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Acetaminophen micropollutant: Historical and current occurrences, toxicity, removal strategies and transformation pathways in different environments

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Abstract

Acetaminophen (ACT) is commonly used as a counter painkiller and nowadays, it is increasingly present in the natural water environment. Although its concentrations are usually at the ppt to ppm levels, ACT can transform into various intermediates depending on the environmental conditions. Due to the complexity of the ACT degradation products and the intermediates, it poses a major challenge for monitoring, detection and to propose adequate treatment technologies. The main objectives of this review study were to assess (i) the occurrences and toxicities, (2) the removal technologies and (3) the transformation pathways and intermediates of ACT in four environmental compartments namely wastewater, surface water, ground water, and soil/sediments. Based on the review, it was observed that the ACT concentrations in wastewater can reach upto several hundreds of ppb. Amongst the different countries, China and the USA showed the highest ACT concentration in wastewater (≤ 300 $\mu\text{g/L}$), with a very high detection frequency (81-100%). Concerning surface water, the ACT concentrations were found to be at the ppt level. Some regions in France, Spain, Germany, Korea, USA, and UK comply with the recommended ACT concentration for drinking water (71 ng/L). Notably, ACT can transform and degrade into various metabolites such as aromatic derivatives or organic acids. Some of them (e.g., hydroquinone and benzoquinone) are toxic to human and other life forms. Thus, in water and wastewater treatment plants, tertiary treatment systems such as advanced oxidation, membrane separation, and hybrid processes should be used to remove the toxic metabolites of ACT.

Keywords

Micropollutant, acetaminophen, pharmaceutical and personal care products, intermediates, wastewater treatment

1. Introduction

In recent years, acetaminophen (ACT) is one of the most consumed pharmaceutical and personal care products (PPCPs) in many countries. For instance, in 2009, ~ 54.3 and 22.6 g ACT/inhabitant per year was reported in France and Spain, respectively (Ortiz de García et al., 2013). Likewise, the Taiwan citizens used ~580 million ACT doses in 2004 (Lin and Tsai, 2009). After consumption, ACT is excreted in both native and metabolized forms to the sewer systems, wastewater treatment plants (WWTPs) and other aquatic/natural environments. ACT in wastewater has been detected frequently in various countries from Asia, Europe and Americas. It inflicts significant negative impacts to the aquatic and ecological systems. Additionally, through drinking water and food consumption, it can enter the human body and cause significant health effects (Baron et al., 2014). The long-term exposure would result in cancer, endocrine disruption, antibiotic-resistant and several chronic diseases (Fisher and Curry, 2019). Therefore, the proper removal of ACT and its metabolites/degradation products from water, prior to being discharged to the environment, is important in order to preserve the environmental quality.

For the removal of ACT from water, numerous treatment technologies have been developed and tested both at the laboratory and pilot scales. These include biological processes, advanced oxidation processes (AOP), constructed wetlands (CWs), adsorption and membrane processes. Evidently, the principles and working mechanisms of these technologies are different and they remove ACT at different efficiencies depending on the concentration of ACT, its source, geographical and environmental conditions. For example, biological processes are green and safe, but high concentrations of ACT can inhibit the microbial activity. In turn, AOPs are rather fast and efficient for high concentrations of ACT; however, AOPs consume more chemicals and they are energy intensive. The degradation mechanism is also different for a biological process and a AOP. For instance, in the case of AOPs, the hydroxyl radicals ($\cdot\text{OH}$), in the

presence of photon energy would create chemical breakdown of the ACT molecules and transform them into different ACT metabolites. In a biological process, the microorganisms or the biocatalyst degrade/mineralize the ACT by enzyme mediated biochemical reactions and convert ACT into metabolites. Consequently, the different treatment technologies should be differentiated clearly and selected depending on the level of treatment required.

After degradation by the different treatment technologies, intermediates/by products are formed which entail another issue of secondary ACT pollution. The transformation pathway, and the metabolites of ACT occur synergistically in wastewater treatment systems and other aquatic environments. In essence, several transformation processes have been proposed and more than 20 by-products have been identified during the past 15 years (Andreozzi et al., 2003; de Luna et al., 2013). However, these metabolites pose different toxicities. Some of them are more detrimental than the parent forms such as *N*-acetyl-*p*-benzoquinone imine (Liang et al., 2016). From a health viewpoint, such aromatic intermediates can result in failure of liver functions in humans (Fisher and Curry, 2019). Hence, the transformation pathways and by-products of ACT should be identified and studied systematically.

From all the above concerns, this review study aims to assess the following aspects: (i) the occurrences and toxicities, (ii) the different treatment/removal technologies, and (iii) the transformation pathways and intermediates of ACT in four environmental compartments (i.e. wastewater, surface water, ground water, and soil/sediments). By clarifying such stated issues, this review delineates and proposes a sustainable management and treatment option for ACT pollution.

2. Occurrences of acetaminophen in various environments

Human wastes, domestic and industrial wastewater are the major sources of ACT, a persistent micropollutant in the natural environment. Various household activities dispose ACT to the sewage systems and ACT is collected in the WWTPs. After the treatment process(es) in

WWTPs, ACT still remains in the effluent and is released to water reservoirs and contaminates soil, sediment and groundwater. Thus, ACT occurs mainly in four environments: sewage and WWTPs, surface water, groundwater and soil and sediments.

2.1 Sewage and wastewater treatment plants

In 1998, a number of WWTPs in Germany were examined if the treatment systems contained ACT; however, surprisingly, it was not detected (Ternes, 1998). Although it could one isolated finding, ACT has been detected across continents, at varying concentrations and detection frequencies (Fig. 1). In 2006, ACT in wastewater was investigated in South Korea, China, United States of America (USA), France, United Kingdom (UK) and many other countries worldwide. The concentration of ACT ranged from 0.1 to 300 µg/l and its detection frequency reached up to 100%.

In Asia, several countries reported their wastewater being contaminated by ACT such as South Korea, China and Taiwan. From Fig. 1, it is evident that the documented sites were mostly in mega cities and their nearby regions (e.g., Busan, Ulsan and Xiamen) with high-density population. In the case of South Korea, ACT accounted for 18 - 80% of the total PPCPs in wastewater in the year 2007 (Kim et al., 2007a; Sim et al., 2010). From the year 2008 to 2012, ACT concentration in sewages and WWTPs increased by ~11-fold from 6.8 to 75 µg/l (Sim et al., 2010; Kim et al., 2012). The main reason was attributed to the high ACT consumption rate in South Korea. In the year 2004, Korean consumed 9 tons ACT and the ACT consumption rate only started to rise from 2008 to 2012 (Sim et al., 2010). Similarly, in China, the ACT concentration was recorded at 3.4 µg/l in sewages and WWTPs and it was ranked as the highest amongst all the assessed PPCPs (Sun et al., 2016b). Therefore, researchers suggested ACT as the marker for PPCPs pollution in China. In comparison with the Korean survey, the Chinese citizens also used ACT widely and the survey showed values ranging from 10 - 18 g/d per 1000 inhabitants (Gao et al., 2016). In Taiwan, ACT was the most detected compound in WWTPs

effluent because the Taiwanese citizens have consumed 579 million doses of ACT (different forms) in 2004 (Lin and Tsai, 2009). This was 4 times higher than the propranolol dose of 156 millions, being the second most-consumed PPCPs.

In Europe, the pattern of ACT contamination differed from those observed in Asia. Countries such as Greece and France showed 100% ACT detection frequency in WWTPs (Gros et al., 2010; Papageorgiou et al., 2016). Although its detection frequencies were higher than in Asia, nevertheless, the total amount of ACT accounted for only 1 - 2% of the total PPCPs in wastewater compared with 18 - 80% in Asia (Rabiet et al., 2006). These values can be considered to be acceptable because European citizens used 320 mg/d per 1000 inhabitants, much less than the values of 10 - 18 g/d per 1000 inhabitants of the Asian region (Kosma et al., 2010).

Concerning the United States, the ACT concentration in WWTPs was more pronounced than other countries. For example, in the year 2006, $\sim 0.96 \mu\text{g ACT/L}$ was reported in Baltimore, and these values subsequently increased 100-fold $\mu\text{g/l}$ after 2012 (Hedgespeth et al., 2012; Blair et al., 2013; Kosma et al., 2014). Besides, in the United States, ACT accounted for $\sim 45\%$ of the total PPCPs present in the hospital effluent (Oliveira et al., 2015). Its concentration was $\sim 220 \mu\text{g/l}$ and the highest values were observed during the winter season due to the pattern of consumption (Yu et al., 2013). ACT is being used in hospitals; thus, its concentration in wastewater was 3-fold higher than those observed normally in municipal WWTPs. In the case of Colombia, ACT concentration in sewage and WWTPs varied from 9.2 to 39.2 $\mu\text{g/l}$ (Botero-Coy et al., 2018), which is nearly similar to the amounts reported in WWTPs samples from the Asian region.

During 8 years, from 1998 to 2006, ACT was detected increasingly in many countries and regions. Since the invention of ACT in 1955 for medication purposes, ACT was consumed even more. Although it was not detected in German WWTPs in the year 1998, it might be

possible that the ACT concentration was below the detection limit in that study. In the following years, modern analytical techniques, tools and technologies are well-developed and these instruments can detect even low concentrations. Additionally, micropollutants have attracted a growing interest amongst researchers from various disciplines, ranging from public health, engineering, geochemistry to policy and governance.

[Insert Fig. 1]

2.2 Surface water

In developing countries, industrial effluent, municipal wastewater, hospital wastewater and septic tank effluent are often not collected and treated properly. This causes the wide spread prevalence of ACT in surface water. Unlike in the case of sewage and WWTPs, the concentration of ACT in surface water reduced chronologically with respect to the years. At the early stage, ACT was detected in surface water at the ppb concentration levels (10 µg/l in 2002) (Kolpin et al., 2002). In recent reports, the concentration of ACT decreased to ppt levels (Lv et al., 2014; You et al., 2015; Lin et al., 2016c).

Similar to sewage and WWTPs, ACT was detected in surface water of several Asian countries such as South Korea, China, Taiwan and Singapore. In South Korea, ACT was present in many rivers with the highest occurrence frequency (80%) and concentration (33 ng/l) than other PPCPs (Kim et al., 2007a). For example, they existed in the three biggest rivers in South Korea: Han, Nakdong and Youngsan, respectively. Particularly, they were present in 9/12 of the water samples collected from rivers (Choi et al., 2008); 6/8 of the water samples collected from wastewater treatment plants and surface waters (Kim et al., 2007a), and 2/5 of the river water samples (Sim et al., 2010). In China, ACT concentration in surface water was comparable to the values reported from South Korea. Specifically, ACT existed in the range of 9.8 to 197 ng/l in Taihu lake and Jiulong river, while other PPCP concentrations were found to be below the detection limit (Lv et al., 2014; Lin et al., 2016c; Sun et al., 2016b). In Taiwan and Singapore,

ACT was dominant (33 - 95%) among the total PPCPs in surface waters (Lin and Tsai, 2009; You et al., 2015). Incidentally, these water reservoirs received discharges from various industrial activities and supplied drinking water to the local communities in the region.

Concerning Europe, in France and Spain, the ACT detection frequency in surface water was in the range of 28 - 41% (Vulliet and Cren-Olivé, 2011; Vazquez-Roig et al., 2012) and its concentration varied from 0.4 to 71 ng/l. However, the studied (sampled) regions were remote areas like national parks and mountain lakes. Elsewhere, the Ensanche region of Northwest Spain recorded a maximum ACT concentration of 5.71 µg/l (wet weather) and 0.72 µg/l (dry weather), respectively (Del Rio et al., 2013). This area was used as a catchment for wastewater discharge by the local communities.

In United States, the ACT concentration and detection frequency in Michigan lake was 2.5 - 17 ng/l and 25%, respectively (Ferguson et al., 2013). Michigan lake was the catchment serving drinking water for a larger part of the community in the region. It also received wastewater from the local communities. Thus, ACT concentration in these densely populated areas overtook the open water/catchment sites. In the Mississippi river, ACT concentration ranged from 24.7 - 65.2 ng/L, which was higher than the values reported from Michigan lake (Zhang et al., 2007). The Mississippi river carried ~ 66% suspended solids (SS) from the mainland of the United States to the ocean. Interestingly, the presence of suspended solids adsorbed and reduced a significant amount of ACT and other PPCPs present in the river water. Previously, Boyd et al. (2003) tested water samples collected from the Mississippi river and Pontchartrain lake and reported that ACP were below the detectable levels.

In general, ACT detection frequencies (< 50%) and ACT concentrations in surface waters of Europe and America was less than those reported in Asia. In surface water, ACT concentration is usually influenced by several environmental, geographical and social factors. The most important parameter was, however, the pollution - given that Europe and United States has

less population density compared to Asia. Geographical condition such as rainfall also affected the ACT concentration in surface water. For example, according to a field study, Michigan lake received runoff and rainfall that diluted the ACT concentration several fold after the monsoon season (Ferguson et al., 2013). Nevertheless, from the yearly trends, it is evident that the ACT concentration in surface water has reduced in recent years. Such drop in the ACT levels can be attributed to the better performance of WWTPs, innovations in research, awareness and enactment of policies and regulations. Besides, the discharge standards for micropollutant have been gradually been established in many countries. In 2008, the United States Environmental Protection Agency (USEPA) developed a “*White Paper Aquatic Life Criteria for Contaminants of Emerging Concern: Part I Challenges and Recommendations*” and, in the meantime, *Directive 2000/60/EC* and *2008/105/EC* were published by the European Commission. In Asia, discharge standards for micropollutants is still scarce or they are still at the policy approval level. Some of the new treatment technologies and discharge standards have compromised ACT concentration < 71 ng/l that makes the water suitable for drinking purposes (Vulliet and Cren-Olivé, 2011). However, in the case of European countries, although the levels of ACT were reported to be high in some reports, the policies and guidelines are substantially stronger and well-implemented than in many Asian countries.

2.3 Groundwater

The sources of ACT pollution in ground water are similar to those observed in surface water, industrial effluent, municipal WWTP, septic tank and landfill. The leakage of septic tank and landfill can contain concentrated pollutants in the range of 100 - 1000 ng/l of ACT (Lapworth et al., 2012). ACT contaminated ground water has been reported in many countries and regions. In France and Serbia, ACT appeared in 17% and 15% of the groundwater samples tested (Grujić et al., 2009; Vulliet and Cren-Olivé, 2011). In the Tennessee River basin (USA), ACT concentration was in the range of 2.1 - 12.3 ng/l and it was present in ~ 13% of the groundwater

samples (Conley et al., 2008). In California, the ACT detection frequency and maximum concentration were 0.32% and 1.89 $\mu\text{g/l}$, respectively (Fram and Belitz, 2011). Thus, ground water is less contaminated than wastewater and surface water because the ACT containing stream is usually filtered by the soil layers as it penetrates gradually into the soil layers (He et al., 2016). Nevertheless, studies related to the identification/quantification of ACT in ground water is scarce compared to wastewater and surface water. Hence, the available reports related to ground water contamination due to ACT might not reflect the actual problem adequately. In developing countries, septic tanks are used widely but their quality and durability still remains a challenge and persisting problem. Anew, the management policies concerning landfills in Asia is rather poorly defined and incomplete. Those must be considered for micropollutant control in the future.

2.4 Sediment and soil

Similar to drinking water, ACT has also contaminated the soil and sediment environments, e.g. the Pego-Oliva marsh in Spain. ACT was detected in 87% of the soil and 91% of the sediment samples with maximum concentrations of 15.1 ng/l and 1.8 ng/g, respectively (Vazquez-Roig et al., 2012). Notably, ACT settles and accumulates in sediment and soil faster than in surface water. In samples collected from the Masan Bay in South Korea, ACT was an indicator of micropollutant pollution. It was detected in > 50% of the sediment samples with a concentration of ~ 2.2 ng/g sediment (Choi et al., 2014). The Masan Bay was one of the most polluted coastal area in South Korea due to effluent discharges from heavy industries and highly urbanized cities. According to the authors, the ACT detection frequencies in soil and sediment were high because ACT could adsorb onto the solid phase and settle easily than in surface waters. Although its concentration in sediment and soil still remained at the ppt level, it could increase gradually in the next coming years due to (bio)accumulation and (bio)magnification.

The salient observations can be summarized as follows: (i) ACT concentration in wastewater is constantly increasing since 1998 to the present values of several 100 ppb; (ii) in surface water, ACT concentration decreased to ppt from the same time but has contaminated the larger surface areas, (iii) groundwater is less polluted with ACT than surface water, and (iv) soil and sediment environments accumulated ACT from surface water. These evidences clearly illustrate that ACT can be an indicator for the presence of micropollutants in several countries. Although the pattern of ACT contamination in those countries were different, China and the USA showed the highest ACT detection frequency ranging from 81 - 100%, compared to 22 - 73% in France, Spain and Singapore. In some reports from United States, UK, Colombia and Taiwan, ACT concentrations were $> 300 \mu\text{g/l}$. France recorded the lowest ACT detection frequency ($< 39\%$) and concentration $< 0.1 \mu\text{g/l}$. Table 1 classifies the countries depending on their levels of ACT contamination.

[Insert Table 1]

3. Toxicities of acetaminophen

ACT is toxic to both aquatic and human life. It causes genetic code damage, oxidative degradation of lipids and denaturation of protein in cells. The toxicity of ACT can vary from low to moderate depending on acute and chronic exposure conditions (Kosma et al., 2010). The effective concentration (EC_{50}) and exposure time to ACT are summarized in Table 2.

[Insert Table 2]

The toxicity of ACT has been studied in several hosts such as bacteria, algae, macrophytes, protozoan and fish. Amongst those, the freshwater invertebrate and cell *in-vitro* showed the lowest effective concentration, i.e. $< 50 \text{ mg/l}$ (Henschel et al., 1997; Kim et al., 2007b). This implies that these species were sensitive to ACT. In turn, bacteria and macrophyte species were recalcitrant to ACT. Most of the authors have reported that their EC_{50} values were $> 400 \text{ mg/l}$ (Henschel et al., 1997; Kim et al., 2007b).

ACT can be present in drinking water and it would endanger public health. However, the risk assessment method of PPCPs in drinking water has not been established officially. Instead, two main procedures have been proposed in the literature, i.e. the measured and predicted concentrations. For instance, [Vulliet and Cren-Olivé \(2011\)](#) followed this approach to estimate the maximum levels of ACT in drinking water. The maximum value for drinking water was reported as 71 ng/l and the daily ACT intake was 142 ng/l. The ACT concentrations of some surface water sources have reported to be > 71 ng/l, such as the Hérault River Basin of France, River Taff and River Ely of the UK, Sindian and Dahan river of Taiwan, Jiulong River of China and many areas of the United States ([Rabiet et al., 2006](#); [Kasprzyk-Hordern et al., 2008](#); [Lin and Tsai, 2009](#); [Lv et al., 2014](#)).

4. Removal technologies for acetaminophen (ACT)

Several technologies have been developed, both at the laboratory and field scale, for the removal of micropollutants. They range from biological, physical, chemical to hybrid and advanced technologies. The common technologies for ACT removal including biological processes, AOPs, plant uptake, adsorption, membrane processes, hybrid processes and other technologies were reviewed and discussed. In essence, they differ from originalities and mechanisms. For example, the AOPs are regulated by chemical reactions and physical processes, e.g., Fenton's reagent/photo-Fenton process. The adsorption and membrane processes are largely physical treatments, while plant uptake (phytoremediation), activated sludge process and anaerobic process refer to biological treatment.

4.1 Biological processes

Biological processes refer to the removal of micropollutants using suitable biocatalysts under aerobic or anaerobic environments. The pollutant removal mechanisms of biological processes comprise of biosorption, biodegradation and bioaccumulation. In practice, the commonly used biological processes include the activated sludge process, anaerobic process, microalgae based

photobioreactor and microalgae based pond system. However, during wastewater treatment, these technologies yield different advantages and limitations for ACT removal.

Activated sludge process has proven to be effective for the removal of ACT from wastewater. For example, in the Baltimore WWTP (USA), it could remove 99% ACT in 14 d (Yu et al., 2006). A half of ACT dose was biotransformed within 4 d. In the Coslech WWTP (UK), an activated sludge process eliminated 100% ACT from wastewater (Kasprzyk-Hordern et al., 2009). Although ACT was removed efficiently in the system, according to the authors, it was not mineralized completely and bioaccumulation, physical adsorption and biodegradation contributed to > 99% removal efficiency. After treatment, the wasted sludge can be composted, incinerated or treated in an anaerobic digester.

Similar to an activated sludge process, anaerobic systems could also remove > 75% ACT from wastewater. According to a recent study, ACT was retained in the anaerobic sludge biomass to a value of 35 g/kg (Narumiya et al., 2013). The superiority of anaerobic process(es) compared to a conventional anaerobic process is that this process could tolerate high dose of ACT, ranging from 50 to 1000 mg/l. Over this dose, ACT would inhibit the anaerobic microbial community in the reactor (Alvarino et al., 2014). In addition, ACT concentrations > 250 mg/l could hamper/inhibit the nitrification and denitrification rates.

Regarding microalgae, a high rate algae pond could handle wastewater containing 9 µg ACT/l from 4 to 8 d (Matamoros et al., 2015). When compared to the microorganisms present in the activated sludge process and the anaerobic process, microalgae are less tolerant to ACT stress. The effective ACT concentration causing toxicity to algae ranges from 134 - 240 mg/l; whereas the inhibitory concentration for certain bacteria ranged between 550 and 650 mg/l (Table 2). Hence, in order to enhance the overall removal efficiency, algal cells were immobilized to inert matrices such as sponge, bead and nanoparticles. As a result, the immobilized algal cells were

able to tolerate ACT, achieving 100% efficiency at a concentration of 100 $\mu\text{g/l}$ in 8 d (Yu et al., 2011).

From these previous reports, it is clearly evident that biological processes could treat wastewater containing high levels of ACT, upto hundreds of ppb. From a practical viewpoint, in WWTPs, biological processes are prone to receive fluctuating concentrations/loading rates of wastewater. In order to withstand the shock load effects on the biological system, the application of an equalization tank will help to maintain the ACT concentrations at values < 50 mg/l for anaerobic treatment and $500 \mu\text{g/L}$ for aerobic treatment, respectively. Algal pond systems can still be considered as a post-treatment step because it can easily tolerate low ACT concentrations present in wastewater. However, some of these biological processes require long start-up or acclimation time, high surface (land) area, long solids and hydraulic retention time and the removal efficiency depends on the composition and concentration of pollutant(s) present in the wastewater. Nevertheless, complete mineralization of the ACT is still not accomplished in biological treatment systems, thus, a tertiary treatment step as AOPs, plant uptake, adsorption and/or membrane processes are usually required. The tertiary treatment step could also be used as a pre-treatment step to reduce the load of wastewater to the biological process, thereby reducing the size of bioreactors and completely eliminate ACT from the treated effluent.

4.2 Plant uptake processes

Plant can uptake organics, inorganics and a wide variety of recalcitrant pollutants present in wastewater (Vo et al., 2018). Thus, it can also be considered as an option for ACT removal. In natural/constructed wetlands, the plants uptake ACT via the root, and its accumulated and thereafter translocated. In addition, the plant rhizosphere offers co-benefits for other removal processes, by promoting microbial growth in the wetland and alleviating clogging of the media bed. Although plant contributes greatly to the removal of ACT, depending on the plant species,

the removal efficiency could vary largely. For instance, *P. australis* removed ~51 - 99% ACT from contaminated water, while *T. latifolia* reduced 46.7 - 99.9% ACT (Ranieri et al., 2011). Some plant species could also contribute to the transformation of ACT (Huber et al., 2009; Wu et al., 2013).

The fate and metabolism of ACT was investigated in the tissues of *Armoracia rusticana* (Huber et al., 2009). After 6 h of incubating the plant species in ACT containing wastewater, ACT and its metabolites were detected in the plant tissues. The metabolites consisted of 18% ACT, 64% paracetamol glucoside, 17% paracetamol glutathione and 1% cysteine conjugate, respectively. However, after 168 h, 88% ACT in the plant root system had reduced and transformed to other metabolites. Similarly, *Brassica juncea* was able to uptake 22% ACT within 3 d. The authors confirmed that the shoot was responsible for determining the fate of ACT transformation and its metabolites (Bartha et al., 2010). The conjugation of ACT - glutathione and glucose occurred in the plant tissues and these mechanisms are somewhat similar to those occurring in mammals. The transformation process of ACT in plant tissues depends on the plant species, lasting from 6 h to 3 d. Using plants, wastewater containing ACT < 5 µg/l can be handled effectively and this technique can be used as a post-treatment step to reduce ACT to ppt levels.

4.3 Advanced oxidation processes

4.3.1 Chemical-based Fenton processes

Chemical-based Fenton reaction is one of the commonly reported AOP. The chemical-based Fenton includes classical Fenton, Fenton-like and bio-Fenton processes. It produces hydroxyl radical groups that plays a major role in the degradation/mineralization of ACT (Eq. 1 & 2):

The ACT removal efficiency of chemical-based Fenton process is affected by the pH, H₂O₂ and Fe²⁺ concentrations. The importance of those parameters varies in the order: Fe²⁺ > H₂O₂ >

pH (Su et al., 2012). The increase of Fe^{2+} and H_2O_2 concentration can enhance the ACT removal efficiency, whereas the prevailing pH conditions can also synergistically or antagonistically affect the ACT removal. At higher pH conditions, Fe^{3+} precipitates to amorphous $\text{Fe}(\text{OH})_3$ and reduces the regeneration of Fe^{2+} . In a recent study, the optimal conditions were reported to be: pH - 3.0, H_2O_2 - 25 mM and Fe^{2+} - 0.1 mM, to remove 5 mM of ACT from contaminated water (Su et al., 2013a). The amorphous form of iron present in sludge damages the equipments in WWTPs. The type of iron sources used in the chemical based Fenton process is also important in the Fenton reaction. For example, artificial ferrous iron removes ACT 5% higher than the iron source present in laterite soil (Basavaraju et al., 2011).

Referring to the mechanism, Fenton reaction degrades ACT in 2 stages including an initially occurring reaction at higher rates, followed by a reaction at slower rates (de Luna et al., 2013). In the first stage, $\text{Fe}^{2+}/\text{H}_2\text{O}_2$ reaction occurs within 30s to generate large amount of $\cdot\text{OH}$, while the second stage of $\text{Fe}^{3+}/\text{H}_2\text{O}_2$ occurs after 30s in which the Fe^{3+} combines with H_2O_2 to degrade ACT. Depending on the degree of treatment required, the reaction time of a Fenton's process could be optimized.

The chemical-based Fenton's reaction has been performed in different reactors such as an aerated reactor, fluidized-bed reactor and wetlands. In an aerated reactor, it removed 99% ACT at an initial concentration of 5 mM (Su et al., 2012). In a fluidized-bed reactor, 99.6% ACT removal was observed at an initial concentration of 5 mM, within 40 min (de Luna et al., 2013). Bio-Fenton's process has also emerged as a novel technology as it uses the iron present in laterite soil environments and H_2O_2 from the plant rhizosphere of a constructed wetland (Phong et al., 2016). The H_2O_2 of the root tissue and iron species of laterite soil activated bio-Fenton reaction and degraded 99.5% of ACT at a concentration of 100 $\mu\text{g}/\text{l}$.

The chemical-based Fenton's reaction is almost instantaneous and highly efficient for ACT removal. The ACT removal efficiency of a chemical-based Fenton's process is typically > 75% (Table 3). As seen from Table 3, depending on the degree of treatment required, the retention times have been varied from 40 to 120 min in order to remove high concentrations of ACT (10 mg/l) at pH 3.0. Besides, a wide range of $[\text{Fe}^{2+}]:[\text{H}_2\text{O}_2]$ ratios has been reported in the literatures, varying from 1:40 to 1:250.

[Insert Table 3]

4.3.2 Photo-based Fenton processes

The conventional Fenton's reaction can be modified as the photo-based Fenton's process when coupled to a light source. The photo-based Fenton's process degrades ACT 2-fold faster than the traditional Fenton's reaction (Manu and Mahamood, 2011). The photo-based Fenton's process encompasses both photolysis and photocatalytic oxidation. Commonly, the photo Fenton's reaction uses a light source such as as monochromatic UV, metal halide and xenon lamp. The light emitting diode (LED) with polychromatic function is commercially available and it is more advantageous than traditional UV lamps. TiO_2 -based and carbon-based materials are the preferred photocatalysts used in this process.

The photo Fenton's process removes ACT depending on the wavelength of the incident UV light source. The shorter wavelengths offer higher energy to create the required $\cdot\text{OH}$ radicals and degrades ACT more efficiently. For example, Kim and Tanaka (2009) tested two UV systems encompassing a UV/lamp 1 (254 nm) and a UV/lamp 2 (254 nm and 185 nm). According to the authors, the UV/lamp 1 degraded 20% ACT and UV/lamp 2 removed 40% ACT, respectively. Similarly, UVA of wavelength 360 nm removed 99% ACT at an initial concentration of 5 mM within 40 min (Su et al., 2013b). In the case of UV-LED, it provides higher light intensity compared to the traditional UV mercury lamp. Thus, it creates a stronger

oxidation state and removes ACT with high efficiency (Xiong and Hu, 2012). The UVA-LED, at a wavelength 365 nm was able to remove 200 ppb of ACT completely within 15 min. The photocatalytic Fenton's process involves the use of a suitable, inert catalyst in the photo Fenton system. Catalysts would increase the amount of $\cdot\text{OH}$ group and provide sufficient surface area for the adsorption of the pollutant. Hence, it improves the ACT removal efficiency. The common catalysts used in this process are carbon-based and TiO_2 -based materials, such as BiOCl_xI_y nanospheres (Wang et al., 2016b), modified reticulated vitreous carbon (Arredondo Valdez et al., 2012), nano-porous TiO_2 (Xie et al., 2016) and $\text{BaTiO}_3/\text{TiO}_2$ (Kurniawan et al., 2018). The photocatalytic systems could remove > 95% ACT, at concentrations as high as 96 mg/l (Arredondo Valdez et al., 2012). Among the different operation parameters, pH is important and its optimum value depends on the type and physico-chemical properties of the catalyst used. For example, a pH of 3.5 was found to be the optimal for TiO_2 catalysts (Yang et al., 2008; Zhang et al., 2008), whereas it was 7.0 for $\text{BaTiO}_3/\text{TiO}_2$ (Kurniawan et al., 2018), or 9.0 for $\text{WO}_3/\text{TiO}_2/\text{SiO}_2$ (Yanyan et al., 2017).

For a photo-based Fenton process, proper light source and catalyst are key operational parameters that affects the performance. An UV light source is preferable than a metal halide or xenon lamp source (Table 4). Compared with these light sources, UV handles higher ACT load, with shorter exposure times. Among the UV light source, UVC wavelength was two-fold better than the conventional UVA process (Yang et al., 2008). The exposure time of an UVC process is also 4-fold lower than the UVA process. This was presumably because ACT absorbed the photon energy of UVC better than UVA. If the UV light source and catalyst dose is optimized, the ACT removal efficiency can be improved. For example, a stand-alone process without a light source requires ~ 20 - 25 d to remove 100 mg ACT/l (He et al., 2015), or it just could remove little doses of 3 μM ACT within 30 min (Im et al., 2015). However, the integrated system could remove 96 mg ACT/l within a short contact time of 60 min (Arredondo Valdez

et al., 2012). From a practical viewpoint, the economics of the process should be considered as it is a rather expensive process and generates secondary pollutant such as iron containing sludge.

[Insert Table 4]

4.3.3 Electro-based Fenton processes

The electro-based Fenton is another modification of the conventional Fenton's process. This electro-based Fenton's process uses electrodes to generate the $\cdot\text{OH}$ radicals and subsequently removes ACT from wastewater. Compared to the chemical-based and photo-based Fenton's processes, it does not produce iron oxyhydroxide sludge and the overdose of H_2O_2 is controlled. The electrodes of the electro-based Fenton's processes act as the electron donor and acceptor for the Fenton reaction. However, the efficiency relies on the characteristics of the electrode materials. Choosing an appropriate material for the electrode is important since after prolong operation, the electrode can be deteriorated. Some typical examples of electrodes include Pt and Ti-based, porous Ti/boron-doped diamond, Pt sheet and Pt gauze. These materials have demonstrated good ACT removal efficiencies. For example, the planar and porous Ti/boron-doped diamond (BDD) electrodes mineralized 100 mg ACT/l (He et al., 2015). The porous electrode was superior to the planar type because it offers high surface area and active sites for the electrochemical reaction to occur. To enhance the ACT removal efficiency, catalyst dose and a light source could also be integrated with the electro-based Fenton process. For example, system with nano-schwertmannite and nano-goethite catalysts removed 500 μg ACT/kg of sediment, completely within 3 d (Yang et al., 2016). Concerning the light source, it has been reported to have a very low effect in enhancing the ACT removal efficiency (de Luna et al., 2012). For instance, the electro-Fenton and photoelectro-Fenton processes removed $\sim 97 - 98\%$ of the ACT present in polluted water environments.

The electro-based Fenton's process includes the MFC Fenton system, cross-flow-electro Fenton system, and the double cathode electro Fenton system, respectively. Compared with other reactor types and processes, MFC Fenton is more environmentally friendly, although it requires longer reaction times (Zhang et al., 2015). Similar to the photo-based Fenton process, the electro-based Fenton process can also remove ACT from high (ppm) concentrations to the ppt levels. The electro based Fenton process can be applied as a tertiary treatment option in WWTPs. Nevertheless, it is noteworthy to mention that the electro based Fenton process is rather expensive compared to other processes described herein, because it consumes a lot of electricity, chemicals and catalysts. Anew, periodic maintenance is required for this process since the amorphous $\text{Fe}(\text{OH})_3$ adheres to the electrodes and decreases the overall ACT removal efficiency.

4.3.4 Ozonation

Ozonation is an established AOP used commonly in drinking water treatment. The ozonation process and its reactions generate free radical groups of O_3^- , $\text{HO}_2^\bullet$ and $\text{O}_2^\bullet$ that has high oxidation states and the spontaneous reactions mineralizes the pollutants. Ozonation has been used extensively for both surface water and wastewater treatment (Trang et al., 2014; Vo et al., 2019). For surface water, ozone dose of 5 mg/l can completely remove ACT within 30 min (Lutpi et al., 2015). However, the removal rates achieved in this process (0.7 to 45.7 per mM.s) depends on the water quality. The higher dissolved organic carbon (DOC) concentration and alkalinity increases the removal rate of ACT (Lutpi et al., 2015). In another study, wastewater containing ACT was removed at the rate of 0.2 mg ACT/l within 25 min (Quiñones et al., 2015). Similar to the Fenton's process, the presence of a suitable (inert) catalyst also supports ozonation and increases the ACT removal efficiency. According to a recent report, by applying a modified MgO catalyst, the MgO/O_3 process showed ACT degradation and mineralization efficiencies that were 18.8 and 7.8-fold higher than the sole ozonation process (Mashayekh-

Salehi et al., 2017). Ozonation could also eliminate ACT entirely to the ppt level, but the operation cost of ozonation is comparable to the Fenton's process. The cost of a photo-based Fenton process is 1.56 €/m³, whereas the ozone-based process costs ~ 0.49-0.59 €/m³ (Quiñones et al., 2015). Fenton process, when incorporated with modified TiO₂ based catalysts can increase the operational costs. In comparison, MgO is a relatively low-cost and environmentally friendly catalyst that has also been extensively used in the field of environmental engineering.

4.4 Adsorption processes

The efficiency of adsorption based processes can be governed by the physico-chemical properties of the adsorbent as well as the chemical reactions occurring at the surface of the adsorbent. Typically, activated carbon is the most commonly used adsorbent that yields relatively stable ACT removal efficiencies. Modified activated carbon based adsorbent includes, chitosan-nano (Amouzgar et al., 2017), granular type (Yanyan et al., 2018) and phosphoric acid modified (Wong et al., 2018) for ACT removal from wastewater. In practice, the adsorption process is assisted with sonication, ozonation and constructed wetlands to enhance the ACT removal efficiency.

Concerning the chitosan nano activated carbon, 94.7% of ACT, at a concentration of 0.2 mg/l can be removed from the aqueous solution when its supported by a sonication step (Amouzgar et al., 2017). Another modified activated carbon media is the granular form that is usually derived from coconut shell (Yanyan et al., 2018). In both cases, the breakthrough capacities of the media were reached within 26 - 48 h of operation, at a concentration of 40 - 120 mg ACT/l. The activated carbon developed from spent tea leaves have also been tested for ACT treatment and removal efficiencies > 99% at an initial concentration of 10 mg/l was reported (Wong et al., 2018). In large scale systems, a WWTP when combined with a horizontal sub-surface flow wetland removed > 98% ACT (Verlicchi et al., 2013). In that study, the influent and effluent

concentrations of ACT were 30 ± 20 and 16 ± 6 ng/l, respectively. In this combined removal process, other removal pathways such as biodegradation, sedimentation and plant uptake are also involved. In a recent study that was aimed at the removal of ACT from drinking water, 20% ACT was removed in a sand filter and a granular activated carbon (GAC) filter, respectively (Lin et al., 2016c). For a conventional drinking water treatment plant, the average ACT removal efficiency is usually $> 96\%$ (Boleda et al., 2011). Therefore, adsorption is a promising and feasible treatment option that contributes to the good removal of ACT in major drinking water treatment plants.

4.5 Membrane processes

Membrane separation process is an emerging technology for ACT removal from different water environments. It is categorized based on the pore size of the membrane and the material of construction. For the pore size, the nanofiltration and reverse osmosis membranes are effective to retain the ACT molecules/particles, rather than the ultrafiltration and microfiltration modules. The pore sizes of nanofiltration and reverse osmosis membranes are less than the size of the ACT molecules. Regarding the fabricated materials, they can either natural or synthetic. The natural material include wool, ceramics, rubber and cellulose. The synthetic membrane include polyethylene amine, metal-organic frameworks (MOF), laccase and polydopamine, polyvinylidene difluoride, hydroxyapatite, cellulose triacetate and polyamide composite. The membrane process can be combined with biological treatment in a membrane bioreactor (MBR). For ACT contaminated ground water, nanofiltration and RO membrane rejected 44.8 - 73% ACT (Radjenović et al., 2008). Similarly, hollow fiber MBR removed ACT at lower efficiencies, i.e. $< 20\%$ (Nguyen et al., 2013). The single process of MF can remove 50 - 90% of ACT from different water environments (Ba et al., 2014). However, if they are supported by an integrated UV process, NF and RO can completely remove ACT from water. Therefore, a

stand-alone MBR or a microfiltration membrane process is not highly efficient for the treatment of ACT at high concentrations.

Another improved membrane process is a novel enzyme coating on the surface of membranes to achieve high ACT removal efficiencies. For example, cross-linked enzyme aggregates of laccase were doped on a polysulfone hollow fiber MF membrane to remove ACT (> 99%) at concentrations < 0.1 mg/l (Ba et al., 2014).

4.6 Hybrid processes

The hybrid process (treatment train) incorporates different technologies such as a biological process, plant uptake, membrane filtration, adsorption and AOPs. In this combined process, the biological processes such as anaerobic/aerobic/oxic (A_2O) would be placed first (as a pre-treatment step) to reduce the pollutant load, followed by either AOP, plant uptake, adsorption and membrane process.

As an example, at the Alcalá de Henares WWTP (Madrid, Spain), the A_2O process was coupled with ozonation to eliminate ACT from wastewater (Rosal et al., 2010). For this case, the A_2O process removed ACT to below detection limits, thus, ozonation was rarely used. Similarly, an integrated system of anoxic/aerobic process and MFC was able to remove > 98% ACT at a concentration of 30 mg/l (Chang et al., 2014). In another study, at the pilot scale, the integrated process removed ~ 94 - 99.9% ACT at initial concentrations varying between 2.6 - 300 $\mu\text{g/l}$ (Gallardo-Altamirano et al., 2018). According to the authors, long-term experiments confirmed that the operating and environmental conditions of A_2O did not affect the ACT removal efficiency. It is noteworthy to mention that, for the hybrid system, each technology contributes differently during the ACT removal process. For example, A_2O contributes to ~ 77% of the 97% ACT removed during the entire process, whereas chlorine disinfection accounted for the remaining 20% ACT removed (Kosma et al., 2010). In a case study involving five WWTPs from Ulsan city (South Korea), the primary treatment process removed 28% of the total PPCPs,

including ACT, and the biological treatment process used in the WWTP was recognized as the main process that ensured > 99% ACT removal in the WWTPs (Behera et al., 2011).

4.7 Other processes

Apart from the above mentioned and illustrated technologies, the non-conventional technologies include ultrasonic treatment (Villaroel et al., 2014) and zero valent aluminum (Zhang et al., 2012). Ultrasonic treatment could degrade ACT to inorganic compounds competitively when compared to other technologies (Villaroel et al., 2014). For instance, ACT was completely removed after 180 min at initial concentrations varying between 33 to 1323 $\mu\text{mol/l}$. In the case of zero valent aluminium technology, the commercial zero valent aluminum under air-equilibrated acidic conditions eliminated > 99% ACT, at a concentration of 2 mg/l and a contact time of 16 h (Zhang et al., 2012). Although these processes are applicable for ACT removal from contaminated water sources, full-scale applications of this process has never been demonstrated due to cost and scale-up implications.

4.8 Comparison of technologies

In practice, all the technologies mentioned in this review could be a part of the WWTP train. Their application would depend on the characteristics of the wastewater, initial ACT concentration, local environmental conditions and the effluent discharge standards. Overall, the biological process (aerobic/anaerobic) is suitable for secondary treatment and it can reduce the ACT concentration from the ppm to ppb levels. The adsorption, AOP, membrane process and plant uptake are rather meant specifically for tertiary treatment. These technologies can act as a post-treatment or polishing step to reduce the ACT concentration from the ppb to ppt level. When space is a constraint at the field-scale, membrane, AOP and adsorption technologies are feasible options. However, in the case of membrane reactors, fouling is a major concern and it also requires high operation and maintenance skills. In the case of AOP and adsorption, chemical consumption and secondary pollution (e.g. due to metabolites) are the major concerns

that will add to the operating costs. In a spacious WWTP, CWs can be considered as a dependable solution.

Most technologies remove ACT efficiently in the range of 80 - 100% (Fig. 2). However, plant uptake and membrane process perform less with average removal efficiencies in the range of ~ 60%. For example, at a ACT concentration of 1200 mg/l, an external airlift membrane bioreactor (MBR) removed ACT better than an activated sludge process (Shariati et al., 2010). Within 2 d of continuous operation, the external airlift MBR treated 100% ACT, while the activated sludge was able to perform only with 50% efficiency. The mechanism of the MBR system involves biodegradation, adsorption and filtration process, whereas biological activity was the sole mechanism governing the removal of ACT in the activated sludge process.

Nevertheless, high removal efficiency does not necessarily mean that ACT is removed completely from the aqueous (water) phase because it can be degraded and transformed into other less toxic or more toxic metabolites. In brief, the following salient features were recognized based on this review on ACT: (i) biological processes can deal with high concentrations of ACT in wastewater (1200 mg/l), however, the biodegradation process requires more time and ACT is not reduced to the ppt levels; (ii) AOPs can degrade ACT at high degradation rates to the ppt levels, but they are rather expensive and might lead to the formation of toxic intermediates, and (iii) other technologies such as plant uptake, adsorption and membrane processes can be integrated with biological process to reduce ACT to the desired ppt levels.

[Insert Fig. 2]

5. By-products transformation and degradation pathways

During wastewater treatment, ACT can be degraded/transformed to several metabolites. As explained previously, some of these intermediates can be more detrimental to human health and the ecological system than the parent ACT compound (Bedner and MacCrehan, 2006). By

applying the existing analytical technologies, some of these metabolites are not adequately detected in the influent wastewater and the treated effluent. Thus, identification of ACT intermediates and their metabolic pathways is essential to evaluate their potential impacts on human health, the environment and other aquatic life forms.

5.1 Mechanisms of acetaminophen transformation

ACT molecules consist of an aromatic phenol ring with an acetamido substitution at the para-position (Fig. 3). These components are targets for the invasion of oxidizing agents such as $\cdot\text{OH}$, CO_3^- and ClO^- , photon energy and ferrate (VI).

[Insert Fig. 3]

The most striking oxidative agent that helps in breaking the aromatic ring is $\cdot\text{OH}$. It would invade the aromatic bonds first during the photo-Fenton process (Trovó et al., 2012). Similarly, O_3 and/or $\cdot\text{OH}$ agents can attack the aromatic ring through normal and ipso mechanisms, following by a series of oxidation processes (Zhang et al. 2008; de Luna et al., 2012; Wang et al., 2016a). These processes open the ring core and cleave the phenol-acetamido bond. Similar to hydroxyl radicals, ClO^- and ferrate (VI) can also attack the benzene ring or the phenol-acetamido bonds (Bedner and MacCrehan, 2006; Wang et al., 2016a). This gives rise to a wide range of ACT metabolites such as hydroquinone, 2-hydroxy-4-(N-acetyl)-aminophenol, or dicarboxylic acids. These metabolites can exhibit both toxic and non-toxic characteristics (Table 5). In addition, the phenol-acetamido and NH-CO amide bonds are also the targets of the oxidative agents. The phenol-acetamido bond can be invaded by CO_3^- , ClO^- and ferrate (VI), while the ferrate (VI) and photon energy breaks down the NH-CO bond (Bedner and MacCrehan, 2006; De Laurentiis et al., 2014; Chang et al., 2015; Wang et al., 2016a). Thereafter, acetamide and/or acetamide derivatives are formed from the acetamido group of ACT.

Unlike chemical treatment where oxidizing reagents are employed, bioenzymes are the driving agents to degrade or transform ACT in biological treatment systems. For instance, monooxygenases such as flavin-containing hydroxylases or cytochromes P-450 could degrade ACT efficiently in different water environments (Li et al., 2014). While the biodegradation intermediates and/or end-products of ACT are somewhat similar to chemical degradation processes, the mechanism involved in these two processes are entirely different. For example, in a microbial fuel cell (MFC) - Fenton system, the acetamido moiety was the preferable target of bioenzymes rather than the aromatic ring (Zhang et al., 2015). Firstly, the phenol-acetamido bond was hydrolyzed by bio-electrons and protons to form *p*-aminophenol and acetic acid, respectively. Subsequently, *p*-aminophenol was oxidized by the $\cdot\text{OH}$ radicals forming various by-products (Zhang et al., 2015).

In brief, the exact intermediates and end-products of ACT formed largely depends on the degradation mechanism and the pathway. Therefore, one should consider what treatment system would be employed to predict the transformation pathways and intermediates of ACT. These information are essential to evaluate the suitability and sustainability of such systems in full-scale applications.

5.2 Aromatic intermediates

The first point of attack during ACT degradation often takes place on the aromatic ring or the acetamido moiety as discussed earlier. In this stage, ring cleavage does not occur and the by-products are often of aromatic nature (Fig. 4). However, the exact intermediates formed depend only on the treatment (physical/chemical or biological) system used.

[Insert Fig. 4]

During the AOP processes, 1,4-benzoquinone, hydroquinone and amides were the main intermediates of ACT regardless of the applied technologies (Andreozzi et al., 2003; de Luna et al., 2012; Chang et al., 2015). However, other intermediates were also reported to be formed

in different technologies, especially alcoholic substances. For example, in a photocatalytic treatment process, the major intermediates were hydroquinone, 1,4-benzoquinone, 1-(2-hydroxyphenyl-5-amino) ethanone and 1-(2-amino-5-hydroxyphenyl) ethanone (Chang et al., 2015). On the other hand, $\text{H}_2\text{O}_2/\text{UV}$ systems generated 1-(2-amino-5-hydroxyphenyl) ethanone, (*N*-(3,4-dihydroxyphenyl) acetamide, and 1-(2-amino-5-hydroxyphenyl) ethanone (Andreozzi et al. 2003; Feng et al., 2015). Notably, the $\text{H}_2\text{O}_2/\text{UV}$ system did not generate the toxic compound *N*-acetyl-para-benzoquinone imine (NAPQI). Therefore, it is a recommended technology to avoid the formation of NAPQI. In turn, hypochlorination disinfection should be applied cautiously since at least 11 by-products of ACT were reported including two toxic compounds 1,4-benzoquinone and NAPQI (Bedner and MacCrehan, 2006). As reported in the literatures, these compounds are even more toxic than ACT.

On the other hand, when the MBR technology was applied, sulfate-related intermediates of ACT were identified: acetaminophen-O-sulphate ($\text{C}_8\text{H}_9\text{O}_5\text{NS}$), acetaminophen-glutathione ($\text{C}_{18}\text{H}_{24}\text{O}_8\text{N}_4\text{S}$), and transformation product ($\text{C}_{12}\text{H}_{10}\text{O}_2\text{N}$) of acetaminophen-glutathione (Tambosi et al., 2010). These compounds are popular intermediates in WWTPs and also formed from human detoxification and excretion processes. In contrast, De Gusseme et al. (2011) reported that hydroquinone was the only by-product of ACT degradation in a membrane reactor.

In soil environments, microorganisms play a critical role as a biocatalyst for ACT mineralization. Li et al. (2014) detected 8 aromatic intermediates of ACT in soil such as 3-hydroxyacetaminophen, hydroquinone and 1,4-benzoquinone, respectively. Similar mechanism can also potentially occur in ACT contaminated sludge of WWTPs. Interestingly, in both environments, hydroquinone and 1,4-benzoquinone are the most commonly detected intermediates.

5.3 Ring-opening and inorganic intermediates

During the first step of the degradation stage, oxidative agents attack the different functional groups and bonds of the ACT molecule including the hydroxyl group, acetamido group and the phenolic ring. For example, $\cdot\text{OH}$ in a bio-electrochemical system oxidizes the hydroxyl group of the phenol ring creating intermediates such as maleic, malonic, malic and lactic acid, respectively (Zhang et al., 2015). Organic carboxylic acids were also observed to be intermediates of the ACT degradation process by other researchers (Andreozzi et al., 2003; de Luna et al., 2012; de Luna et al., 2013). In a fluidized-bed reactor employing the Fenton's process, NH_4^+ , formic acid and 1,2-pentanediol were identified as the main ACT degradation products (de Luna et al., 2013). Similarly, ferrate (VI) reacts with the acetamido group and the aromatic intermediates of ACT to form NO_3^- , maleic acid, oxalic acid and formic acid, respectively (Wang et al., 2016a). Following the oxidation of ACT to organic acids, CO_2 was ascertained as a final mineralized product (Zhang et al., 2012). Thus, briefly stating, ring-opening of ACT and ACT by-products will eventually lead to the formation of different types of organic acids. Further oxidation of these acids, acetamide, and acetamide derivatives would only result in complete mineralization of ACT into NH_4^+ , NO_3^- , and CO_2 , respectively.

5.4 Polymeric intermediates

Polymeric intermediates are usually prevalent and noticed in soil environments (Liang et al., 2016). ACT molecules can interact with each other at either the ortho, para, or amide bonding positions giving rise to numerous dimer and trimer intermediates. For example, nine dimer and trimer intermediates of ACT were discovered in soil (Li et al., 2014). Importantly, a low pH and warm environmental condition will accelerate the ACT polymerization reaction (Xiao et al., 2013). The degradation process would be largely dependent on the soil types, activity of the microorganism, enzymes secreted during the biodegradation processes, pH, moisture content of soil, soil porosity, oxygen availability, and the initial ACT concentration.

Recently, more than 20 intermediates formed during the ACT removal process was reported in the literature. Compounds such as 4-benzoquinone and NAPQI are more toxic than ACT, while some compounds such as NH_4^+ , CO_2 , and NO_3^- are rather less toxic. As observed from the review, the dimer and trimer by-products were also detected, particularly in the soil environment. According to the information presented in Table 5, AOP was the only technology that is capable of degrading ACT to innocuous inorganic end-products. Thus, AOP can be recommended to be applied in WWTPs as a tertiary treatment step. The salient remarks on ACT transformation products and metabolites in environments can be stated as follows: (i) the oxidative agents capable of removing ACT include $\cdot\text{OH}$, O_3 , ClO^- , photon energy and bioenzymes; (ii) the oxidative agents attack and cleave the aromatic ring and acetamido moiety of ACT to form more than 20 aromatic and inorganic intermediates; and (iii) polymeric intermediates are only formed in soil environments.

[Insert Table 5]

6. Conclusions

Historically, ACT pollution has occurred in many countries, at various concentrations and detection frequencies and ACT concentration in wastewater has increased significantly since the year of 1998. China and the USA are the two countries with concerned ACT levels and detection frequencies in wastewater. However, ACT concentration in drinking water has decreased significantly from ppb to ppt levels due to advancements in wastewater treatment systems. Concerning the implementation of policies, European countries and the United States have developed different management policies and legislations/standards for the discharge of micropollutants and their prevention, while the legislation are rather not stringent in most of the Asian countries due to lack of reliable historic data. In addition, to ensure ACT free drinking water source, the application of advanced and hybrid technologies is urgently required at the field scale because ACT can transform to more than 20 different intermediates and end-

products. Anew, ensuring ACT levels less than 71 ng/l in drinking water is still a challenging task as it will require extensive investment costs, technical and management expertise.

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1107 acetaminophen in TiO₂ suspended solution. Journal of Hazardous materials, 157(2–3),
1108 300-307.

1109 **Table 1.** Classification of ACT levels in WWTPs and surface water of countries

ACT concentration range - detection frequency in WWTPs	Countries	ACT concentration range compared with recommended level for drinking water (71 ng/l)**	Countries
Beyond 100 µg/l - 80-100%	China, USA, Greece, UK, Korea, Taiwan	Higher than recommendation	China, USA, Taiwan, UK, Spain, Serbia
Below 100 µg/l – below 50%	France, Spain, Columbia	Lower than recommendation	France, Spain, USA, Singapore, Germany, UK, Korea

1110 *Data from appendix

1111 ** (Vulliet and Cren-Olivé, 2011)

1112

1113 **Table 2.** EC₅₀ of aquatic species exposing to ACT

Species	Effective concentration (mg/L)	Exposure time	Reference
Algae			
<i>Scenedesmus subspicatus</i>	134	72 h	Henschel et al. (1997)
<i>Pseudokirchneriella subcapitata</i>	Over 240	96 h	Daniel et al. (2015)
<i>Scenedesmus dimorphus</i>			
<i>Stichococcus bacillaris</i>			
<i>Chlorella vulgaris</i>			
<i>Chlamydomonas reinhardtii</i>			
Macrophyte species (<i>Lemna minor</i> and <i>Lemna gibba</i>)	446.6	7 d	Nunes et al. (2014)
Protozoan (<i>Ciliates</i>)	112	48 h	Henschel et al. (1997)
Fishes			
<i>Brachydanio rerio</i>	378	48 h	Henschel et al. (1997)
<i>Oryzias latipes</i>	Over 160	48-96 h	Kim et al. (2007b)
Freshwater invertebrate (<i>Daphnia magna</i>)	50	24 h	Henschel et al. (1997)
	26.6 - 30.1	48 - 96 h	Kim et al. (2007b)
Marine bacterium (<i>Vibrio fischeri</i>)	650	30 min	Henschel et al. (1997)
	549.7	15 min	Kim et al. (2007b)
Cells <i>in vitro</i>	19	18 h	Henschel et al. (1997)

1114

Table 3. Summary of chemical-based Fenton reaction

Process	[Fe ²⁺]	[H ₂ O ₂]	pH	Initial ACT concentration	Removal efficiency (%)	Retention time	References
Photo-Fenton	H ₂ O ₂ /Laterite iron = 30:0.75 (w/w)	30 mg/L ACT/H ₂ O ₂ ratio 1:3 (w/w)	3	10 mg/L	79 76	120 min	Manu and Mahamood (2011)
Fenton with artificial ferrous catalyst (FeSO ₄)	[H ₂ O ₂]:[Fe ²⁺] = 60:1		3	10 mg/L	80	60 min	Basavaraju et al. (2011)
Fenton with iron source from laterite soil	[H ₂ O ₂]:[Laterite soil] = 40:1				75		
Electro-Fenton	0.1 mM	15 mM (fixed value)	2 4	5mM	99 100	120 min	Su et al. (2012)
Novel Fenton aerated reactor	0.1 mM	25 mM	3	5 mM	99	40 min	Su et al. (2013a)
Fluidized-bed Fenton	0.06 mM*	19.87 mM*	3	5 mM	99.6	40 min	de Luna et al. (2013)
Bio-Fenton (Phyto-Fenton)	n.d	200-800 nmol g ⁻¹ fresh weight	n.d	1 & 100 ppb	55-99.8%	5 d	Phong et al. (2016)

Remark: n.d: no data; *treated solution

1119 **Table 4.** Summary of photo-based and electro-based Fenton process

Process	Light source	Catalyst dose	pH	Initial ACT concentration	Removal efficiency (%)	Retention time	References
Suspended TiO ₂	Metal halide lamp 250 W, $\geq$ 365nm)	1.0 g/l	3.5	100 μ mol/l	95	100 min	Zhang et al. (2008)
Suspended non-porous TiO ₂	UVA (8W, 365 nm)	0.4 g/l	9.5	2 mM	50	300 min	Yang et al. (2008)
	UVC (15W, 254nm)			4 mM	95	80 min	
TiO ₂ /reticulated vitreous carbon assisted UV	UV mercury vapor lamp (350 nm peak)	1 g binding on reticulated vitreous carbon anode	n.d	96 mg/l	95	60 min	Arredondo Valdez et al. (2012)
Non-porous TiO ₂ -P25	UVA/LED (365 nm) 1-3 mW/cm ²	0.2 mg/l	5.6	200 ppb	100	15 min	Xiong and Hu (2012)
ZSM-5 supported TiO ₂	UV lamp (254 nm) 0.97 mW/cm ²	TiO ₂ : ZSM-5 as 40 wt%	6.8	15 mg/l	96.6	180 min	Chang et al. (2015)
Planar and porous Ti/BDD electrodes	None	-	-	100 mg/l	100	20 – 25 h	He et al. (2015)
US/Fenton/TiO ₂ NT	None	TiO ₂ NT as anode US 1000 kHz	3	3 μ M	85.3	30 min	Im et al. (2015)
Non-porous TiO ₂ -P25	UVA/LED (365 nm) 5 mW/cm ²	10 ppm	5.6	200 ppb	-	20 min as 20% time of periodic illumination	Xiong and Hu (2016)
		100 ppm		20 ppm	70-100*	60 min	
Carbon self-doped (C-doped) TiO ₂	LED (440–490 nm)	1.0 g/l	6.9	0.1 mM	94	30 min for adsorption 9 h for photo-degradation	de Luna et al. (2016)
Nano-porous TiO ₂	UV visible lamp (365, 405 and 435 nm) 130 mW/cm ²	-	-	40 ppm	86.96	60 min	Xie et al. (2016)
Hollow core-shell mesoporous	UV mercury vapor lamp	0.1 g/l	-	50 mg/l	94	60 min	Lin et al. (2016a)

TiO ₂ microspheres	(500W, 245 nm)							
TiO ₂ doping K ₂ S ₂ O ₈	LED (450 nm peak) 16.85 mW/cm ²	1 g/l	9	0.1 mM	100	9 h		Lin et al. (2016b)
Fenton like with nano-Schwertmannite catalyst, assisted EK	5.631×10^{-6} to 1.126×10^{-5} mol g ⁻¹	1.126×10^{-4} to 2.253×10^{-4} mol/g	Anode as 2 Cathode as 12 Sediment as 6-12	500 µg/kg sediment	100	14 or 28 d		Yang et al. (2016)
WO ₃ /TiO ₂ /SiO ₂	Full waveband xenon lamp coupled with a cutoff filter (500 W, 800 nm > λ > 200 nm)	1.5 g/l	9	5 mg/l	95	4 h		Yanyan et al. (2017)
BaTiO ₃ /TiO ₂	Xenon lamp (500 W, 200 nm < λ < 800 nm)	1 g/l	7	5 mg/l	95	4 h		Kurniawan et al. (2018)

* Retrieved from graph

1122 **Table 5.** Main metabolites of ACT degradation

Applied technology	Driving agent	Main by-products	Reference
Chemical-based Fenton	$\cdot\text{OH}$	Hydroquinone, amide, ammonia, formic acid and 1,2-pentanediol	de Luna et al. (2013)
Photo-based Fenton	$\cdot\text{OH}$, ν	Ring-opening products, CO_2 , ammonium, nitrates ions	Yang et al. (2008)
Photo-based-Fenton	$\cdot\text{OH}$, ν	Hydroxylated intermediates, acetamide	Trovó et al. (2012)
Photo-based Fenton	$\cdot\text{OH}$, ν	Hydroquinone and 2-hydroxy-4-(<i>N</i> -acetyl)-aminophenol	Andreozzi et al. (2003)
Photo-based Fenton	ν , CO_3^{2-}	Hydroxylated derivatives, ring-opening compounds, dimers and trimers	De Laurentiis et al. (2014)
Photo-based Fenton	$\cdot\text{OH}$, ν	Hydroquinone, 1,4-benzoquinone, 1-(2-hydroxyphenyl-5-amino) ethanone and 1-(2-amino-5-hydroxyphenyl) ethanone	Chang et al. (2015)
Photo and electro-based Fenton	$\cdot\text{OH}$, ν	Benzoquinone, hydroquinone and carboxylic acid	Arredondo Valdez et al. (2012)
Electro-based Fenton	$\cdot\text{OH}$	Hydroquinone, amide, 1-penten-3-ol, 2-methyl, 4-heptanol and 2,3-butadiol	de Luna et al. (2012)
Chlorination process	ClO^-	1,4-benzoquinone, <i>N</i> -acetyl- <i>p</i> -benzoquinone amine, chloro-4-acetamidophenol and dichloro-4-acetamidophenol	Bedner and MacCrehan (2006)
Membrane (MBR)	-	Acetaminophen-O-sulphate, acetaminophen-glutathione	Tambosi et al. (2010)
Others	$\cdot\text{OH}$	Hydroquinone, formic acid, ammonia and CO_2	Zhang et al. (2012)
Others	Ferrate (VI)	Hydroxylated derivatives, maleic acid, oxalic acid and formic acid	Wang et al. (2016a)
Others	MnO_2	Dimers and trimers	Xiao et al. (2013)

Fig. 1. Occurrence of ACT in various environments in (a) America, (b) Asia and (c) Europe

Fig. 2. Comparison of ACT removal efficiency by technologies. X-axis exhibits the technologies and their mean ACT removal efficiencies and standard deviations (in the brackets). Error bars represent the standard deviations of the data.

(Amouzgar et al., 2017; Arredondo Valdez et al., 2012; Ba et al., 2014; Behera et al., 2011; Boleda et al., 2011; Chang et al., 2015; Chang et al., 2014; de Luna et al., 2013; de Luna et al., 2016; Gallardo-Altamirano et al., 2018; Gros et al., 2010; He et al., 2015; Huber et al., 2009; Im et al., 2015; Kasprzyk-Hordern et al., 2009; Kim and Tanaka, 2009; Kurniawan et al., 2018; Lin et al., 2016a; Lin et al., 2016b; Lutpi et al., 2015; Manu and Mahamood, 2011; Manu et al., 2011; Mashayekh-Salehi et al., 2017; Narumiya et al., 2013; Nguyen et al., 2013; Phong et al., 2016; Quiñones et al., 2015; Radjenović et al., 2008; Ranieri et al., 2011; Rosal et al., 2010; Su et al., 2013a; Su et al., 2013b; Su et al., 2012; Verlicchi et al., 2013; Villaroel et al., 2014; Wong et al., 2018; Xie et al., 2016; Xiong and Hu, 2017; Yang et al., 2016; Yang et al., 2008; Yanyan et al., 2017; Yanyan et al., 2018; Yu et al., 2006; Yu et al., 2011; Zhang et al., 2012; Zhang et al., 2008)

Fig. 3. Oxidative agents encounter on bonding of ACT molecule

Fig. 4. Selected intermediates of ACT degradation

Highlights

- China and the USA showed the highest acetaminophen (ACT) concentration
- Advanced oxidation processes (AOPs) removed ACT to the ppt level
- More than 20 by-products and intermediates of ACT were detected
- Treated wastewater was not totally free from the toxic effects due to ACT metabolites

Acetaminophen

Occurrence & Toxicity

Treatment Technologies

By-products Transformation

ACT

Metabolites

China and the USA:
highest ACT
concentration in
WWTPs influent (300
 $\mu\text{g/l}$)

AOP degraded ACT to
non-toxic intermediates

More than 20
intermediates detected