 kDa ceramic membrane element the supply pressure and flow were kept unchanged. The temperature of the permeate varied between 18.5 and 20.9 °C, turbidity between 0.70 and 1,99 FNU, conductivity between 1396 and 1421 µS/cm and redox potential from 162.9 to 196.4 mV.

With a 1 kDa membrane element, the supply pressure and flow rate were kept the same (maximum pressure of the equipment 10 bar). The permeate temperature was 18.9 °C, turbidity 1.40 FNU, conductivity 1232 µS/cm and redox potential 31.6 mV.

The test run was performed with a 5 kDa membrane. About 70 liters of permeate were collected during the test run. 5 liters of concentrate were collected. Samples were taken from the permeate and concentrate. The permeate samples were delivered to Eurofins for analysis and the concentrate was analyzed in the Fortum Waste Solutions laboratory for COD, TOC, alcohols, solids and VOC.

### 6.2.2 Ceramic ultrafiltration of raw API water

The test run for raw API water was started with a 1 kDa membrane. When running with pure water, the 1 kDa membrane worked well, but the permeation deteriorated as soon as the treated water was changed to API water. 1.5 liters of permeate could be collected. Gas formation and foaming were observed in the filtration. Conductivity in the collected permeate was 758  $\mu\text{S}/\text{cm}$ , temperature 15.7 °C, turbidity 1.96 FNU, redox potential 185.8 mV and pH 6.9. A sample of the permeate was delivered to Fortum Waste Solutions' laboratory for COD, TOC, alcohol and VOC determinations.

### 6.2.3 Activated carbon filtration

The test equipment for activated carbon filtration consisted of a filtration column with a volume of 2 liters. The filtration column was filled with 1 kg of hydrated activated carbon, (AquaSorb<sup>TM</sup> 1200) manufactured by Jacobi Carbon. The filtration rate was 2.96 bed volumes/h, so the residence time in the filter was about 20 minutes. The column was fed with a Watson-Marlow 323S hose pump. Activated carbon was a coal-based granulate with a surface area of 950  $\text{m}^2/\text{g}$ .

## 7 Description of test runs

The test runs started with an ultrasonic cavitation test run. Decisions about the next test phases were made based on the results of laboratory analyses and field measurements and sensory observations made during the work.

### 7.1 Performance of the sonocavitation method

At the beginning of the work, the test equipment was assembled and tested with clean water, so that we could be sure that there were no residues from previous test runs in the equipment. Before the start of the first test run, the solids filter was replaced with a new one (degree of filtration 50  $\mu\text{m}$ ) and the flow rate of the equipment was adjusted to work. In this context, it was noticed that the flow of the sonocavitation device could not be kept constant with a flow lower than 240 L/h, so it was decided to do test runs with a flow of 240 L/h, with which the flow could be kept constant.

After the preparatory work, the sonocavitation device was calibrated empty (air as medium). During the ramp-up phase of the first test run, the frequency was increased until a power of 1000 W was reached, with which the device operated smoothly. In addition to the viscosity of the medium, the cavitation power is affected by temperature and density, so a power of 1000 W cannot be considered reliable. The device had a counter that measured frequency, temperature and amplitude, so the results of the device can be considered more reliable than those determined by calculation. During the use of the device, the amount of energy transmitted to the water was monitored and the results were recorded in the field measurement protocol.

During the test runs, the pH, conductivity, temperature, turbidity and redox potential of the treated material were monitored and the measurement results were recorded in the field measurement protocol. Sensory observations made during test runs were recorded and photos were taken of the tests. For safety reasons, the test equipment was run under supervision throughout the test runs, which caused interruptions to processing.

### 7.1.1 The first sonocavitation test run, with raw API water

The sample volume of the first test run was 120 L. In the first test run, it was observed that the sample foamed very strongly at first, after which the sample cleared. The first test drive lasted all in all 18 h and 46 min, the temperature of the sample increased from 6.7 °C to 34.2 °C. The pH was initially 6.62, between 6.81 and finally 5.81. Color of the test water was brown. The turbidity was 31.90 FNU at the beginning and 3.42 FNU at the end of the first test run, the lowest turbidity was 2.10 FNU. The conductivity was initially 1597 µS/cm and finally 1406 µS/cm, the lowest measurement result was 1368 µS/cm. The redox potential was 192.2 mV at the beginning of the test run and 219.5 mV at the end, the highest measurement result was 246.2 mV.

During the first test run, the oxygen content of the gas released from the system was measured in volume percentages (O<sub>2</sub> % vol.). Initially, the oxygen content rose up to 21.8 % and stabilized at a normal level of 20.9 %. Volatile organic compounds (VOC) were detected during the entire test run period between 0.121 µg/ L and 0.471 µg/ L. Hydrogen sulphide (H<sub>2</sub>S), chlorine (Cl<sub>2</sub>) and a lower explosive limit (% LEL) concentration were also measured during all test driving periods, but the concentrations of these gases were not detected during the entire period.

During the first test run, the equipment was used intermittently, when after turning off the equipment, the temperature of the treated water dropped and clear solid particles started to form in the water. Due to the high COD and TOC content of the water, solid matter was thought to lower the efficiency of the method (this can also increase the efficiency of the method), so it was decided to remove the solid matter in the next process step and in the second test run it was decided to filter the raw API water with ceramic membrane filtration before sonocavitation.

### 7.1.2 The second sonocavitation test with ceramic ultrafiltration treated API-water

The sample volume of the second test run was 70 L. The sample water was yellowish in color, no visible solid particles were separated from it. The duration of the second test drive was 6 h 20 min. The pH of the sample water was at the beginning 6.48 and it finally decreased to a level of pH 5.91. The conductivity of the treated water was 1531 µS/cm at the beginning

and 1438  $\mu\text{S}/\text{cm}$  at the end. The temperature was 9 °C at the beginning and 38 °C at the end. The turbidity of the treated water was 15.00 FNU at the beginning and 6.87 FNU at the end, the highest turbidity value was 20.90 FNU. Visually, solid matter formed in the water during the test run and the color of the water turned brownish. The redox potential of the water was 205.9 mV at the beginning of the test run and 219.1 mV at the end, the highest redox value was 224.0 mV. During the drive, abundant foaming of the water was not noticed at any point during the test drive.

Regarding the gas measurements, the oxygen content remained at a normal level throughout the test run, one measurement result was slightly elevated at 21.2 %. Volatile organic compounds were formed less than in the first test run and the measurement results were between 0  $\mu\text{g}/\text{L}$  at the beginning and 0.144  $\mu\text{g}/\text{L}$  at the end.

#### 7.1.3 The third sonocavitation test with ceramic ultrafiltration and sonocavitation treated API water at pH 3

The sample volume of the third test run was 40 L. At the beginning of the test run, the pH of the water was adjusted to about 3 by adding 35 mL of Kemira PIX-105 ferric sulfate chemical. The pH of the water at the beginning of the test run was pH 5.85 and after the addition of the precipitation chemical, the pH stabilized at the level of pH 3.03. The conductivity of the treated water was initially 1452  $\mu\text{S}/\text{cm}$  and after the addition of the chemical 1997  $\mu\text{S}/\text{cm}$ . The temperature of the test running water was 30.4 °C at the beginning and 41.1 °C at the end. The water turbidity was 15.00 FNU at the beginning, 287.00 FNU immediately after adding the chemical and finally 18.30 FNU. The lowest turbidity was 2.74 FNU. The redox potential was initially 239.1 mV, immediately after pH adjustment it was 504.1 mV and the redox potential leveled off at around 444.0 mV for the rest of the test run.

In the gas concentration, the oxygen concentration increased from the normal level to a concentration of 21.0 % to 21.1 % during the test run. The concentration of volatile organic compounds increased from a concentration of 0  $\mu\text{g}/\text{L}$  to a concentration of 0.261  $\mu\text{g}/\text{L}$  at its highest.

## 7.2 Performance of ceramic membrane filtration

At the beginning of the ultrasonic cavitation experiments, it was noticed that solid matter formed in the water, so it was decided that to make the process more efficient, the solid matter should be removed as best as possible. Ultrafiltration equipment with ceramic membranes was used to remove the solid matter. The separation capacity of the ceramic membranes was between 1 kDa and 25 kDa. At the beginning of the ultrafiltration experiments, short trial runs were made with different ceramic membranes in order to choose a suitable membrane for API water.

## 7.3 Performance of activated carbon filtration

Two test runs were made with activated carbon filtration. In the first test run, the water treated with ultrasonic cavitation and a 5 kDa ceramic membrane filtration was filtered with activated carbon filtration. The pH of the water varied between pH 5.55 and 7.01, the conductivity was between 1185 and 1404  $\mu\text{S}/\text{cm}$ , the temperature varied between 7.2 and 10.8 °C and the turbidity was from 5.54 to 32 FNU. In the turbidity measurement, it was noticed that the sample was very clear and of good quality. Redox varied between 194.7 and 228.8 mV. The filtered sample water was analyzed for COD, TOC, alcohols, solid matter and VOC compounds in Fortum Waste Solutions' laboratory.

The second activated carbon filtration test was performed with test water that had been pretreated with a 5 kDa ceramic membrane filtration and ultrasonic cavitation treatment. The pH of the sample water was 7.21 after filtration, conductivity 1208  $\mu\text{S}/\text{cm}$ , turbidity 5.78 FNU and redox potential 185.5 mV. The temperature of the sample water was 15.1 °C after filtering. The sample water was analyzed for the following compounds in the accredited laboratory:

- pH
- Conductivity
- Evaporation residue 105 °C
- Suspended solids

- BOD<sub>7</sub>
- Total Organic Carbon
- Chloride
- Sulphate
- Fluoride
- Total Dissolved Solids (TDS) 105 °C
- Adsorbable Organic Halogen Compounds
- Ammonium Nitrogen
- Nitrogen (Kjeldahl)
- Perchlorates
- Chlorates
- Cyanide
- Hardness
- Bromate
- Bromide
- Volatile Organic Compounds
- Methanol
- Pharmaceutical Compounds

## 8 Results and discussion

### 8.1 pH

pH measurements were made with a portable hand-held meter regularly during the test runs. The pH of the samples sent to the laboratory was also analysed. The results of field measurements and laboratory analyses are presented in Figure 7.

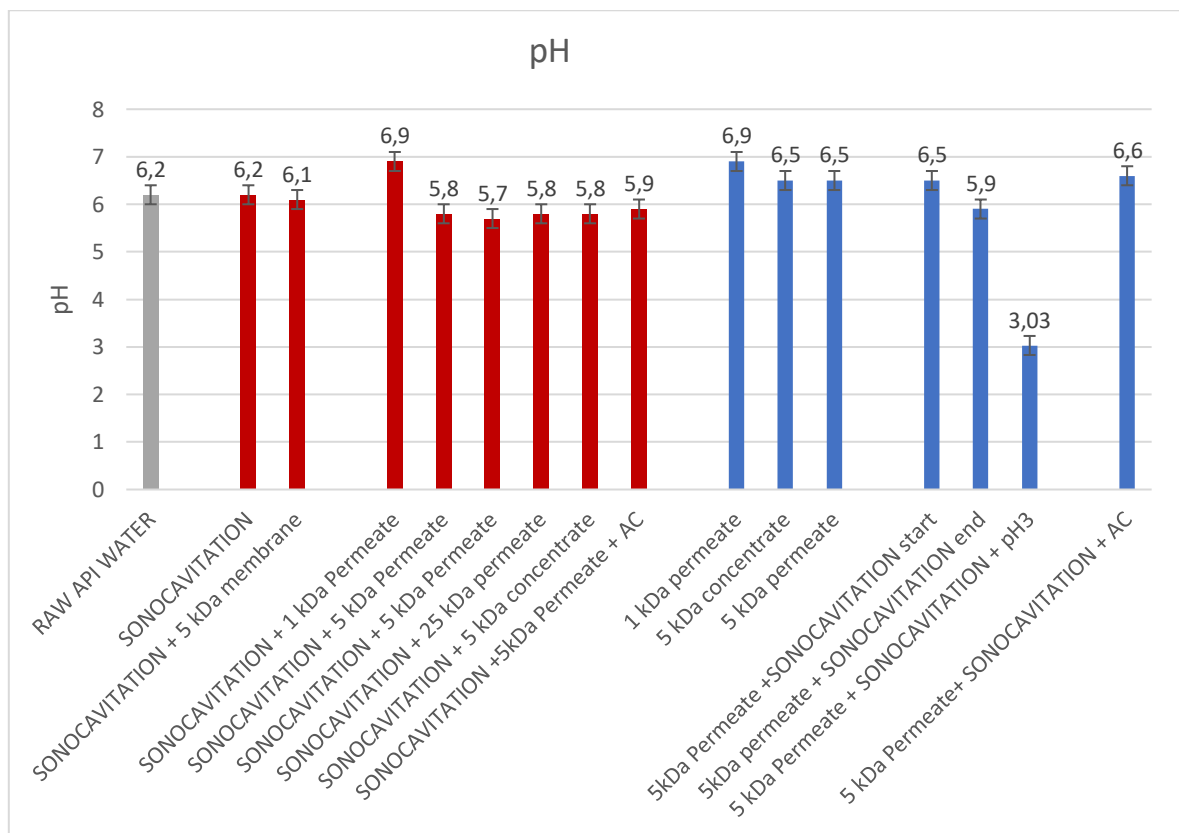


Figure 7. The results of the pH measurements of the samples

During the ultrasonic cavitation test run, the pH change was slow and relatively small, varying from the raw API water pH 6.2 to the lowest pH 5.7 and the highest pH 6.9. As the test run continued, the pH decreased somewhat in the treated water.

Filtration of the test water had no or very little effect on the pH.



In a test run where the sample water was initially filtered with a 5 kDa ceramic membrane and treated with ultrasonic cavitation and then the water pH was adjusted to about pH 3, the pH remained constant (pH 3.03) throughout the test run, 8 h and 9 min.

A high pH (>pH 9) test run was not done in this work, because there was a risk that more oxidation by-products would then form in the water.

## 8.2 Conductivity

The electrical conductivity of the treated water was measured regularly during the test run with a portable hand-held meter and laboratory analyses. The electrical conductivity of raw API water was 160 mS/cm. The results of the conductivity measurements are shown in Figure 8.

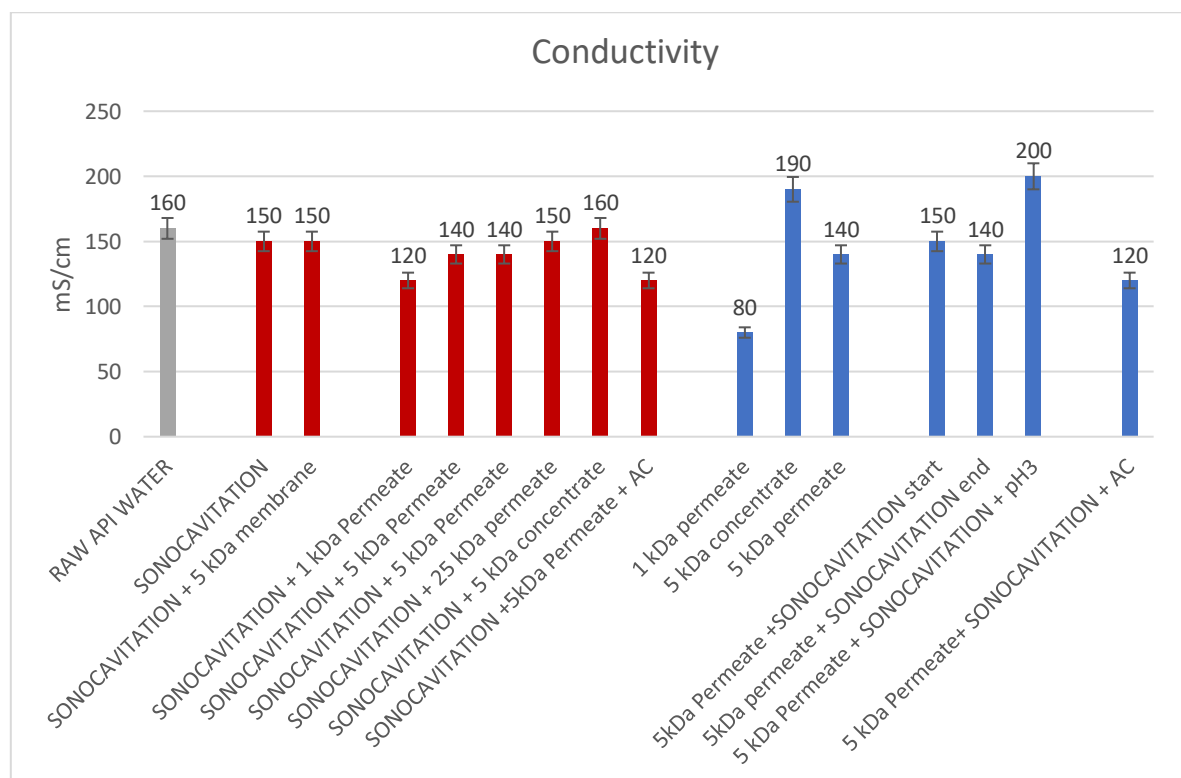


Figure 8. The results of the conductivity measurements of the samples

In the ultrasonic cavitation treatment, the conductivity decreased slightly, being the lowest at 140 mS/cm. Ceramic membrane filtration reduced the conductivity more effectively, the lowest conductivity was 80 mS/cm in 1 kDa filtration, but in this test run it was not possible to run the entire amount of water due to the too high filtration pressure. In 5 kDa filtration,

the conductivity of the permeate was 140 mS/cm and in the concentrate 190 mS/cm. Activated carbon filtration reduced the conductivity from 140 mS/cm to 120 mS/cm.

### 8.3 Temperature

The temperature of the water treated in ultrasonic cavitation rose to a maximum of 41.1 °C. The lowest temperature of the treated water was 6.7 °C. At a low pH, the water temperature were about 3 degrees warmer than in the neutral pH range.

Throughout the experiments, the samples were kept in a cool place (6°C). During the treatment, the temperature of the sample water increased in all stages. In ultrasonic cavitation the most, in ceramic membrane filtration and activated carbon filtration, pumping increased the temperature of the treated water. At no point during the experiments was the water being treated heated or cooled according to the target.

### 8.4 Redox potential

The redox potential of raw API water was somewhat oxidizing at 192.2 mV. In the ultrasonic cavitation treatment, hydroxyl radicals were produced in the water, so the redox potential of the water increased somewhat. The redox potential results measured in field measurements and measured by laboratory analysis are compiled in Figure 9.

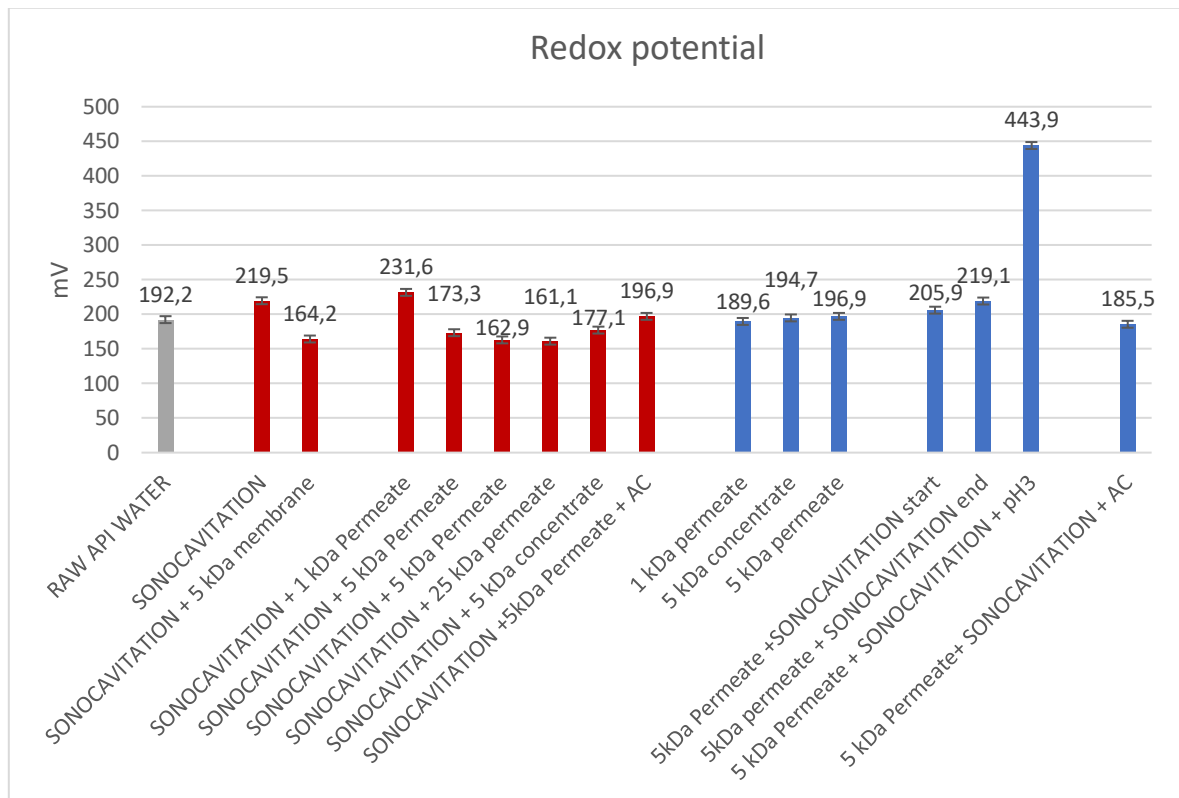


Figure 9. The results of the redox potential measurements of the samples

The variation was low in all test runs, except for the test run, where the pH of the test tap water filtered with a 5 kDa ceramic membrane and treated with ultrasonic cavitation was adjusted to about pH 3, when the redox potential rose to the highest level of +500 mV and then stabilized at the level of 440-450 mV during the end of the test run.

### 8.5 Turbidity

Turbidity was measured from the treated water with a portable field meter. Raw API water turbidity was 32 FNU. The water was brown in colour, but no solid particles were visible. The field measurement results are shown in Figure 10.

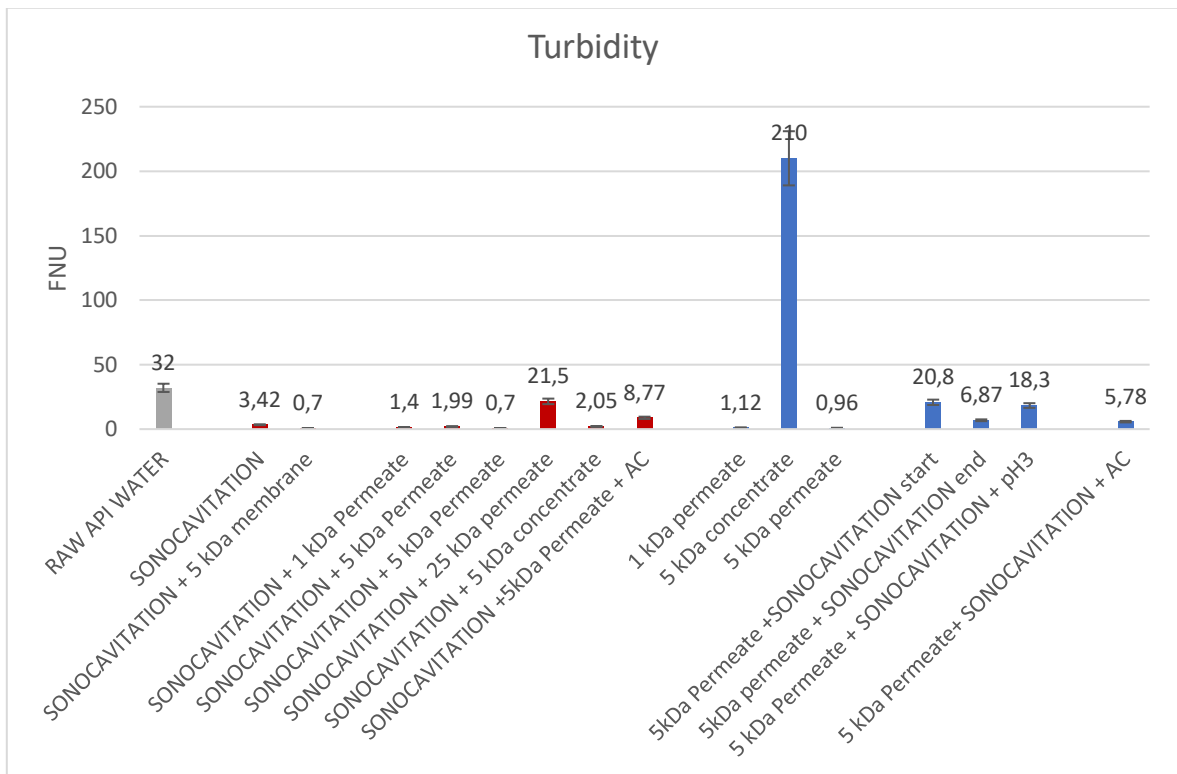


Figure 10. The results of the turbidity measurements of the samples

The raw API water became clear and turned yellowish very quickly in the ultrasonic cavitation treatment. As the ultrasonic cavitation treatment continued, clear solid particles began to form in the water. In the filtration, the 25 kDa ceramic membrane filtration did not remove the turbidity from the water much, but with the 1 kDa and 5 kDa ceramic membrane filters, the water became clear.

The second batch of test runs was done by initially filtering raw API water with 5 kDa membrane filtration. The turbidity of the permeate was 1.12 FNU and the concentrate 210 FNU.

In the results of the clear samples to the naked eye, there was hardly any noticeable difference. However, the best water quality as assessed by visual turbidity was in activated carbon filtered samples. However, the measurement results for these were 8.77 FNU and 5.78 FNU. The high reading of the measurement results is partially explained by the possibility that small particles of activated carbon were released into the water from the activated carbon filter, which were not visible to the naked eye, or there is some substance

in the water, for example an organic solvent or alcohol, which scatters or absorbs the measurement light.

## 8.6 Water content and total dissolved solids

Water content was determined from raw API water. Raw API water contained more than 97% water, which was determined by laboratory analysis. Total dissolved solids (TDS) were determined from four different samples. The results are shown in Figure 11.

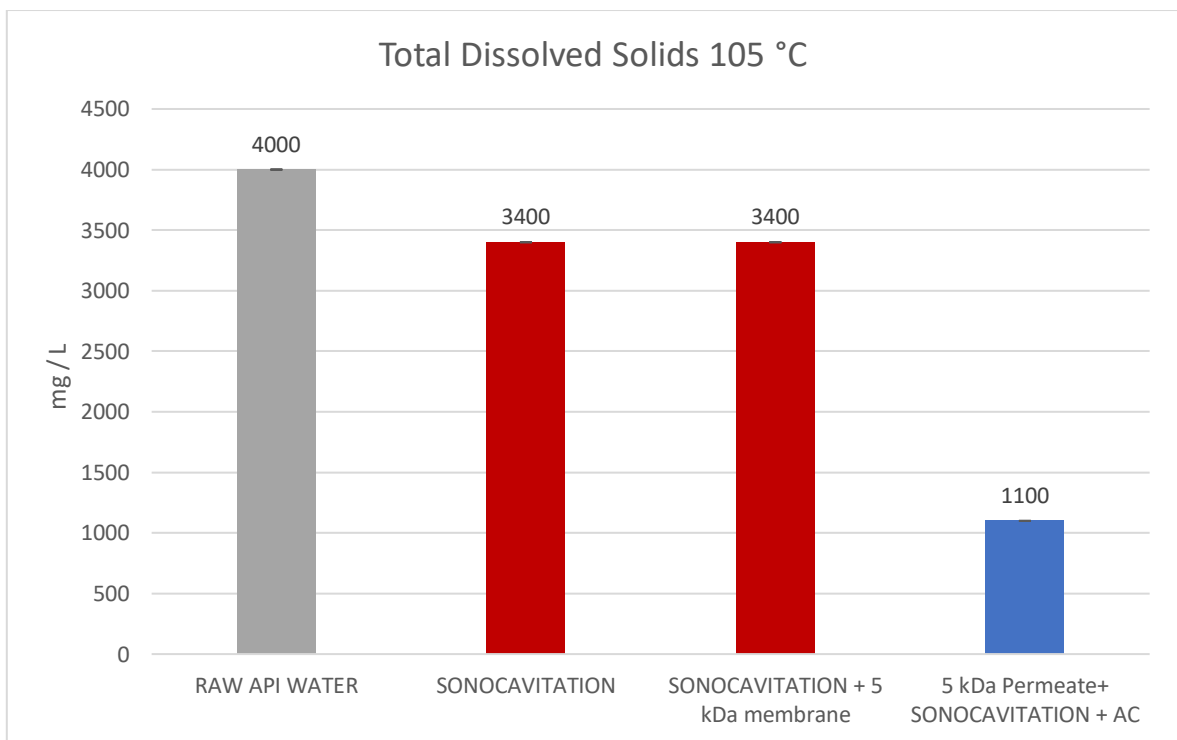


Figure 11. The results of the total dissolved solids analysis of the samples

The total soluble solid content of the raw API water was 4000 mg/L. In ultrasonic cavitation, dissolved substances were suspended, which could be seen as a 15% decrease in concentration in laboratory analyses. 72.5% of the original concentration was in adsorbable form, which could be seen in the laboratory analysis after activated carbon filtration.

## 8.7 Volatile organic compounds in the aqueous phase

Ultrasonic cavitation treatment effectively removed volatile organic compounds from water. The sample results are presented in Table 3.

Table 3. Volatile organic compounds in water

Parameter	Unit	RAW API WATER	SONOCAVITATION	SONOCAVITATION + 5 kDa membrane	5 kDa Permeate+ SONOCAVITATION + AC
Acetone	mg/ L	150 ±40.5	16 ±4.32	6.9 ±1.863	3.8 ±1.026
Toluene	mg/ L	2400 ±648	3 ±0.81	6 ±1.62	<1 ± 0.027
Dichloromethane	mg/ L	3200 ±992	0.6 ±0.186	1.0 ±0.31	<5 ±1.55
Tetrahydrofurane	mg/ L	3.3 ±1.551	0.20 ±0.940	0.04 ±0.188	<0.01 ±0.0047
Heptane	µg/ L	20 ± 6.8	<5 ± 1.7	<5 ±1.7	<5 ±1.7
1-butanol	mg/ L	7.5 ±2.775	3.9 ±1.443	3.3 ±1.221	0.2 ±0.074
Tert-butanol	mg/ L	0.26 ±0.091	0.12 ±0.042	0.080 ±0.028	0.06 ±0.021
1,2,3,5-tetramethylbenzene	µg/ L	0.8 ±0.240	<0.1 ±0.030	<0.1 ±0.030	<0.1 ±0.030
1,2,3-Trimethylbenzene	µg/ L	0.7 ±0.238	<0.1 ±0.034	<0.1 ±0.034	<0.1 ±0.034
1,2,4,5-Tetramethylbenzene	µg/ L	0.3 ±0.093	<0.1 ±0.031	<0.1 ±0.031	<0.1 ±0.031
1,2,4-Trimethylbenzene	µg/ L	0.6 ±0.204	<0.1 ±0.034	<0.1 ±0.034	<0.1 ±0.034
Chlorobenzene	µg/ L	0.3 ±0.105	<0.1 ±0.035	<0.1 ±0.035	<0.1 ±0.035
Naphthalene	µg/ L	5.0 ±1.550	<0.5 ±0.155	<0.5 ±0.155	<0.5 ±0.155
DIPE (Di-isopropyl ether)	µg/ L	3.6 ±0.9	<0.1 ±0.025	<0.1 ±0.025	<0.1 ±0.025
ETBE (ethyl tert-butyl ether)	µg/ L	3.1 ±0.713	<0.1 ±0.023	<0.1 ±0.023	<0.1 ± 0.023
Ethyl acetate	mg/ L	3.8 ±1.178	0.03 ±0.093	<0.01 ±0.031	<0.01 ±0.031
Methyl acetate	mg/ L	0.19 ±0.008	<0.01 ±0.004	<0.01 ±0.004	<0.01 ±0.004
Chloromethane	µg/ L	18 ±7.74	<1 ±0.43	<1 ±0.43	<1 ±0.43

Ultrasonic cavitation effectively removes volatile organic hydrocarbons. The concentration of tetrahydrofuran dropped from the treatment from a concentration of 3.3 mg/L to a concentration of 0.20 mg/L, in which case the reduction was 94 %. Acetone reduction was 89 %. Regarding longer chain alcohols, the reduction was more modest for 1-butanol 48 % and for tert-butanol 54 %. Regarding other organic hydrocarbons, significant reductions were achieved or the concentrations were below the laboratory determination limit.

### 8.8 Volatile organic compounds in the gas phase

Gas formation in the process was monitored by regular gas concentration measurements for oxygen, lower explosive limit, hydrogen sulphide, volatile organic compounds and chlorine. The measurement results of the field measurements are presented in Table 4. The results of the samples are presented as instantaneous one-time measurement results.

Table 4. Volatile organic compounds in the gas phase, filed measurement results with a portable gas meter

RUN TIME (h:min)	O <sub>2</sub> (% vol.)	LEL (% LEL)	H <sub>2</sub> S (µg/ L)	VOC (µg/ L)	Cl <sub>2</sub> (µg/ L)
Test run 1: Sonocavitation					
0:00	20.9	0	0	0.121	0
2:30	21.8	0	0	0.186	0
3:00	21.7	0	0	0.238	0
0:00	20.9	0	0	0.291	0
0:45	20.9	0	0	0.345	0
1:45	21.7	0	0	0.424	0
2:45	21.7	0	0	0.468	0
3:45	20.9	0	0	0.452	0
0:00	20.9	0	0	0.140	0
0:58	20.9	0	0	0.186	0
1:31	20.9	0	0	0.317	0
5:57	20.9	0	0	0.301	0
0:00	20.9	0	0	0.186	0
0:52	20.9	0	0	0.296	0
1:22	20.9	0	0	0.336	0
2:40	20.9	0	0	0.415	0
3:50	20.9	0	0	0.471	0
4:36	20.9	0	0	0.461	0
0:00	20.9	0	0	0.214	0

1:08	20.9	0	0	0.319	0
4:17	20.9	0	0	0.384	0
5:09	20.9	0	0	0.431	0
0:00	20.9	0	0	0.151	0
1:15	20.9	0	0	0.170	0
4:18	20.9	0	0	0.219	0
RUN TIME (h:min) Test run 2: 5 kDa membrane + sonocavitation	O <sub>2</sub> (% vol.)	LEL (% LEL)	H <sub>2</sub> S (µg/ L)	VOC (µg/ L)	Cl <sub>2</sub> (µg/ L)
0:00	20.9	0	0	0.000	0
1:57	20.9	0	0	0.086	0
5:54	21.2	0	0	0.121	0
0:00	20.9	0	0	0.096	0
5:28	20.9	0	0	0.144	0
RUN TIME (h:min) Test run 3: 5 kDa membrane + sonocavitation + pH 3	O <sub>2</sub> (% vol.)	LEL (% LEL)	H <sub>2</sub> S (µg/ L)	VOC (µg/ L)	Cl <sub>2</sub> (µg/ L)
0:00	20.9	0	0	0.000	0
2:00	21	0	0	0.117	0
2:19	21.1	0	0	0.226	0
2:25	21	0	0	0.203	0
5:28	21	0	0	0.242	0
8:26	21	0	0	0.261	0

In the first test run, the oxygen concentration rose from the normal concentration (20.9%) to a maximum concentration of 21.7%. The concentration of volatile organic compounds was more abundant in the first test run due to the higher starting concentration and the release of volatile organic hydrocarbons.

In the second test run, the starting concentration was lower due to the 5 kDa pre-filtration. Volatile organic hydrocarbons were released less (max. 0.144 µg/ L). The oxygen content also remained lower (max. 21.2%).

In the third test run, the pH of the water was lowered to the level of pH 3. At the lower pH, the oxygen content increased slightly and the concentration of volatile organic compounds increased to a maximum level of 0.261 µg/ L.

No hydrogen sulfide or chlorine were released from the process in any of the test runs.



## 8.9 Total Suspended Solids

The solid content was determined in the laboratory from raw API water and from different stages of the process. The results of the laboratory analyses are compiled in Figure 12. No visible solids were detected in the raw API water. The colour of the water was brown. In the ultrasonic cavitation treatment, visible black/brown particles formed in the water. This observation was accentuated when the water cooled between trials.

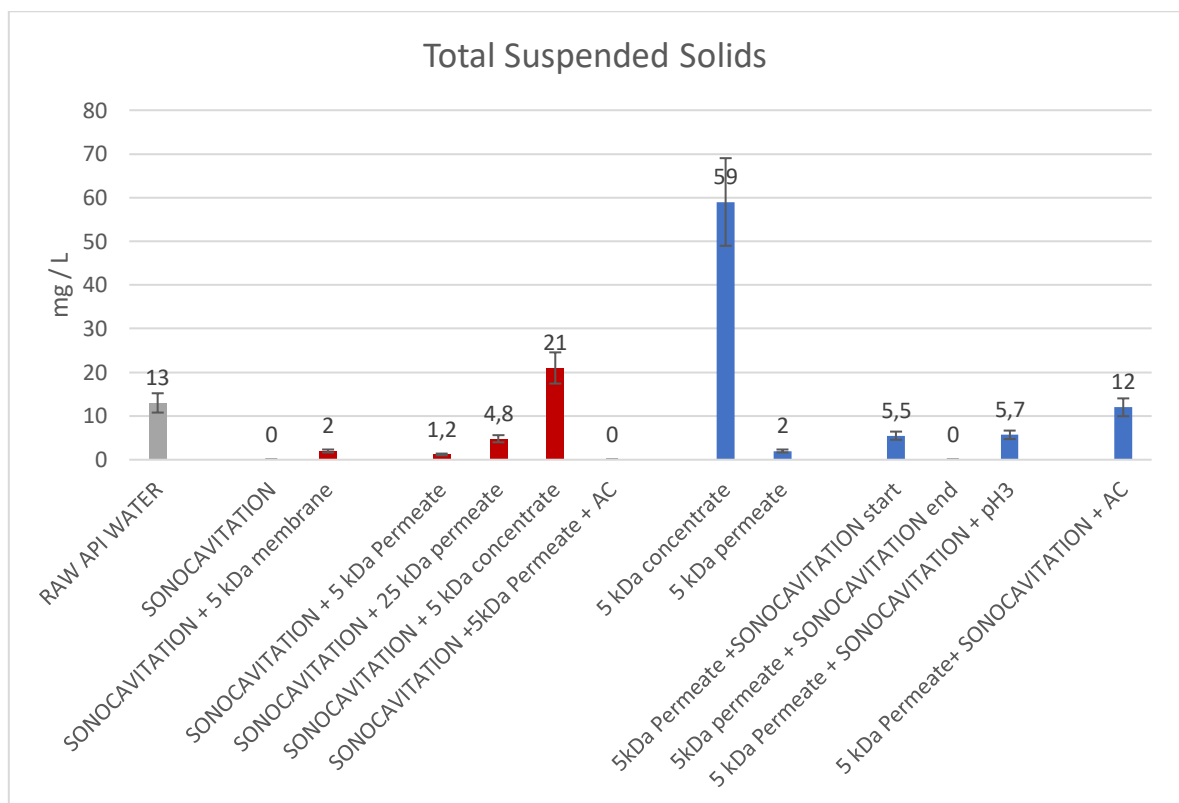


Figure 12. The results of the total suspended solids analysis of the samples

The raw API water contained 13 mg/L of solids. In the ultrasonic cavitation treatment, the water became clear quickly, but after the water cooled, clearly visible black/brown solid particles formed.

Due to the effect of hydroxyl radicals on the effect of organic compounds in the water, solid particles were formed in the water for a long time after the end of the treatment. This can be

seen in the solid concentration between the 5 kDa filtration and the ultrasonic cavitation test run, which was 2 mg/L at the end of the filtration and 5.5 mg/L at the beginning of the ultrasonic cavitation.

The concentration of the solid, which was carried out with ceramic 5 kDa membrane filtration, was successful. The solid content in the permeate was 2 mg/L and in the concentrate 59 mg/L.

### 8.10 Chemical oxygen demand (COD)

Chemical oxygen consumption in raw API water was 38000 mg/L. The concentrations of the laboratory analyses based on the results of the test runs are shown in Figure 13. Due to the high COD concentration, it was decided to use ceramic membrane filtration at the beginning of the second ultrasonic cavitation test run. With 1 kDa filtration, the COD concentration dropped to the level of 15000 mg/L, unfortunately the osmotic pressure in the solution was already so high at this stage that the water could not be filtered with the test run device (maximum pressure 10 bar).

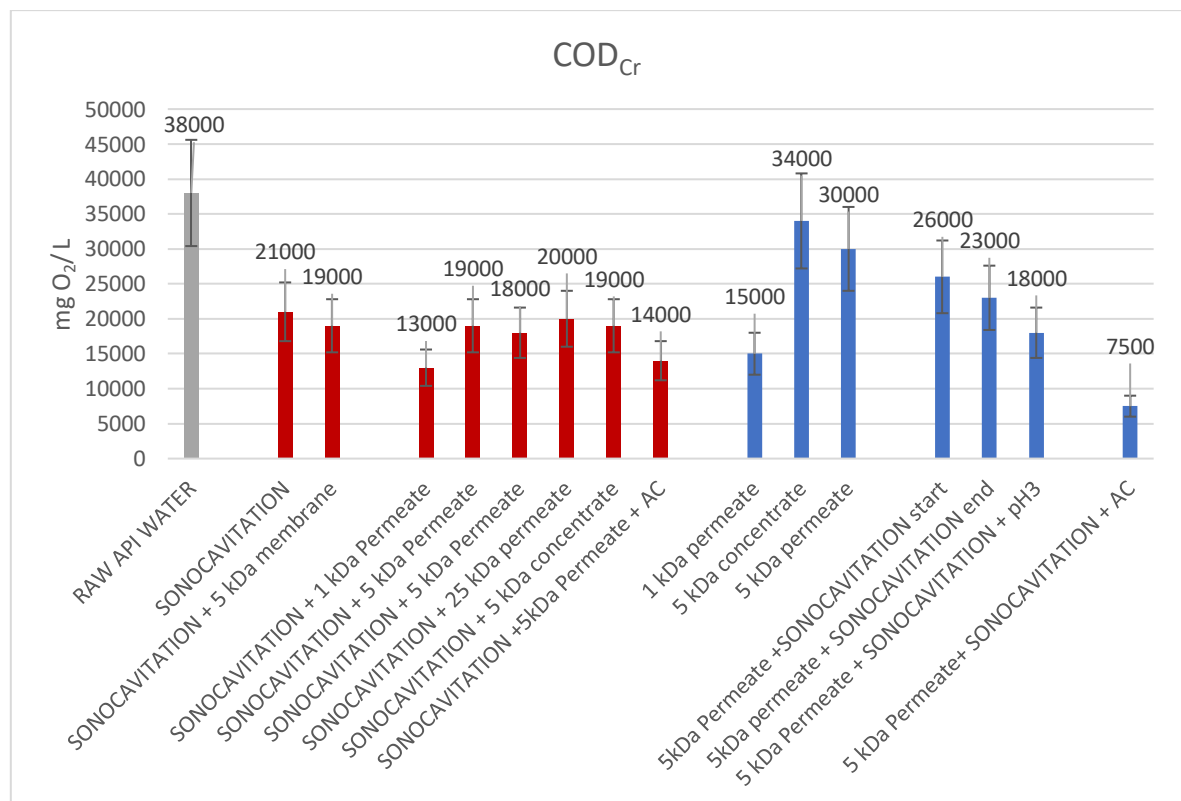


Figure 13. The results of the total suspended solids analysis of the samples

The 5 kDa ceramic membrane filtration effectively removed solid matter from the treated water, but the filtration was not effective for the ionic salts (chloride and sulfate) that caused the load. In addition, alcohols and other organic substances in molecular form (including API compounds) penetrated the membrane and the cleaning result remained modest.

The most effective reduction of COD was achieved in the second test run with activated carbon treatment, where the input concentration of 23000 mg/L was reached to a concentration of 7500 mg/L, in which case the reduction of COD was 67 %.

### 8.11 Biological oxygen demand

Biological oxygen demand (BOD<sub>7</sub>) was measured in raw API water and three other samples. The results are shown in Figure 14.

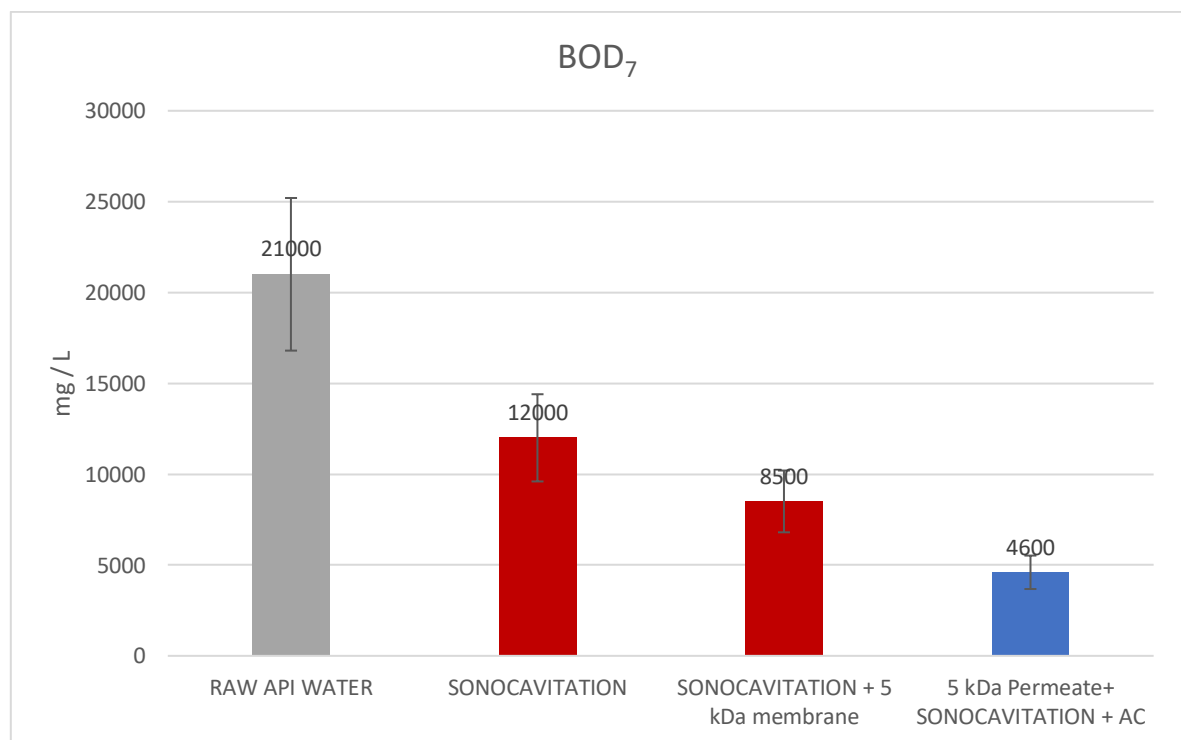


Figure 14. The results of the BOD<sub>7</sub> analysis of the samples

The BOD<sub>7</sub> concentration of raw API water was 21000 mg/L. With ultrasonic cavitation, the concentration decreased to the level of 12000 mg/L, the reduction was 43 %. 5 kDa ceramic

membrane filtration reduced the concentration to 8500 mg/L. After the activated carbon treatment, the final concentration was 4600 mg/L. The total reduction of BOD<sub>7</sub> was 62%.

### 8.12 Total organic carbon (TOC)

The TOC concentration in the water after ceramic 5 kDa membrane filtration and ultrasonic cavitation treatment was 1900 mg/L. The reduction of the original concentration was 83%.

The concentrations for ultrasonic cavitation treatment, ceramic membrane filtration and activated carbon treatment are shown in Figure 15.

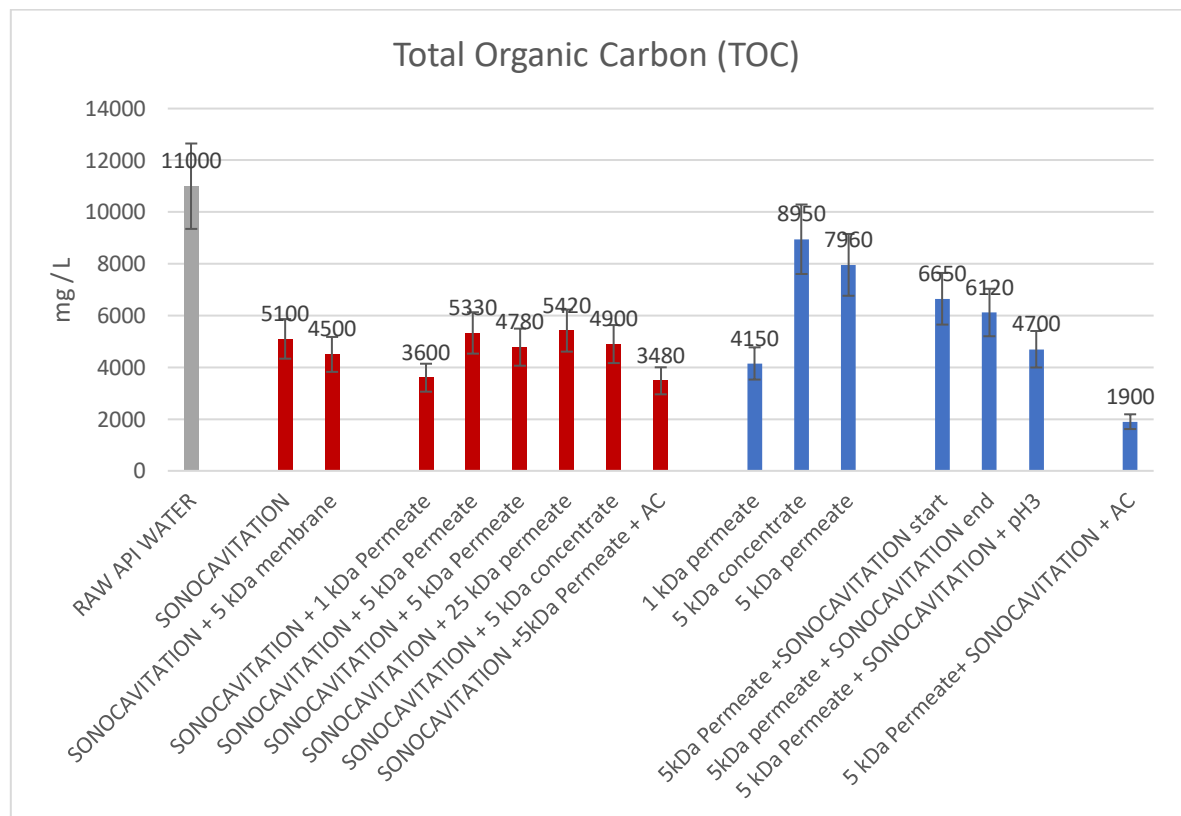


Figure 15. The results of the total organic carbon analysis of the samples

The best single process reduction to an initial TOC of 11000 mg/L was achieved with 1 kDa ceramic membrane filtration (63 %). Ultrasonic cavitation alone reduced the concentration by 59%, from 11000 mg/L to 4500 mg/L.

### 8.13 Ammonium nitrogen and total nitrogen

The nitrogen content did not change much during the treatment. The laboratory analyses from the test runs are shown in Figure 16.

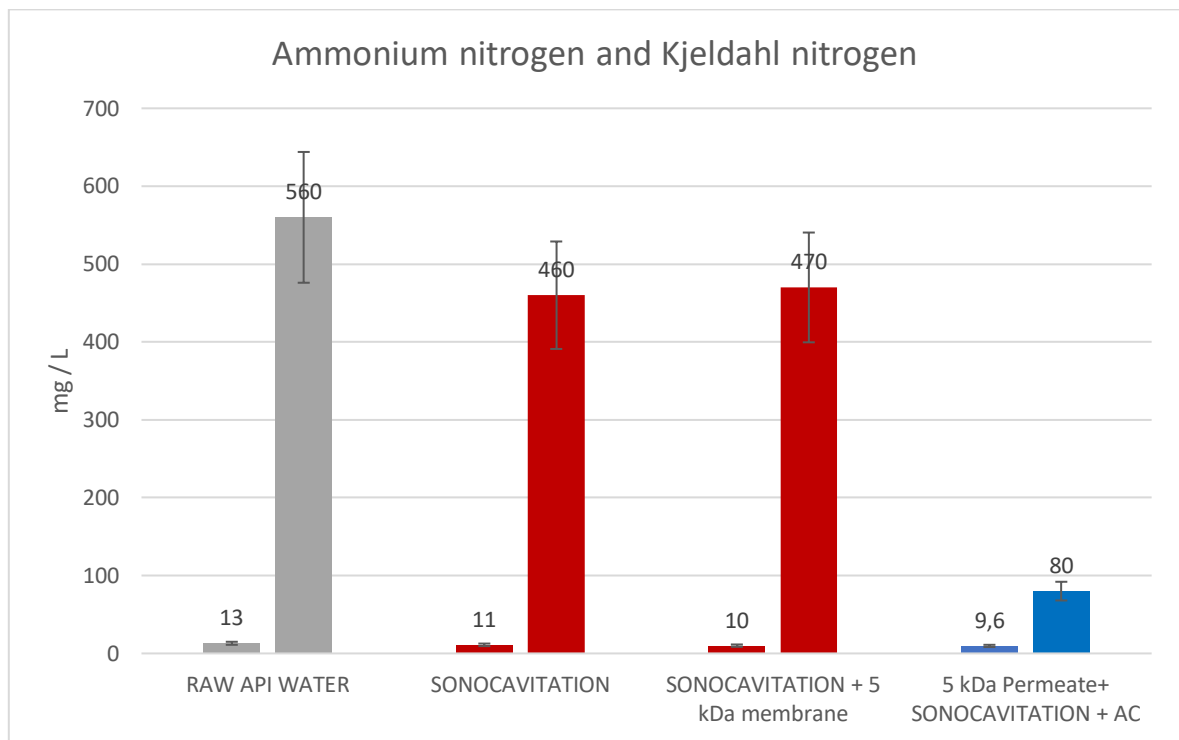


Figure 16. The results of the ammonium nitrogen and Kjeldahl nitrogen analysis of the samples

The total nitrogen content dropped by 86% in the activated carbon treatment. Nitrogen was largely adsorbed on the activated carbon.

### 8.14 Sulfate

Sulfate is in an ionic form in aqueous solution. Figure 17 shows the sulfate concentration during the test runs.

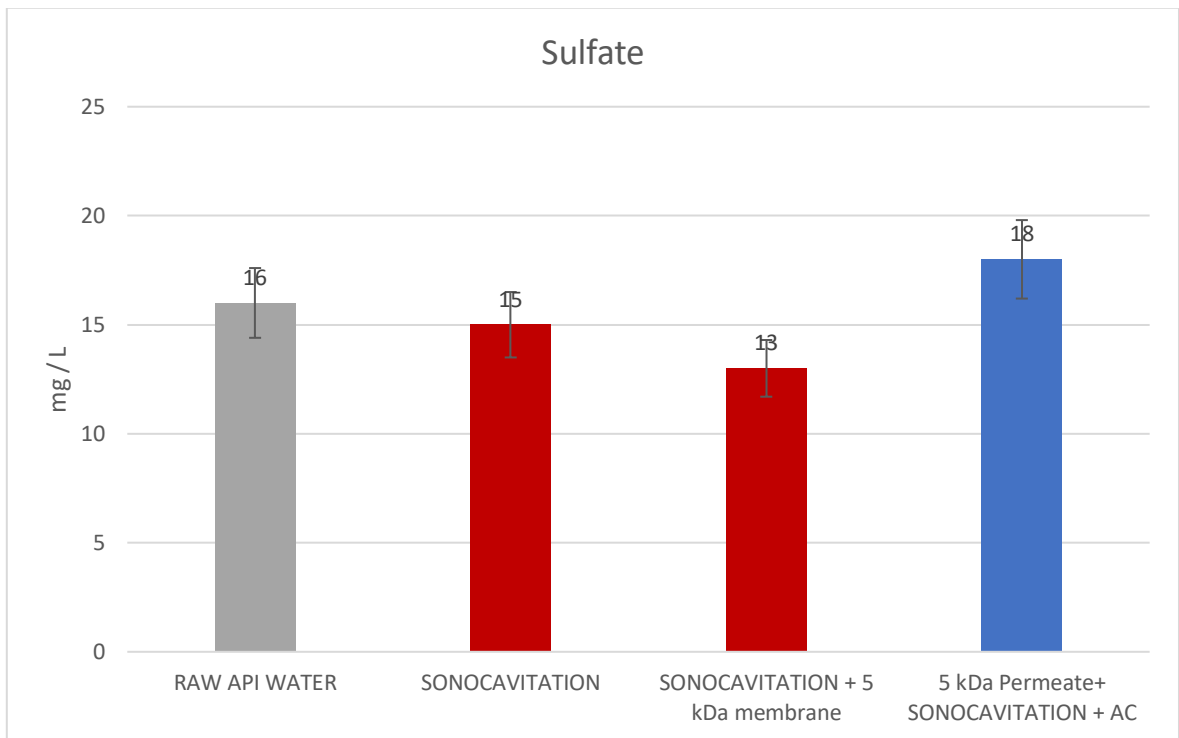


Figure 17. The results of the sulfate analysis of the samples

Raw API water had a relatively low sulfate content. There was little change in concentration during the process. A small-scale sulfate reduction could have resulted from the reaction between the pyrolysis/hydroxyl interface, where the sulfate has crystallized and ended up as a solid.

### 8.15 Chloride

Ultrasonic cavitation treatment did little to remove chloride, which was present in the aqueous solution in ionic form. The results of the laboratory analyses are shown in Figure 18.

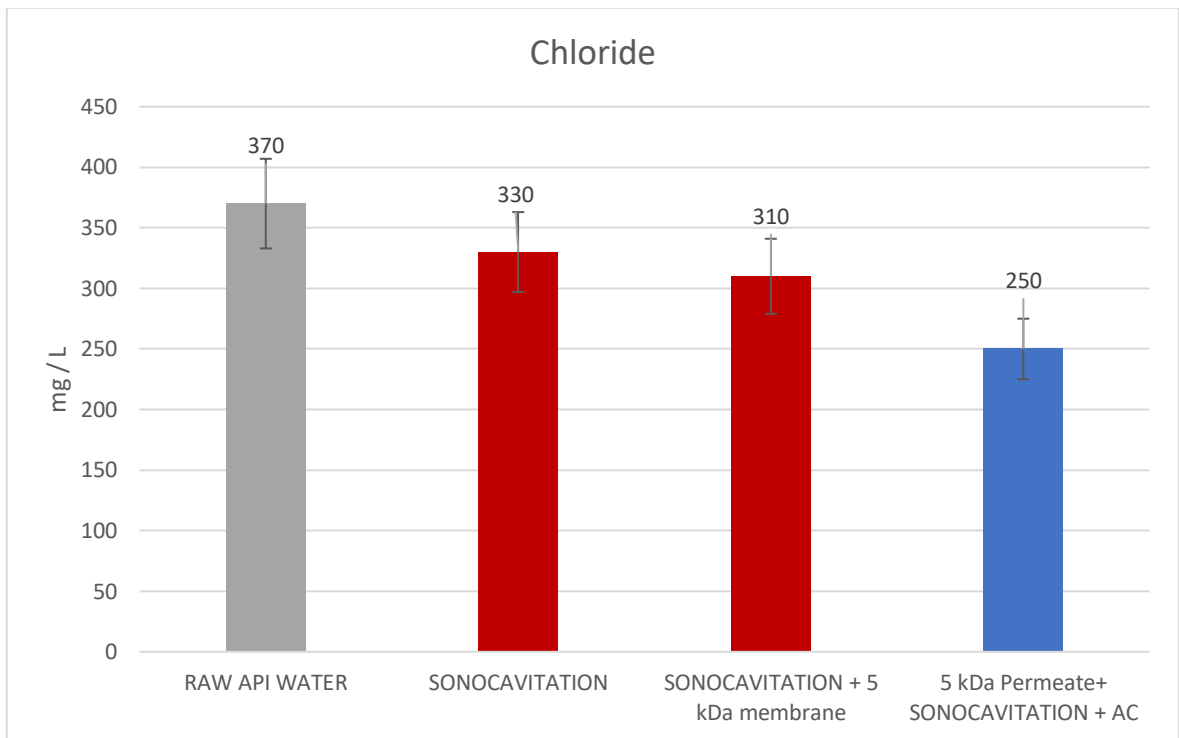


Figure 18. The results of the chloride analysis of the samples

Chloride is removed by membrane filtration in reverse osmosis. In this test arrangement, the filtration step was not sufficient for the filtration to take place, due to the 5 kDa size of the filtration step. The decrease in concentration that caused the reduction was due to AOX formation and partly to crystallization with other substances as complexes.

### 8.16 Chlorate and Perchlorate

Raw API water contained 49.8  $\mu\text{g/L}$  perchlorate. Three samples were taken after the treatment: after the ultrasonic cavitation treatment, after the ultrasonic cavitation and ceramic membrane filtration treatment, and after the ultrasonic cavitation, ceramic ultrafiltration and activated carbon treatment. In these samples, the concentration of perchlorate was below the detection limit of  $<10 \mu\text{g/L}$ . The chlorate content of the samples was examined, but none of the examined samples presented concentrations of chlorate exceeding the detection limit of  $<50 \mu\text{g/L}$ .

### 8.17 Adsorbable organic halogen compounds

The formation of adsorbable organic halogen compounds (AOX) was monitored with the help of samples taken from the process. The results are shown in Figure 19.

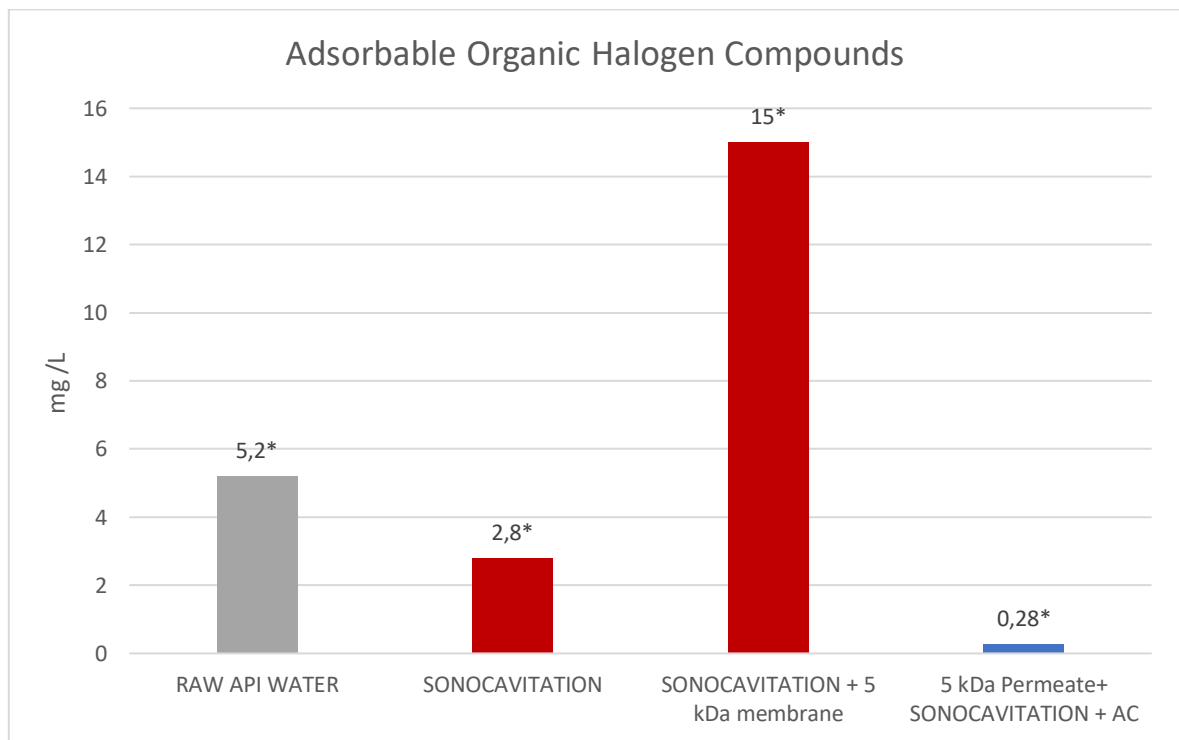


Figure 19. The results of the AOX compounds analysis of the samples. \*The laboratory that performed the analysis did not provide measurement uncertainty information

Adsorbable organic halogen compounds samples were taken from different stages of the process. The concentration of raw API water was 5.2 mg/L. The concentration decreased to 2.8 mg/L in ultrasonic cavitation treatment but it increased to 15 mg/L after 5 kDa filtration. This was probably due to the matrix of the sample water, where the solid content interfered with the determination of the AOX concentration.

The increase in AOX concentration was so significant that it was decided to filter the sample with activated carbon filtration, which proved to be an effective method for removing AOX compounds from the treated water.



## 8.18 Alcohols

Most of the loading of raw API water was due to alcohols. Raw API water contained isopropanol 14000 mg/L, ethanol 160 mg/L and methanol 190 mg/L. Concentration of isopropanol in different samples is shown in Figure 20.

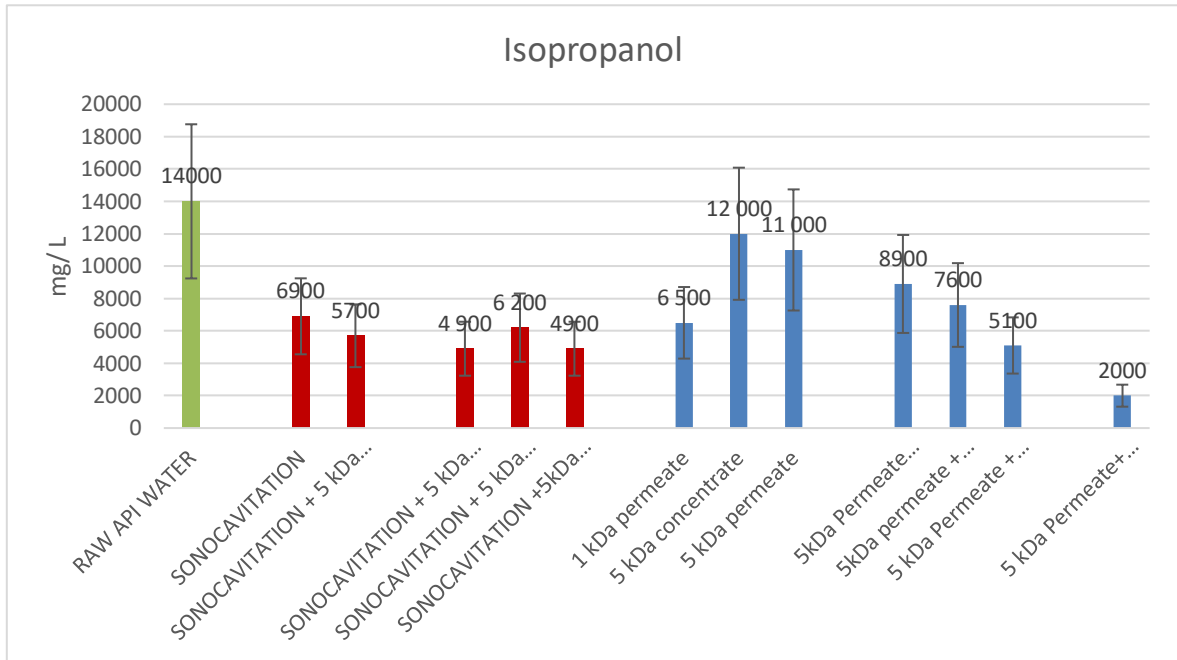


Figure 20. The results of the isopropanol analysis of the samples

After the first test run, the concentration of isopropanol was 6900 mg/L, i.e. the reduction in the concentration of isopropanol was 51%. In the second test run, the water was initially filtered with a 5 kDa ceramic membrane. After membrane filtration, the concentration of isopropanol was 11000 mg/L, the reduction was 21%. After the activated carbon treatment, the isopropanol concentration was 2000 mg/L, the total reduction in the trial run treatment was 86%.

The concentrations of ethanol and methanol varied during the test runs in the concentration range of 68-190 mg/L for ethanol and 110-200 mg/L for methanol.

## 8.19 Oxidation By-products

The bromate content of the samples was examined, but in none of the examined samples bromate concentrations exceeding the detection limit of <0.025 mg/L were found.

The concentrations of oxidation by-products are shown in table 5.

Table 5. Oxidation By-products

Parameter	Unit	RAW API WATER	SONOCAVITATION	SONOCAVITATION + 5 kDa membrane	5 kDa Permeate+ SONOCAVITATION + AC
Acrylonitrile	µg/ L	<0.5 ±0.200	7.9 ±3.160	4.3 ±1.720	<0.5 ±0.200
Benzene	µg/ L	<0.1±0.032	0.2 ±0.064	0.4 ±0.128	<0.1 ±0.032
Ethylbenzene	µg/ L	0.2 ±0.048	<0.1 ±0.024	0.5 ±0.120	<0.1 ±0.024
m,p-Xylene	µg/ L	0.1 ±0.034	0.3 ±0.102	1.5 ±0.510	0.2 ±0.680
o-Xylene	µg/ L	<0.1 ±0.026	0.2 ±0.052	0.6 ±0.156	<0.1 ±0.026
Bromide	mg/ L	1.9*	0.88*	1.1*	<1*

\*The laboratory that performed the analysis did not provide measurement uncertainty information

In ultrasonic cavitation, the concentrations of the substances shown in the table increased compared to the reference sample of raw API water. The increases in concentrations were very small and may be due to the decomposition of other organic compounds.

## 8.20 Active Pharmaceutical Ingredients

145 different pharma compounds were analysed from raw API water. One pharma compound at a concentration of 4.9 g/L was found in the Raw API water sample. The results of the analysed samples are shown in Figure 21.

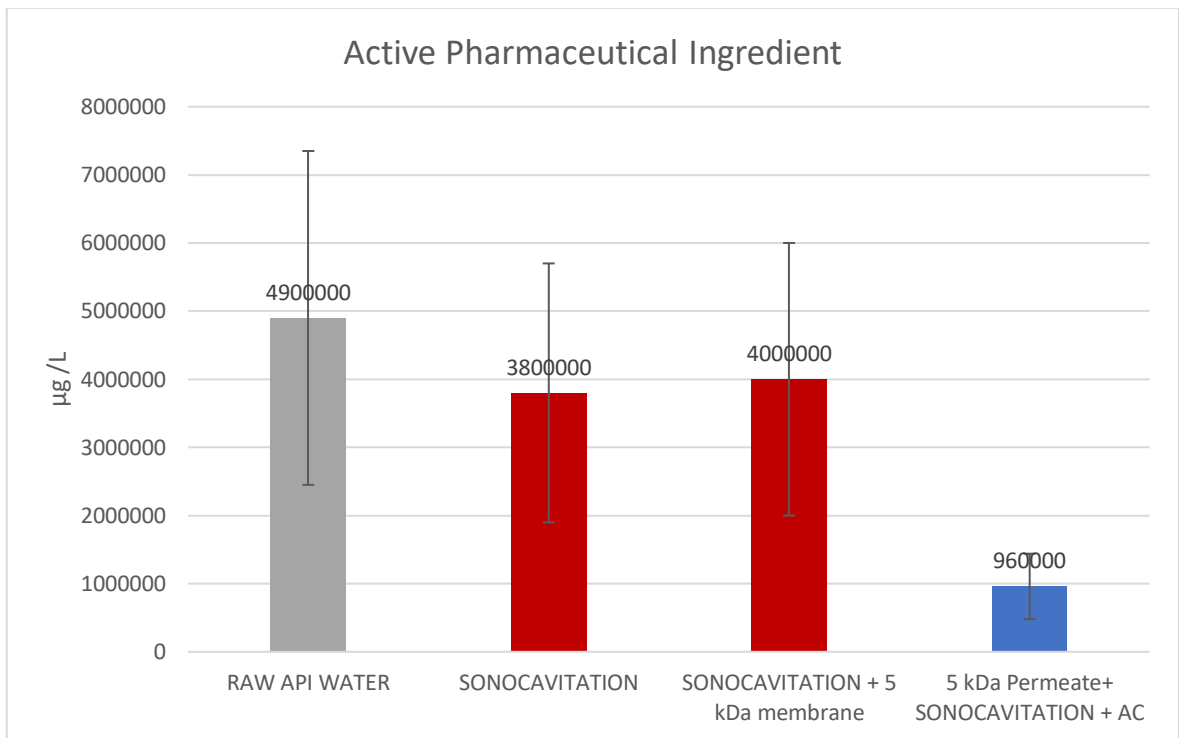


Figure 21. The results of the API analysis of the samples

In the first test run with ultrasonic cavitation treatment, the API content of the final sample was 3.8 g/L, the reduction was 22%.

In the second ultrasonic cavitation test run, where the water was filtered with a 5 kDa ceramic membrane, the head sample concentration was 4.0 g/L and the reduction was 18%. In the third test run, the sample filtered with a 5 kDa ceramic membrane was treated with ultrasonic cavitation and activated carbon filtration. The concentration of the final sample was 0.96 g/L and the reduction was 80%. Due to the high concentration level, API samples were diluted 1000-fold during analysis.

### 8.21 Energy consumption of ultrasonic cavitation

The total operating time of the sonocavitation trial run was 18 h 46 min, the 5 kDa membrane + sonocavitation trial run lasted 5 h 45 min and the 5 kDa membrane + sonocavitation + pH 3 trial run lasted 8 h 9 min. The flow through the ultrasonic cavitation equipment was 240

L/h in all of the test runs. The volume of the flow chamber of the ultrasonic cavitation equipment was 2.5 L. A summary of the test times is shown in Table 6.

Table 6. Energy consumption of ultrasonic cavitation

<b>Test</b>	<b>Energy (kWh)</b>	<b>Sample volume</b>	<b>Passes through flow cell</b>	<b>Retention time in flowcell (s)</b>	<b>Energy consumption kW/ g TOC</b>	<b>Energy consumption g TOC/ kW</b>
Sonocavitation	19.40	120	2	75	3.288	0.304
5 kDa membrane + sonocavitation	5.75	70	3.43	129	10.849	0.092
5 kDa membrane+ sonocavitation + pH 3	7.33	40	6	225	5.162	0.194

The reduction of test runs in terms of COD and TOC is presented in appendices 3 and 4.

## 9 Conclusions and future perspectives

In all the test runs cavitation was observed and in addition to that pyrolysis occurred in ultrasonic cavitation whereby very complex organic compounds were oxidized and decomposed. In all the test runs the flow rate was 240 L/h. The effect of pyrolysis can be increased by extending the residence time in the flow cell. The smallest possible design flow of the flow chamber of the equipment used in the test runs was 1.0 L/min., i.e. 60 L/h and the largest was 8.0 L/min., i.e. 480 L/h. Flow rate and retention time has a big impact on how the oxidation process works when handling APIs. With a high flow rate oxidation occurs mainly due to the effect of hydroxyl radicals and with a low flow rate pyrolysis increases.

The effect of pH on oxidation was significant. At low pH (pH 3), the redox potential increased significantly by more than two-fold, so the oxidation potential was higher, which was also reflected in the results. The effect of oxidation can be enhanced by adding a catalyst. The ferric sulfate used in these experiments lowered the pH, but instead of trivalent iron, zero-valent iron should be added to the process so that the catalyst would remain in solution and would not be precipitated by hydroxyl radicals to form iron hydroxide.

It is possible to form AOX compounds in ultrasonic cavitation. This was observed in this test run and the AOX concentration increased significantly. The raw API water contained 370 mg/L of chloride. Therefore, the possibility of AOX formation must be taken into account in all stages of the process.

Formation of chlorate, perchlorate and bromate is possible in the ultrasonic cavitation process. Bromate is formed in water under conditions where there are very low concentrations of organic compounds that can compete with the bromide ion for the OH-radical. Bromate can therefore form in very clean waters. Perchlorate was detected in the raw API water, but this compound disappeared under ultrasonic cavitation and the concentration did not increase. It is assumed that the perchlorate originates from a synthesis made with pure solutions in the synthesis of API compounds. The formation of chlorates or

bromates was not observed in this work, but it is possible when the concentrations of other compounds decrease.

Alcohols are used as raw materials in the manufacture of medicines. Many API compounds are dissolved in alcohol. The highest concentrations in API water were isopropanol and lower concentrations of ethanol and methanol. Isopropanol breaks down under the influence of hydroxyl radicals, and as a breakdown product, e.g. acetone, a significant concentration of which was found in the water. Ultrasonic cavitation enhances the decomposition of alcohols and the release of volatile compounds into the gas phase. In ultrasonic cavitation, alcohols break down due to pyrolysis and hydroxyl radicals.

As for ethanol and methanol, it must be taken into account that their combined concentration decreases during processing, since methanol is a breakdown product of ethanol. The measurement of carbon dioxide from the gas phase is also a recommended process control parameter.

Alcohols are hydrophilic (and many APIs are hydrophobic). For this reason, their treatment by adsorption is challenging. In this work, it was ruled out that ultrasonic cavitation could significantly increase the removal of hydrophobic API compounds that could be removed by adsorption onto activated carbon. Since the API is dissolved in alcohol in the manufacture of pharmaceutical compounds, its nature becomes hydrophilic and the alcohol must first be decomposed to enhance adsorption.

The solid matter formed in the water during the ultrasonic cavitation treatment caused the decision to remove it with ceramic membrane filtration. The best reduction was achieved with a filtration rate of 1 kDa, but the yield was poor when using this membrane. The 1 kDa filtration degree is at the beginning of the ultrafiltration scale and at the end of the nanofiltration scale, so the pressure required for filtration is greater than with a higher filtration degree (the equipment is typically run at 20 kDa). membrane and 3.5 bar pressure). The maximum pressure of the membrane filtration equipment was 10 bar., so we had to choose a higher degree of filtration. Filtration with a 5 kDa membrane was successful and the solid matter was removed from the water effectively, after filtration a small yellowish color remained in the water.

Ultrasonic cavitation can degrade API compounds and substances used as raw materials in pharmaceutical synthesis, such as tetrahydrofuran, alcohols and organic solvents. However,

the chemical and organic load of API raw water is so great that the process must be enhanced and optimized in order to get the concentrations of the treated water so low that the treated water does not cause harmful effects on the environment.

More research on the composition and behavior of API water is needed to develop a working treatment method. For example, a change in nitrogen concentration, where a significant decrease in nitrogen concentration occurs in activated carbon treatment, should be better investigated. Nitrogen is usually in ionic form in water and is weakly adsorbed on activated carbon. Due to the significant nitrogen reduction achieved with activated carbon, it should be determined whether the nitrogen is in organic form in the water. Next, due to the pungent smell and color observed in the API water, the amine concentrations should be determined in addition to the significant reduction achieved with activated carbon.

Ultrasonic cavitation should be performed at a lower flow to maximize the effect of pyrolysis in the treated API water. The oxidation of organic compounds should be enhanced by lowering the pH of the water to 3, in which case the redox potential increases and the conditions for oxidation reactions improve. In addition, the reaction could be catalyzed by e.g. zero-valent iron.

Ceramic membrane filtration should be done with a membrane as tight as possible, which improves the quality of the filtered API water. More research is needed on whether the first step in the production-scale treatment process is membrane filtration of raw API water or filtration of API water treated with ultrasonic cavitation. Membrane filtration produces rejects, the quantity and quality of which must be determined more precisely for the final treatment process. The energy consumption of membrane filtration should also be optimized in terms of the entire process.

More research is also needed on whether solid matter needs to be removed from ultrasonic cavitation processed water or whether solid matter particles are useful in the pyrolysis phase of cavitation and at the interface between the cavitation bubble and the bulk solution. It would be good to investigate increasing the amount of hydroxyl radicals in the bulk solution. For example by adding hydrogen peroxide to the treated water to lower the TOC/increase the oxidation of alcohols. The effect of the reactions taking place in the bulk solution could be enhanced with the help of ultraviolet light now that there is already some information that no chlorates, bromates or perchlorates are produced in the treated water during the treatment.

In all further tests that are carried out for API water, it must be remembered that the quality of the API water to be treated changes and it is necessary to know the raw API water as well as possible in order to succeed in safe working and effective processing.



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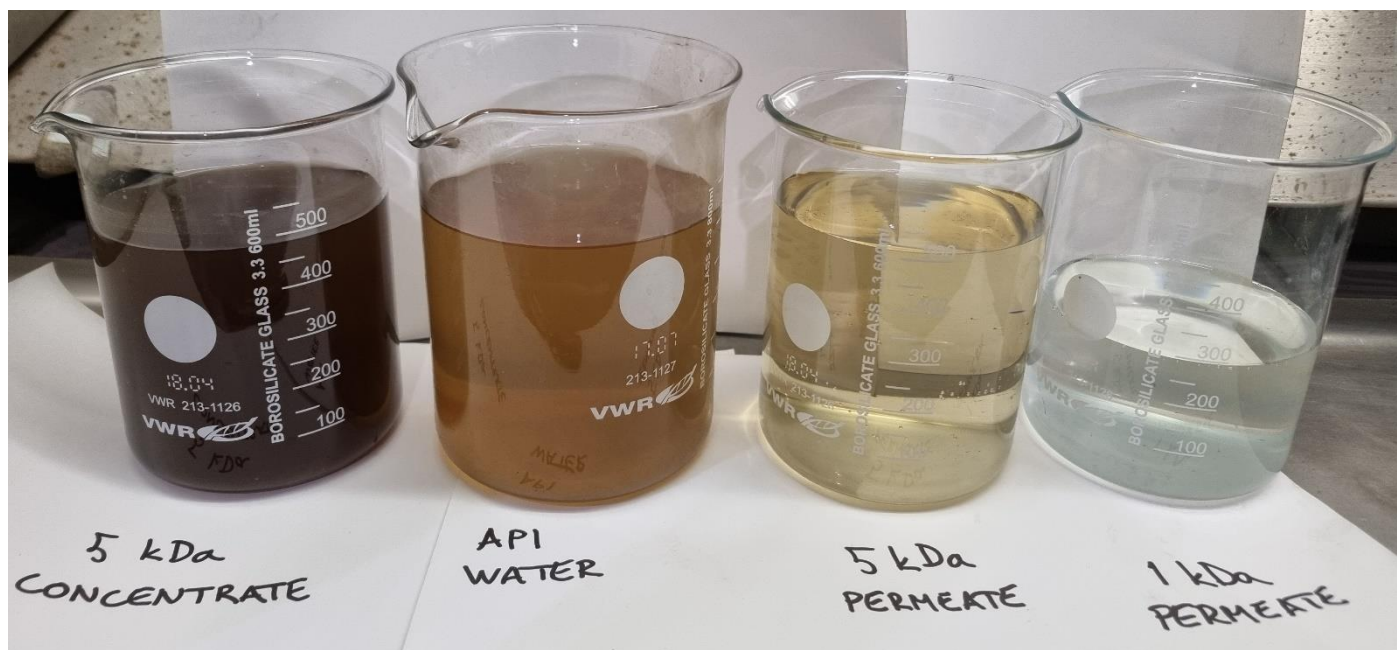
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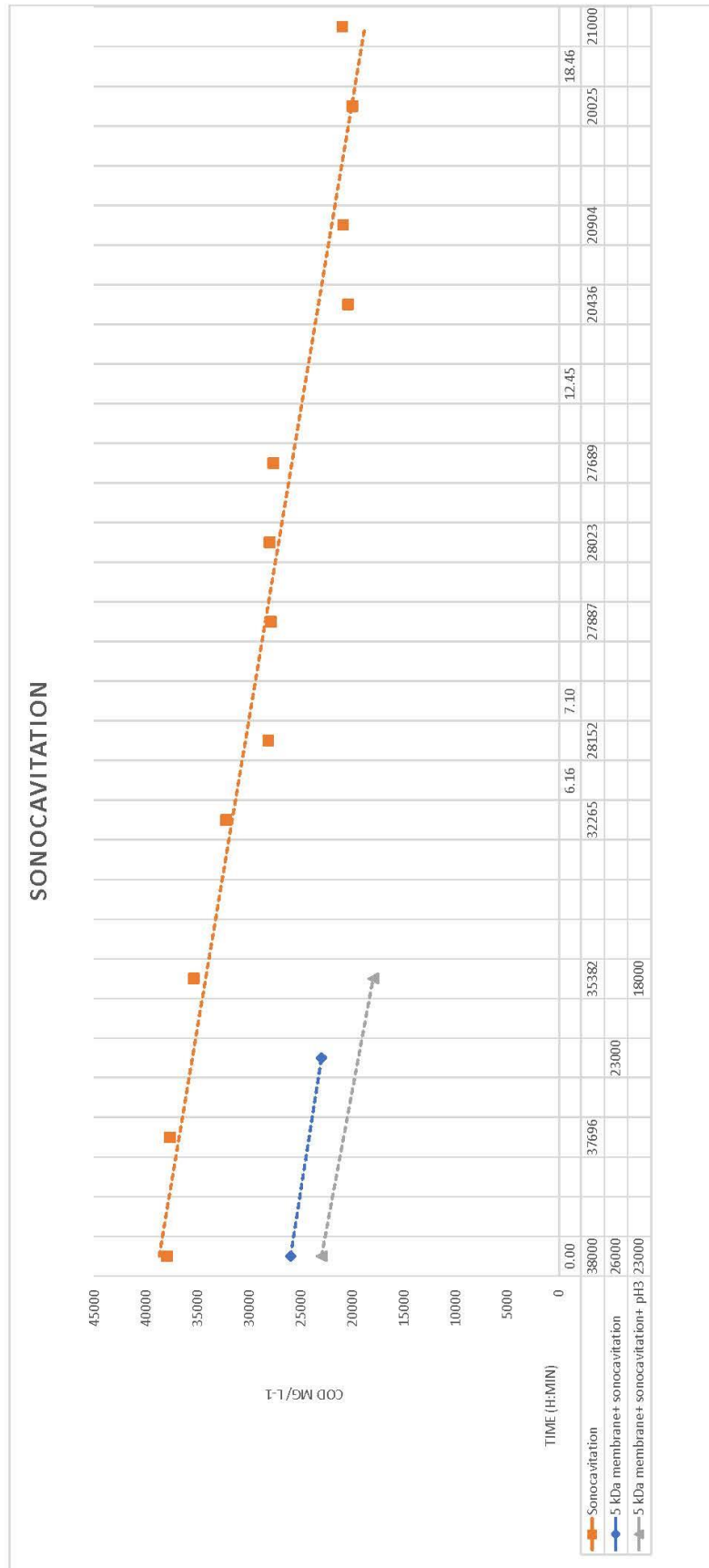
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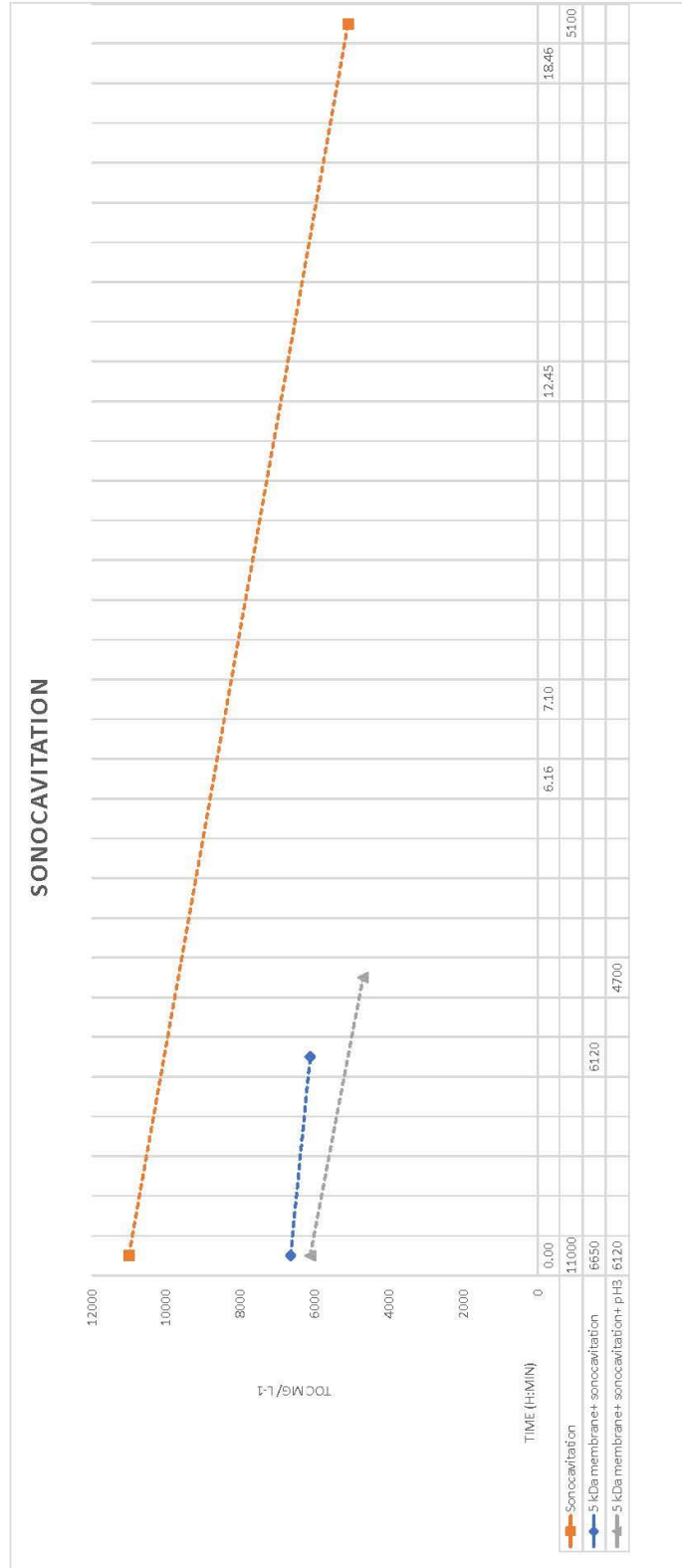
**Appendix 2:** Picture showing raw API water sample of 5 kDa membrane filtrated concentrate membrane filtrated 5 kDa permeate sample and 1 kDa membrane filtrated permeate-sample



Appendix 3: Figure showing COD reduction and time relation



Appendix 4: Figure showing TOC reduction and time relation





**Appendix 5:** Picture of raw API water (left) and sonocavitated (right) samples

