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FATE OF PHARMACEUTICALS IN DRINKING WATER UTILITIES

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FATE OF PHARMACEUTICALS IN DRINKING WATER UTILITIES

By

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ABSTRACT

FATE OF PHARMACEUTICALS IN DRINKING WATER UTILITIES

By

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Studies suggest that drinking water treatment is effective at decreasing the amount of pharmaceuticals present in source water. Primary treatment processes such as coagulation and sedimentation are not effective on their own, while a combination of filtration and disinfection processes is effective at reducing the concentrations of most pharmaceuticals. The type of oxidant used also determines the degree at which a pharmaceutical is removed from source water. Ozone or the combination of ultraviolet (UV) light with hydrogen peroxide seem to be the most effective oxidation processes. Chlorine oxidation is known to produce chlorinated byproducts when it reacts with organic compounds. In bench-scale studies, the reaction of the pharmaceutical, acetaminophen with free chlorine was studied. Acetaminophen reacts with free chlorine to produce the byproduct 1,4-benzoquinone. Results indicate that acetaminophen is most reactive with free chlorine at pH 9.0 and least reactive at pH 6.0. As pH increased, degradation of acetaminophen also increased. The formation of 1,4-benzoquinone was also affected by pH and reached a maximum of 68.7% of the initial acetaminophen concentration when the pH was at 6.0, the molar ratio at 1,275, and after a contact time of 30 minutes. At all pH values the rate of degradation of acetaminophen was slowest at a molar ratio of about 100, and the highest at a molar ratio of about 10,000.

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INTRODUCTION

"We forget that the water cycle and the life cycle are one."

- Jacques Cousteau

The research presented below addresses the detection of pharmaceuticals in environmental waters and the fate of these pharmaceuticals during drinking water treatment. The results of full- and bench-scale studies are presented to evaluate the effectiveness of primary treatment (i.e. coagulation, flocculation, sedimentation), filtration, and disinfection on pharmaceutical removal from source water. Disinfection, which has the potential to produce oxidation byproducts, is evaluated in more detail than primary treatment and filtration. The fate of pharmaceuticals in drinking water utilities is affected by the individual pharmaceutical's chemical structure and properties, the type and combination of treatment process used. Factors affecting oxidation of pharmaceuticals include the water pH, contact time, oxidant dosage, initial pharmaceutical concentration, water matrix, and the individual pharmaceutical's chemical structure and properties. Experiments on the chlorination of acetaminophen provide a case study on how a pharmaceutical might be transformed during disinfection of drinking water. Current risk assessments suggest that risk of human exposure to pharmaceuticals via drinking water is very low, but more research is needed on mixture toxicity of low levels of pharmaceuticals, and the effects of pharmaceuticals on microbial systems. Overall, the research presented below gives the reader an idea of the complexity and uncertainty of the issue of pharmaceuticals in the environment.

CHAPTER 1

LITERATURE REVIEW AND SYNTHESIS

Summary

Pharmaceuticals have recently been identified as emerging contaminants in environmental waters. The presence of pharmaceuticals in wastewater effluent and source water for drinking water utilities may have implications on human and ecological health. Water and wastewater treatment processes are capable of transforming pharmaceuticals, but each compound responds differently to treatment, making it difficult to predict the fate of pharmaceuticals as a whole. Drinking water oxidants such as chlorine, ozone, and advanced UV oxidation have been shown to degrade and transform a wide variety of pharmaceuticals. A review of literature suggests that conventional water treatment may effectively remove the majority of tested pharmaceuticals. Certain compounds, such as carbamazepine, appear to undergo treatment without transformation, thus requiring further study.

Chlorine and ozone are shown to react with various pharmaceuticals, and often times oxidation results in the formation of byproducts that may or may not be harmful to humans and the environment. In most cases, UV irradiation does not degrade pharmaceuticals unless an advanced oxidation process is applied. Ozone appears to be the most effective at oxidizing different classes of pharmaceuticals present in waters. Predictive quantitative structure activity relationship (QSAR) models may be key to determining which pharmaceuticals persist during drinking water treatment. However, the current state of knowledge does not provide clear answers regarding potential human risk of exposure to pharmaceuticals via water consumption.

Occurrence and Sources

Pharmaceutical contamination of aquatic systems is an emerging issue in environmental science and engineering. Pharmaceuticals are biologically active compounds that may produce adverse effects in humans, animals, and plants. Increasing numbers of studies reveal that pharmaceuticals are found in natural waters, wastewater, and drinking water. When water undergoes treatment, such as oxidation, pharmaceuticals may be transformed into compounds that are less or more harmful to humans and the environment than the parent compound. The oxidation rates and oxidation byproducts of pharmaceuticals will largely depend on their concentrations in the environmental waters. In the United States there is more consumption of new pharmaceuticals and high-strength or long-acting formulations than in other countries [Danzon and Furukawa, 2008]. This suggests that more persistent and/or newer man-made compounds may occur in U.S. waters.

a. Occurrence of Pharmaceuticals in Wastewater, Drinking Water and Surface Waters

The presence of pharmaceuticals in raw and treated wastewater has been well documented with concentrations averaging from less than 10 μg/L in finished wastewater to greater than 100 μg/L in raw wastewater to [Batt *et al.*, 2006; Boyd *et al.*, 2003; Brun *et al.*, 2006; Buser *et al.*, 1999; Buser *et al.*, 1998; Carballa *et al.*, 2004; Castiglioni *et al.*, 2006; Castiglioni *et al.*, 2005; Clara *et al.*, 2005; Ellis, 2006; Ferrari *et al.*, 2003; Giger *et al.*, 2003; Gobel *et al.*, 2005; Golet *et al.*, 2003; Golet *et al.*, 2002; Gomez *et al.*, 2007; Gros *et al.*, 2006; Gross *et al.*, 2004; Han *et al.*, 2006; Heberer, 2002; Jelicic and Ahel,

2003; Jones *et al.*, 2005; Karthikeyan and Meyer, 2006; Kummerer *et al.*, 1997; Lee *et al.*, 2003; Lindberg *et al.*, 2005; Lindqvist *et al.*, 2002; McArdell *et al.*, 2003; Metcalfe *et al.*, 2003; Petrovic *et al.*,2003; Quintana *et al.*, 2005; Radjenovic *et al.*, 2007; Renew and Huang, 2004; Santos *et al.*, 2007; Sedlak and Pinkston, 2001; Tauxe-Wuersch *et al.*, 2005; Ternes, 1998; Thomas and Foster, 2004; Tixier *et al.*, 2003; Vieno *et al.*, 2005; Wennmalm and Gunnarsson, 2005; Yang and Carlson, 2004; Zuccato *et al.*, 2006]. Examples of pharmaceuticals that have been detected in wastewater are common prescription and veterinary drugs such as beta-blockers (*e.g.* metoprolol, propranolol), analgesics (*e.g.* ibuprofen, naproxen), and antibiotics (*e.g.* erythromycin, trimethoprim, ciprofloxacin, tetracylcline, clindomycin, sulfonamides, tetracycline, fluoroquinolone, macrolides, and trimethoprim). For example, Santos *et al.*, (2007) detected ibuprofen in wastewater influent and effluent at concentrations of 12.1 – 373 and 0.78 – 48.2 μg/L, respectively. Naproxen was also detected at 1.1 – 27.4 μg/L in wastewater influent and 0.22 – 4 .3 μg/L in effluent . Gomez *et al.* (2007) detected acetaminophen, codeine, diclofenac, and ibuprofen in wastewater influent at mean concentrations of 134, 5.2, 1.5, and 84 μg/L, and in wastewater effluent at mean concentrations of 0.22, 3.7, 0.9, and 7.1 μg/L, respectively.

Although most of the published literature focuses on occurrence in sewage effluents, pharmaceuticals have also been detected in raw and treated drinking water, mostly at levels less than 1 μg/L [Boyd *et al.*, 2003; Heberer, 2002; Loraine and Pettigrove, 2006; Moll *et al.*, 2001; Perret *et al.*, 2006; Petrovic *et al.*, 2003; Rodriguez-Mozaz *et al.*, 2004; Stackelberg *et al.*, 2004; Stolker *et al.*, 2004; Ternes *et al.*, 2002; Vieno *et al.*, 2005; Zuhlke *et al.*, 2004]. For example, Loraine and Pettigrove (2006)

detected ibuprofen in finished drinking water at a mean concentration of 0.93 μg/L. In Italy, three sulfonamide antibiotics were detected in store-bought mineral waters at concentrations ranging from 0.009 to 0.080 μg/L [Perret *et al.*, 2006]. In 2004, the US Geological Survey conducted a study on the fate of 106 contaminants throughout a conventional drinking water treatment plant [Stackelberg *et al.*, 2004]. Pharmaceuticals present in raw water samples included carbamazepine, trimethoprim, erythromycin-H_2O, acetaminophen, codeine, and sulfamethoxazole. Carbamazepine was detected at a maximum concentration of 0.258 μg/L in finished water samples [Stackelberg *et al.*, 2004].

The presence of pharmaceuticals has been confirmed in surface waters (rivers and lakes) as well, with concentrations generally less than 1 μg/L [Abuin *et al.*, 2006; Batt *et al.*, 2006; Bound and Voulvoulis, 2006; Boyd *et al.*, 2005; Boyd *et al.*, 2003; Buser *et al.*, 1999; Buser *et al.*, 1998; Calamari *et al.*, 2003; Cha *et al.*, 2006; Giger *et al.*, 2003; Gros *et al.*, 2006; Hirsch *et al.*, 1999; Hua *et al.*, 2006; Kolpin *et al.*, 2002; Kosjek *et al.*, 2005; McArdell *et al.*, 2003; Perret *et al.*, 2006; Rabiet *et al.*, 2006; Rodriguez-Mozaz *et al.*, 2004; Stackelberg *et al.*, 2004; Stolker *et al.*, 2004; Stumpf *et al.*, 1999; Ternes, 1998; Vanderford *et al.*, 2003; Wennmalm and Gunnarsson, 2005; Wiegel *et al.*, 2004; Yang and Carlson, 2004; Zuccato *et al.*, 2006]. For example, Bound and Voulvoulis (2006) reported concentrations of ibuprofen and acetaminophen up to 3 and 0.56 μg/L, respectively. Rabiet *et al.* (2006) detected acetaminophen, carbamazepine, and diclofenac in surface water at concentrations of 0.011 – 0.072, 0.024 – 0.056, and 0.001 – 0.033, respectively. The U.S. Geological Survey conducted the first major study of pharmaceuticals and personal care products in surface waters during 1999 and 2000

[Kolpin *et al.*, 2002]. The study focused on locations likely to be contaminated by wastewater effluent. Kolpin *et al.* (2002) detected pharmaceuticals, hormones, and other organic contaminants in 80% of 139 streams sampled. The most frequently detected pharmaceuticals by Kolpin *et al.* in U.S. streams included trimethoprim, acetaminophen, erythromycin, estriol, lincomycin, and sufamethoxazole at detection frequencies of 27.4, 23.8, 21.5, 21.4, 19.2 and 19.0% and at median concentrations of 0.013, 0.11, 0.1, 0.019, 0.06, and 0.07 μg/L, respectively. Other pharmaceuticals that have been found in surface waters are naproxen, clofibric acid, ketoprofen and clarithromycin.

b. Sources of Pharmaceuticals

There are several proposed pathways responsible for pharmaceutical contamination of water. Figure 1 shows possible pathways for pharmaceuticals to enter the water supply. Pharmaceuticals taken by humans in daily life are partially metabolized and excreted into wastewater. If not transformed during treatment, a portion of these contaminants can be released in wastewater treatment plant effluents and discharged in receiving water bodies.

Pharmaceuticals will either be transformed or remain unchanged during treatment by wastewater treatment processes, then released into surface water. Pharmaceuticals, originating from wastewater or manure, may be present in surface water or ground water used as a source for raw drinking water. Once inside the drinking water treatment facility, a pharmaceutical may again be transformed during treatment or it may remain unchanged. Upon distribution of treated drinking water, there is a possibility of human exposure to unchanged or transformed pharmaceuticals.

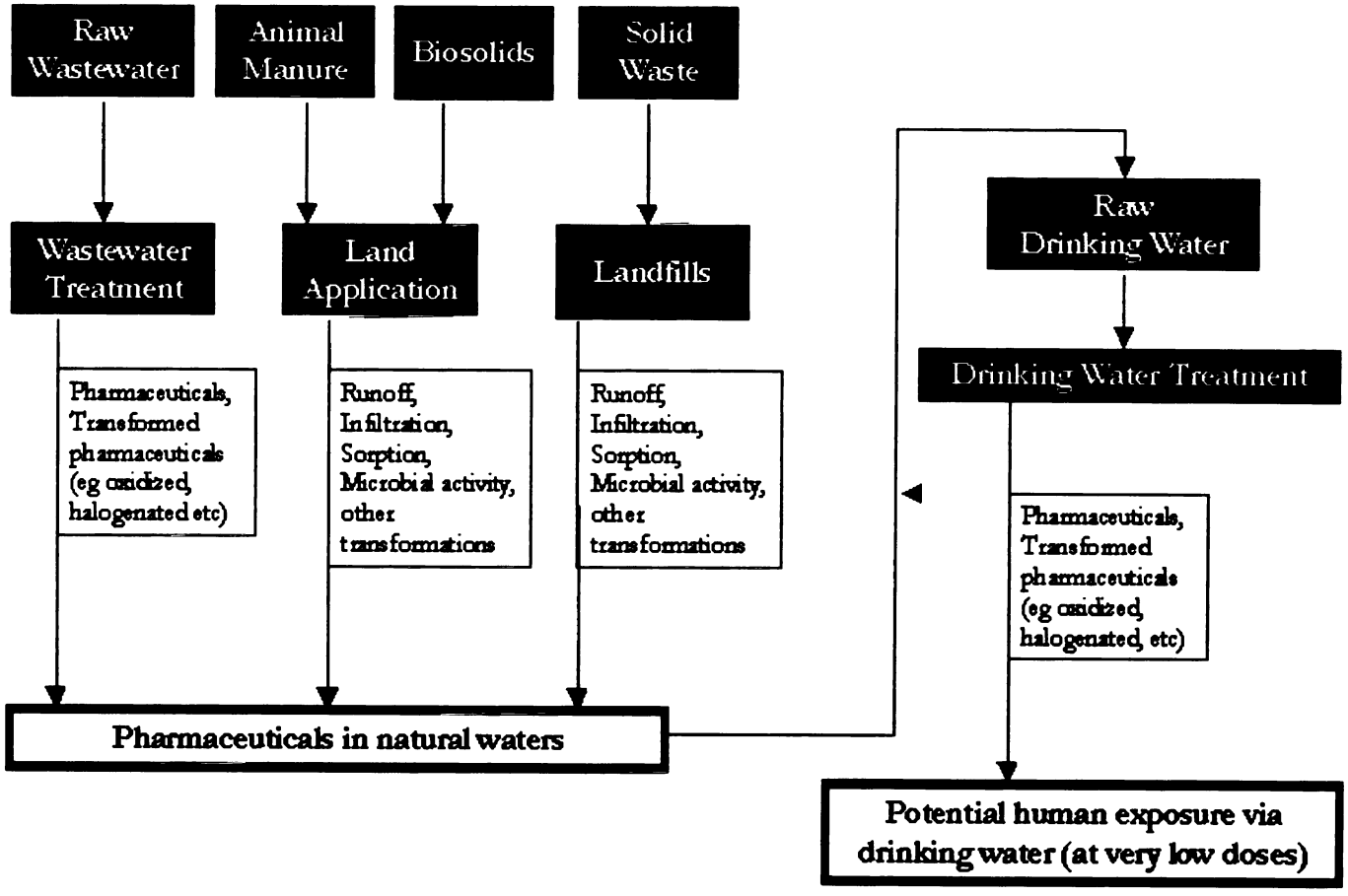


Figure 1. Source of Pharmaceuticals in Water

Animal production is another point source responsible for the wide dissemination of pharmaceuticals in water, particularly from industrialized animal agriculture, or Concentrated Animal Feeding Operations (CAFOs). Industrialized animal agriculture is used to provide livestock for human consumption, typically with animals living in dense populations. Antibiotics and hormones are commonly administered to livestock for disease control and added into feed at sub-therapeutic levels to improve the feeding efficiency, growth rate, and animal health. About 70% (12,600 tons) of antibiotics produced for medical and agricultural purposes in the U.S. are used for non-therapeutic treatment of livestock [Mellon *et al.*, 2001]. As much as 75% of the antibiotics used for animal growth are excreted back into manure [Campagnolo *et al.*, 2002], of which the U.S. produces 133 million tons of dry weight per year [Burkholder *et al.*, 2007]. The most common growth promoters of livestock are tetracycline, chlorotetracycline, and bacitracen [Jindal *et al.*, 2006; Mackie *et al.*, 2006]. Other antibiotics commonly used in animal agriculture include macrolide, sulfonamide, and β-lactam antibiotics [Huang *et al.*, 2001]. All of the antibiotics listed above are also used in human therapy, which instigated a ban on growth promoting antibiotics by the European Union in order to preserve the effectiveness of human antibiotics [Union of Concerned Scientists, 2006]. After a period of storage manure is often land-applied as plant fertilizer, and as consequence the pharmaceuticals are discharged to surface and ground water via surface runoff and percolation. Studies indicate application of swine manure to crops results in temporary increases of antibiotic resistant bacteria (Sengelov et al., 2003; Halling-Sorensen et al., 2005). Other potential sources of pharmaceuticals include biosolid application sites and landfill sites.

c. Conclusions

The presence of pharmaceuticals in wastewater, drinking water and surface water is well documented. Commonly detected pharmaceuticals include ibuprofen, acetaminophen, carbamazepine, and various antibiotics. Primary sources of pharmaceuticals in surface water are likely from human usage and land application of animal manure. When pharmaceuticals present in surface water are not removed by drinking water treatment, human exposure to very low levels of one or more pharmaceutically-active compounds may occur.

Fate of Pharmaceuticals in Drinking Water Utilities

The fate of pharmaceuticals during water treatment depends on the compound's physicochemical properties and the types and sequence of processes used in the treatment plant. Physical processes such as settling, flocculation, and filtration show varying removal efficiencies of pharmaceuticals (Gobel *et al.*, 2007; Nakada *et al.*, 2007; Stackelberg *et al.*, 2007; Peng *et al.*, 2006; Clara *et al.*, 2005; Ternes *et al.*, 2002). Disinfection processes, such as chlorine oxidation, are expected to degrade or transform pharmaceuticals since a reactive oxidative substance is added to the water. Most pharmaceuticals are organic substances which are expected to be highly susceptible to oxidation. Full-scale studies indicate that an appropriate combination of processes will effectively reduce the amount of pharmaceuticals leaving a drinking water treatment plant [Nakada *et al.*, 2007; Stackelberg *et al.*, 2007; Boyd *et al.*, 2003; Ternes *et al.*, 2002].

a. Removal of Pharmaceuticals during Full-Scale Drinking Water Treatment

Table 1 and Table 2 summarize removal of pharmaceuticals during full-scale drinking water treatment. Table 1 provides overall removal, while Table 2 provides removal during individual treatment processes. Pharmaceuticals that are not detected after treatment are often referred to as 'removed' by the treatment.

Few studies have looked at removal of pharmaceuticals during full-scale drinking water treatment. Full-scale studies are valuable because they provide information regarding the effectiveness of individual processes on pharmaceutical removal, as well as concentrations in source and finished water. Stackelberg *et al.* (2007) sampled water from a drinking water treatment plant (DWTP) in the United States that utilized screening, clarification, primary chlorine disinfection, sand/GAC filtration, and secondary chlorine disinfection. The DWTP treated 235 million liters per day. The degree of removal by each process varied for each organic compound investigated. Forty-five organic compounds were detected in the source water, including pharmaceuticals, flame retardants, plasticizers, pesticides, and others. Overall, GAC filtration resulted in an average percent removal of 53% for all compounds, disinfection resulted in 32% removal, and clarification resulted in 15% removal. Only the pharmaceuticals acetaminophen, carbamazepine, erythromycin, and sulfamethoxazole were detected in at least 25% of source water samples. After primary disinfection, sulfamethoxazole and acetaminophen were not detected, while carbamazepine and erythromycin were removed by 20% and 92%, respectively. The initial concentrations before primary disinfection were 30, 15, 191, and 10 ng/L, respectively. The combination of clarification, chlorine disinfection, and sand/GAC filtration was effective

at reducing the studied pharmaceuticals. These results were similar to a previous study conducted by Stackelberg *et al.* (2004) at the same DWTP. The utility was located in a very urbanized area, with at least 50 wastewater treatment plants discharging into streams or tributaries supplying source water to the DWTP. In the original study, the treatment process train followed screening, the addition of powdered activated carbon (PAC), coagulation, primary disinfection, flocculation, sedimentation, sand/GAC filtration, and secondary disinfection. Several changes were made to the treatment process before the second study, including discontinuing the addition of PAC, adding microsand to the clarification process, and reversing the order of clarification and primary disinfection. Similar to the second study, carbamazepine was the only investigated pharmaceutical that was not entirely removed by conventional drinking water treatment.

Boyd *et al.* (2003) took samples at various stages of treatment from two different drinking water treatment plants. One plant in Louisiana, USA used PAC addition, coagulation, flocculation, sedimentation, chlorination, filtration, and a final chloramination. Only naproxen was detected at 68 ng/L, but was completely removed after the combination of chlorination, filtration, and chloramination. The second plant was located in Windsor, Ontario and used ozonation, coagulation, flocculation, sedimentation, filtration, and a final chlorination. Clofibric acid and naproxen were detected in the influent at 103 and 63 ng/L , respectively. Neither of the compounds were detected in the final effluent.

Ternes *et al.* (2002) also monitored selected pharmaceuticals during drinking water treatment. Samples were obtained from two different DWTPs. One plant used pre-ozonation, flocculation, main ozonation, multiple-layer filtration, and GAC filtration for

the treatment train, while the other plant used sedimentation, flocculation, GAC filtration, underground passage, bank filtration, and slow sand filtration. The study found the combination of ozonation and GAC filtration effective at reducing carbamazepine, diclofenac, and clofibric acid, with all three compounds removed by greater than 90% in the first treatment plant. The initial concentration of these compounds ranged from 10 to 180 ng/L.

TABLE 1. Overall Removal of Pharmaceuticals during Full-Scale Drinking Water Treatment

Pharmaceutical	Influent Concentration (ng/L)	Effluent Concentration (ng/L)	Overall Removal (%)	Treatment Process Train	Reference
Acetaminophen	15[a]	0.3[a]	98	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	Stackelberg et al., 2007[c]
Carbamazepine	191[a] 200[a,b] 80 80 - 180[b]	29[a] 126.5[a,b] BDL BDL – 30[b]	85 36.7[a] >99 83 – 100[c]	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination, Screening, PAC and sulfuric acid addition, coagulation, chlorination, flocculation, sedimentation, GAC filtration, secondary chlorination DWTP1: Pre-ozonation, flocculation, main ozonation, layer and GAC filtration DWTP2: Sedimentation, flocculation, GAC, underground passage, bank and sand filtration	Stackelberg et al., 2007[c] Stackelberg et al., 2004 Ternes et al., 2002
Bezafibrate	80[b] ND	BDL	100[c]	DWTP1: Pre-ozonation, flocculation, main ozonation, layer and GAC filtration DWTP2: Sedimentation, flocculation, GAC, underground passage, bank and sand filtration	Ternes et al., 2002
Clofibric Acid	~10[b] ~10-15[b]	BDL BDL	100[c] 100[c]	DWTP1: Pre-ozonation, flocculation, main ozonation, layer and GAC filtration DWTP2: Sedimentation, flocculation, GAC, underground passage, bank and sand filtration	Ternes et al., 2002
Diclofenac	~35[b] ~65[b]	BDL BDL	100[c] 100[c]	DWTP1: Pre-ozonation, flocculation, main ozonation, layer and GAC filtration DWTP2: Sedimentation, flocculation, GAC, underground passage, bank and sand filtration	Ternes et al., 2002
Erythromycin	10[a]	ND	100	Screening, clarification, chlorination, sand/GAC filtration, secondary hlorination	Stackelberg et al., 2007[c]
Naproxen	63-65 64	ND ND	100 100	DWTP1: PAC addition, coagulation/flocculation/sedimentation, chlorination, filtration, chloramination DWTP2: Ozonation, coagulation/flocculation/sedimentation, filtration, chlorination	Boyd et al., 2003
Sulfamethoxazole	30[a]	ND	100	Screening, clarification, chlorination, sand/GAC filtration, secondary chlorination	Stackelberg et al., 2007[c]

Note: ND: pharmaceutical not detected in sample; NM: not measured; NA: not available; BDL: below detection limits.

[a] Value represents average.

[b] Approximated from figure.

[c] Removal calculated by authors.

TABLE 2. Removal of Pharmaceuticals during Individual Processes in Full-Scale Drinking Water Utilities

Pharmaceutical	Influent Concentration (ng/L)	Primary Treatment (Coagulation, flocculation, settling)		Filtration			Disinfection			Reference
		ng/L	% Removal	ng/L	% Removal	Type	ng/L	% Removal	Oxidant	
Acetaminophen	15[a]	6[a]	60[b]	1[a]	98	Sand/GAC	ND[a]	100[b]	NaOCl	Stackelberg et al., 2007[c]
Carbamazepine Carbamazepine Carbamazepine	191[a] 200[a,d] 80-180[d]	186[a] 82.3[a,d] 100 – 180[d]	3[b] 59.9[a, b] 0 to 14[b]	4[a] 106[a,d] 0 - 10[d]	97[b] 0[a, b] >90[b]	Sand/GAC GAC GAC	149[a] 126.5[a,d] NA	20[b] 0[a,b] >99[e]	NaOCl NaOCl Ozone	Stackelberg et al., 2007[c] Stackelberg et al., 2004 Ternes et al., 2002
Bezafibrate	80[d]	73[d]	8.8[b]	BDL	>95[b]	GAC	NM	NM	Ozone	Ternes et al., 2002
Clofibric Acid	9 - 10[d]	10[d]	0[b]	5[d]	50[b]	GAC	NA	77[e]	Ozone	Ternes et al., 2002
Diclofenac	35 - 65[d]	60[d]	7.7[b]	BDL	>95[b]	GAC	NA	>99[e]	Ozone	Ternes et al., 2002
Erythromycin	10[a]	5.3[a]	47[b]	ND[a]	100[b]	Sand/GAC	0.4[a]	92[b]	NaOCl	Stackelberg et al., 2007[c]
Naproxen	63-65	63-68	0[b]	NA	NA	NA	ND[c]	100[b]	NaOCl	Boyd et al., 2003
Sulfamethoxazole	30[a]	20[a]	33[b]	ND[a]	NA	Sand/GAC	ND[a]	100[b]	NaOCl	Stackelberg et al., 2007[c]

Note: Percent removals were calculated based on pharmaceutical concentration before and after each treatment process (eg. primary treatment, filtration, disinfection). ND: pharmaceutical not detected in sample; NM: not measured; NA: not available; BDL: below detection limit.

[a] Value represents average.

[b] Authors calculated removals from given concentrations.

[c] Filtration followed primary disinfection.

[d] Approximated from figure.

[e] Removal after main ozonation

This section will review the following processes: lime softening, coagulation, sedimentation, filtration, adsorption, and membrane filtration. Oxidation is considered an important process that can effectively degrade or transform pharmaceuticals, and is reviewed in the next section.

b. Lime Softening, Coagulation, Sedimentation

Several studies have investigated the effect of coagulation/flocculation, lime softening, and sedimentation on removal of pharmaceuticals. Sedimentation by coagulation/flocculation and lime softening are not expected to remove pharmaceuticals due to the hydrophilic nature of most pharmaceuticals. Ternes *et al.* (2002) observed little or no removal of carbamazepine, diclofenac, and clofibric acid after coagulation with iron chloride during full-scale drinking water treatment. Similarly, Stackelberg *et al.* (2007) saw incomplete removal of acetaminophen, carbamazepine, erythromycin, and sulfamethoxazole during coagulation with iron chloride at a DWTP. Clarification resulted in percent removals of 3%, 33%, 47%, and 60% for carbamazepine, sulfamethoxazole, erythromycin, and acetaminophen, respectively (Stackelberg *et al.*, 2007).

In a bench scale study by Adams *et al.* (2002), the coagulants, aluminum sulfate and ferric sulfate, were added at doses of 20 - 107 mg/L and 35 - 169 mg/L, with initial antibiotic concentrations of 50 μg/L. Initially the samples were mixed at 100 rpm for 1 min, 30 rpm for 20 min, followed by 3 hours of settling time. For lime softening, lime and soda ash dosages of 232 and 191 mg/L, respectively, were applied in the same way as coagulants, and the pH was adjusted to approximately 11.3. No significant removal of

antibiotics occurred during coagulation or lime softening processes. Similar results were obtained by Westerhoff *et al.* (2005) in coagulation and lime softening experiments involving 22 different pharmaceuticals. In a pilot-scale study, the average removal of 13 different pharmaceuticals was 3% during coagulation with ferric sulfate (Vieno *et al.*, 2007). Choi *et al.* (2008) conducted coagulation experiments on tetracycline antibiotics using poly-aluminum chloride, added at dosages of 5 - 60 mg/L and mixed for 5 minutes. Removal increased with higher dosage from 5 - 40 mg/L, but declined when a dosage greater than 40 mg/L was added. The authors explained this by charge neutralization of the antibiotics at high coagulant dosages, which caused a re-stabilization of antibiotics, thus reducing removal efficiency. These studies indicate chemical precipitation processes are not effective for removing pharmaceuticals.

c. Filtration

i. Adsorptive

Adsorption by activated carbon is commonly used in drinking water treatment for removal of organic chemicals, taste and odor compounds, and NOM, either in powdered (PAC) or granular form (GAC). The adsorption of organic chemicals to activated carbon depends on the chemical's structure, polarity, hydrophobicity, porosity of media, activated carbon dosage, and presence of NOM (Choi *et al.*, 2008; Mestre *et al.*, 2007; Vieno *et al.*, 2007; Westerhoff *et al.*, 2005; Yoon *et al.*, 2003; Yu *et al.*, 2003). Adsorption by GAC may be effective for removing pharmaceuticals with high octanol-water partitioning coefficients (k_{ow}), such as estradiol, ethinylestradiol, and fluoxetine ($\log k_{ow} \geq 4.0$). In a pilot study by Vieno *et al.* (2007) most pharmaceuticals were

removed after a two-step GAC filtration process except those having high hydrophillicity (atenolol, sotalol, ciprofloxacin). Choi *et al.* (2008) found the use of a coal-based GAC column more effective than coagulation, with greater than 68% of tetracycline antibiotics removed. Although not statistically confirmed, coal-based carbon exhibited slightly better removal than coconut-based carbon.

PAC addition may also be effective, but is often only used seasonally to control taste and odor compounds and NOM. Another issue that must be considered is disposal of used PAC in landfills. Adams *et al.* (2002) found a PAC dosage of 50 mg/L effective for removing all antibiotics studied from both pure water and surface water. Westerhoff *et al.* (2005) also found that increasing PAC dosage resulted in greater removal, with a dosage of 20 mg/L removing greater than 80% of pharmaceuticals studied. The researchers observed trends of protonated bases having greater removal than other compounds, particularly compounds with deprotonated functional groups having low k_{ow} values. Yoon *et al.* (2003) investigated the adsorption of 17β-estradiol and 17α-ethynyl estradiol onto six different PAC brands, tested at 5 and 15 mg/L doses and a 4 hour contact time. Hormones were spiked at 100 nM. For the model water, greater than 99% of the hormones were removed by all brands except for one, which had the lowest point of zero charge value. Removals were lower in raw drinking water because of the presence of NOM. Snyder et al. (2006) studied spiked pharmaceutical removal from natural waters in bench and pilot scale experiments. Pharmaceutical removal depended on PAC dose, contact time, and structure/behavior of each compound. The majority of compounds tested were removed by greater than 90% with a PAC dose of 35 mg/L and 5 hour contact time.

In a study by Yu *et al.* (2003), adsorption of naproxen and carbamazepine to bituminous carbon and coconut shell were compared using Freundlich isotherms. Results indicate carabamazepine adsorbs to carbon to a greater extent than naproxen. Naproxen showed greater adsorption affinity for bituminous carbon than coconut shell, while carbamazepine did not display a significant difference. Authors attributed differences between the compounds to naproxen being present in anionic form during the experiments, while carabamazepine remained uncharged.

Mestre *et al.* (2007) studied adsorption of ibuprofen to activated carbon prepared from waste cork powder. One type, CAC, was made using chemical activation with potassium carbonate. The second type, CPAC, was made by physical activation of CAC using steam. Surface chemistry characterization based on point of charge determination indicated CAC had a more acidic surface than CPAC. Adsorption isotherms showed CPAC had a higher adsorption capacity due to more developed porosity. Ibuprofen, which appeared to follow the Langmuir isotherm model, adsorbed to CPAC at higher rates and to a greater capacity than to CAC, likely due to the more developed porosity of CPAC (Mestre *et al.*, 2007). Temperature did not seem to affect adsorption, while increase in pH led to decreased removal. The pK_a of ibuprofen is 4.91, so at a pH greater than 5, electrostatic repulsion occurs between the ibuprofen anion and the activated carbon surface.

The adsorption behavior of acetaminophen and nalidixic acid onto polar and nonpolar adsorbents was investigated using neutral polymeric resins as polar adsorbents and powdered activated carbon as a nonpolar adsorbent (Suntisukaseam *et al.*, 2007). It was found that nalidixic acid, a quinolone antibiotic with a carboxylic functional group,

adsorbed to all media better than acetaminophen. Acetaminophen has a much greater water solubility, lower K_{OW} and higher polarity than nalidixic acid, so it tends to stay in solution. Adsorption onto polymeric resins was found to follow the Langmuir isotherm, while activated carbon adsorption followed the Freundlich isotherm. Greater polarity of the polymeric resins resulted in greater amounts of pharmaceuticals adsorbed per area of adsorbent. For both pharmaceuticals, activated carbon resulted in higher sorption than the polymeric resins.

ii. Sand

Removal by sand filtration is related to a compound's hydrophobic or hydrophilic tendencies. For example, Nakada *et al.* (2007) observed that after sand filtration, hydrophilic compounds, such as carbamazepine, sulfapyridine, sulfamethoxazole, and estriol, had lower removal efficiencies (<50%) than hydrophobic compounds, such as ibuprofen, which were removed by >80% in some cases. At a drinking water treatment plant studied by Stackelberg *et al.* (2007), sand/GAC filtration was employed in between primary and secondary chlorine disinfection, and completely removed the remaining erythromycin, and the remaining carbamazepine by 97%. Ternes *et al.* (2002) took samples after GAC filtration in full-scale drinking water treatment: diclofenac and bezafibrate were removed by greater than 95%, carbamazepine by more than 75%, and clofibric acid by 20%.

iii. Membrane

Verliefde *et al.* (2007) studied removal of 20 pharmaceuticals from surface water by a bench-scale nanofiltration (NF) membrane (1500 l/h feed flow, 10% recovery) and by a NF membrane with subsequent GAC column (80% recovery). Results indicate removal of pharmaceuticals by NF depends on the charge of the pharmaceutical. Rejection values were lowest for positively charged pharmaceuticals and highest for negatively charged pharmaceuticals. Neutral compounds exhibited intermediate removal, likely due to negatively charged membrane surface, or hydrophobicity of neutral compounds (Verliefde *et al.*, 2007). Higher removals were achieved when NF was combined with GAC filtration. Yoon *et al.* (2006) also investigated removal of pharmaceuticals by membrane filtration, by NF as well as by ultrafiltration (UF). According to results, NF membranes retained pharmaceuticals based on hydrophobicity and size of particle, while UF membranes retained pharmaceuticals mainly based on hydrophobicity alone.

Snyder et al. (2006) investigated rejection of pharmaceuticals by a partially fouled UF membrane, and found the majority of compounds in the feed water were not rejected. Compounds that were well-removed included the steroid hormones such as estradiol, estrone, ethinylestradiol, and progesterone. In a pilot RO system, Snyder et al. (2006) found that all pharmaceuticals spiked into feed water were well-rejected by both virgin membranes and fouled membranes. However, pharmaceuticals are then present in greater concentrations in the retentate water, thus requiring further treatment prior to discharge.

d. Conclusions

Drinking water treatment consists of a train of physicochemical processes, which may or may not remove or transform pharmaceuticals into less reactive compounds. Certain combinations of processes are more effective than others, and bench-scale studies indicate that many factors influence the degree at which a pharmaceutical is transformed. Coagulant dosage, type or brand of activated carbon used, and the compound's chemical properties are just a few parameters to consider when planning a treatment train that will minimize the concentration of pharmaceuticals in finished drinking water. Lime softening, coagulation, and sedimentation processes are not effective at removing pharmaceuticals. Adsorptive, sand, and membrane filtration are effective at removing some pharmaceuticals, depending on the compound's chemical structure and properties.

Oxidation of Pharmaceuticals

Oxidation processes are routinely applied at wastewater and drinking water utilities for disinfection and taste and odor control. Most pharmaceuticals are susceptible to oxidation because they are polar organic compounds containing reactive functional groups. Appendix 1 provides the chemical formula, molecular weight, octanol-water partitioning coefficient, acid-dissociation constant, and structure for various pharmaceuticals. Data and structures in this table were obtained from the chemical database, DrugBank (Wishart et al., 2006). Chemical oxidants typically used in water treatment include chlorine, chloramines, and ozone. UV based oxidation processes can also be used. Oxidation occurs when there is a net loss of electrons from an atom.

Oxidants, such as chlorine, are electrophilic molecules that attack the electron-rich areas of a nucleophile.

a. Oxidation by Chlorine-Containing Oxidants

Chlorine is capable of oxidizing many different inorganic and organic compounds (Deborde and von Gunten, 2008). Typically, chlorine is added to water in the form of sodium hypochlorite (NaOCl), or chlorine gas, which exists primarily as hypochlorite ion (OCl^-) and hypochlorous acid (HOCl) in solution. Collectively the two species are referred to as free available chlorine, and the concentration of free chlorine is expressed as mg/L Cl_2. The chlorine species that is dominant in solution depends on the pH, temperature, and total concentration of chlorine [AWWA, 1999]. The pK_a of free chlorine is 7.5 with HOCl predominating at pH levels less than 7.5, and the weaker disinfectant, OCl-, predominating at a pH greater than 7.5. Major parameters that affect oxidation pathways are the pharmaceutical molecular structure, pharmaceutical concentration, chlorine concentration, contact time, pH, temperature, and water composition.

Depending on the molecular structure of the pharmaceutical, chlorine will react differently with different types of compounds. In some cases a pharmaceutical may not react with chlorine at all. For example, Glassmeyer and Shoemaker (2005) investigated the fate of pharmaceuticals during chlorination via bench top experiments. Chlorinated and non-chlorinated mass chromatograms and spectra for pharmaceuticals were compared to determine the effect of chlorination on each compound. The results indicated that each pharmaceutical fell into one of three groups: unchanged by

chlorination, chlorinated, or changed by chlorination but did not appear to become chlorinated. For the conditions tested, the pharmaceuticals that were unchanged were aspirin, and 6α-methyl-17α-hydroxy progesterone acetate. Amoxicillin, cephalexin, cimetidine, trimethoprim, diltiazem, and warfarin were changed by chlorination but did not appear to become chlorinated. Only acetaminophen and gemfibrozil showed definite signs of chlorination.

In some cases, pharmaceuticals react rapidly and are transformed by free chlorine, such as acetaminophen, naproxen, triclosan, diclofenac, and estrogens [Bedner and Maccrehan, 2006; Boyd *et al.*, 2005; Westerhoff *et al.*, 2005]. In other cases, pharmaceuticals exhibit little or no reactivity and do not undergo transformation with free chlorine, such as meprobamate, ibuprofen, ketoprofen, carbamazepine, and erythromycin [Gibs *et al.*, 2007; Pinkston and Sedlak, 2004; Westerhoff *et al.*, 2005].

Even though the majority of chlorination studies have used sodium hypochlorite as the disinfectant, the effectiveness of different forms of chlorine in water treatment (i.e. chlorine dioxide, monochloramine) has also been assessed. Chamberlain and Adams (2006) compared free chlorine with monochloramine as an oxidant and found that monochloramine is less effective at removing pharmaceuticals from drinking water than free chlorine. However, monochloramine is thought to form less halogenated byproducts than free chlorine [Chamberlain and Adams, 2006; Richardson, 2003]. In the Chamberlain and Adams study (2006), the only antibiotic that showed a high degree of reactivity with monochloramine was carbadox. In a study by Pinkston and Sedlak (2004), none of the pharmaceuticals tested reacted fast enough with monochloramine to

be transformed. Also, the synthetic hormone, 17α-ethinylestradiol, was not transformed by monochloramine at typical water treatment doses of a few mg/L (Lee *et al.*, 2008).

Few studies have been published that examine the reactivity of pharmaceuticals with chlorine dioxide. In a study by Huber *et al.* (2005b), chlorine dioxide was applied to groundwater, drinking water, or surface water spiked with various pharmaceuticals. Chlorine dioxide doses ranged from 0.1 to 11.5 mg/L, and pharmaceuticals were spiked at concentrations less than or equal to 1 μg/L. Pharmaceutical solutions were in contact with chlorine dioxide up to 180 minutes, and the pH was kept at ambient levels (7.2-7.9). Some compounds were readily oxidized (diclofenac, 17β-estradiol, estrone, 17α-ethinylestradiol, phenazone, sulfonamide antibiotics), while some compounds did not react at all (bezafibrate, carbamazepine, diazepam, fenoprofen, ibuprofen, ketoprofen). The study showed that chlorine dioxide is effective at oxidizing only specific classes of compounds such as sulfonamides and estrogens. Lee *et al.* (2008) also reported significant transformation of 17α-ethinylestradiol by chlorine dioxide.

b. Ozonation of Pharmaceuticals

The use of ozonation in drinking water treatment is more common in Europe and Asia than in the United States, due to relatively high costs in the United States. Ozone reacts more rapidly with pharmaceuticals than chlorine because of its high reactivity with most organic functional groups [Adams *et al.*, 2002; Alum *et al.*, 2004; Huber *et al.*, 2005a; Nakada *et al.*, 2007; Westerhoff *et al.*, 2005]. For example, Westerhoff *et al.* (2005) applied 2.5 to 4 mg/L ozone to a wide variety of pharmaceuticals at concentrations ranging from 10-250 ng/L. After 10 minutes in contact with ozone, most

of the compounds were oxidized by greater than 80%. The degradation efficiency of ozone is greater when it is applied in combination with hydrogen peroxide, which helps stimulate the generation of OH radicals [Zweiner and Frimmel, 2000]. For example, when ozone was applied directly to water spiked with 2 μg/L each of clofibric acid, diclofenac, and ibuprofen at a dose of 1 mg/L, and the compounds were allowed to react for 10 minutes, only diclofenac was degraded readily [Zweiner and Frimmel, 2000]. However, when hydrogen peroxide was used in combination with ozone, the degradation efficiency of all three compounds increased.

c. UV Irradiation of Pharmaceuticals

Ultraviolet irradiation is used in both drinking water and wastewater treatment. UV processes are often combined with hydrogen peroxide and are used to oxidize taste and odor-causing chemicals and to disinfect water [Rosenfeldt and Linden, 2004]. Typically, low pressure high-output lamps or medium pressure lamps are used in large-scale water disinfection (Linden and Kullman, 2007). A comparison of monochromatic low-pressure (LP) UV lamps with polychromatic medium pressure (MP) lamps was done by Rosenfeldt and Linden (2004) on endocrine disruptors, including the hormones ethinyl estradiol and estradiol. At the same fluence of 1,000 mJ cm^{-2}, the MP lamps resulted in greater degradation of the hormones than the LP lamps. This is due to the low probability of radiation absorption by the hormones using the monochromatic LP lamp which emits at 254 nm (Linden and Kullman, 2007). The polychromatic MP lamp radiation covers wavelengths between 200 and 300 nm, allowing molecules to reach excited states and become unstable.

The addition of hydrogen peroxide (H_2O_2) to UV irradiation results in the photolysis of H_2O_2 into OH radicals, one of the strongest known oxidants [Vogna *et al.*, 2004]. Direct UV irradiation in the absence of H_2O_2 has been found to be a less effective oxidant than the combined process [Adams *et al.*, 2002; Rosenfeldt and Linden, 2004; Rosenfeldt *et al.*, 2007; Vogna *et al.*, 2004]. Adams *et al.* (2002) applied UV radiation to water spiked with 50 μg/L carbadox, trimethoprim, and sulfonamide antibiotics. Their study showed that typical UV dosages, about 30 $mJ \cdot cm^{-2}$, used during disinfection of drinking water were ineffective at removing all compounds. Even at doses 100 times greater the antibiotics were not completely removed. Adams *et al.* (2002) attributed this inefficiency to weak ultraviolet absorption of the specific compounds. Linden and Kullmen (2007) studied degradation of 17β-estradiol and 17α-ethinyl estradiol by direct UV and UV/ H_2O_2 in terms of both chemical degradation and destruction of estrogenic activity. Results indicated the oxidation products of the estrogens were less estrogenically active than the parent compounds. Another interesting finding was that more oxidation of these compounds occurred at environmentally-relevant concentrations and at lower UV doses than suggested by previous research which used higher concentrations and dosages.

d. Comparison of Different Oxidants

The type of oxidant used in water treatment plays a major role in the fate of pharmaceuticals. As shown in Table 5, different oxidants react differently with the same pharmaceutical compounds. In general, studies have shown that pharmaceuticals exhibit

mixed reactivity with free chlorine [Chamberlain and Adams, 2006; Deborde *et al.*, 2004; Gibs *et al.*, 2007; Glassmeyer and Shoemaker, 2005; Qiang *et al.*, 2006; Westerhoff *et al.*, 2005]. The same is true for chlorine dioxide and monochloramine [Chamberlain and Adams, 2006; Huber *et al.*, 2005b; Qiang *et al.*, 2006]. Ozone reacts rapidly with most pharmaceuticals except for some acidic pharmaceuticals, such as clofibric acid, gemfibrozil, ibuprofen, bezafibrate, and meprobamate [Huber *et al.*, 2005a; Ternes *et al.*, 2002; Zweiner and Frimmel, 2000]. Most acidic pharmaceuticals contain a carboxylic acid group, which may not react well with ozone.

UV irradiation of pharmaceuticals seems to only be effective in the presence of hydrogen peroxide [Adams *et al.*, 2002; Rosenfeldt and Linden, 2004; Rosenfeldt *et al.*, 2007; Vogna *et al.*, 2004]. In a full-scale observation, Renew and Huang (2004) sampled effluents from two wastewater treatment plants for antibiotics. One treatment plant used chlorine for disinfection and the other used UV as the disinfectant. The results showed that chlorination removed significantly more antibiotics than UV disinfection.

TABLE 3. Comparison of the Reactivity of Different Oxidants for Selected Pharmaceuticals

Pharmaceutical	NaOCl	ClO_2	Monochloramine	Ozone	UV Irradiation
Naproxen Analgesic	**High reactivity** (Boyd *et al.*, 2005; Westerhoff *et al.*, 2005; Pinkston & Sedlak, 2004)	**Some reactivity** (Huber *et al.*, 2005b)	**Not transformed.** (Pinkston & Sedlak, 2004)	**High reactivity** (Huber *et al.*, 2005a; Westerhoff *et al.*, 2005)	**NA**
17α-Ethinylestradiol Hormone	**High reactivity** (Lee *et al.*, 2008; Westerhoff *et al.*, 2005; Alum *et al.*, 2004; Deborde *et al.*, 2004)	**High reactivity** (Lee *et al.*, 2008; Huber *et al.*, 2005b)	**Low reactivity** **(Lee *et al.*, 2008)**	**High reactivity** (Lee *et al.*, 2008; Huber *et al.*, 2005a; Westerhoff *et al.*, 2005; Alum *et al.*, 2004; Huber *et al.*, 2003)	**Effectively degraded by UV/H_2O_2** (Rosenfeldt & Linden, 2004; Rosenfeldt *et al.*, 2007)
Carbamazepine Antiepileptic	**Some or no reactivity** (Westerhoff *et al.*, 2005; Gibs *et al.*, 2007)	**No reactivity** (Huber *et al.*, 2005b)	**NA**	**High reactivity** (Westerhoff *et al.*, 2005; McDowell et al., 2005; Huber *et al.*, 2003)	**High reactivity with UV/H_2O_2** (Vogna *et al.*, 2004)
Sulfamethazine Antibiotic	**Some reactivity** (Qiang *et al.*, 2006; Chamberlain & Adams, 2006; Adams *et al.*, 2002; Gibs *et al.*, 2007)	**Some reactivity** (Huber *et al.*, 2005b)	**Some reactivity** (Qiang *et al.*, 2006;	**High reactivity** (Adams *et al.*, 2002)	**Some reactivity** (Adams *et al.*, 2002)
Erythromycin Antibiotic	**Some, high, or no reactivity** (Westerhoff *et al.*, 2005; Chamberlain & Adams, 2006; Gibs *et al.*, 2007)	**Some reactivity** (Huber *et al.*, 2005b)	**Some reactivity** (Chamberlain & Adams, 2006)	**High reactivity** (Westerhoff *et al.*, 2005; Huber *et al.*, 2005)	**NA**

e. Mechanisms of Oxidation

Reactions between chlorine and organic molecules may occur by oxidation of functional groups, addition to double bonds, and electrophilic substitution [Brezonik, 1994]. The reactivity of an organic contaminant with chlorine depends largely on its functional groups [Westerhoff *et al.*, 2005], although the reactivity of the oxidant itself is also important. Snyder *et al.* (2003) makes two generalizations about the reactivity of oxidants with pharmaceuticals: protonated forms of pharmaceuticals are less reactive than dissociated acidic forms, and aliphatic pharmaceuticals are less reactive than aromatic compounds. The order of reactivity (highest to lowest) for aromatic or aliphatic compounds is: thiols > amines > hydroxyl > carboxyl [Snyder *et al.*, 2003]. Many pharmaceuticals contain such functional groups as well as phenolic groups. Two of the best documented reactions of $HOCl/OCl^-$ is the reaction of free chlorine with phenols, and chlorine addition to primary and secondary amines [Pinkston and Sedlak, 2004]. In the first reaction, HOCl reacts with the phenolate anion to yield ortho- and para-substituted chloro-phenols. In the reactions with amines, HOCl reacts with the unprotonated amine. For both cases, the maximum reaction rates occur between the pk_a of HOCl (7.5) and that of the phenol or amine [Pinkston and Sedlak, 2004]. Hormones such as estrone, β-estradiol, and 17α-ethinylestradiol contain a phenolic ring and exhibit rapid reactivity with chlorine, suggesting that other compounds containing phenolic rings will undergo rapid elimination during chlorination as well [Deborde *et al.*, 2004].

Dodd and Huang (2004) investigated the transformation of the antibiotic, sulfamethoxazole, during chlorination. Results showed that chlorine attacks the aniline-

nitrogen of sulfamethoxazole directly leading to the halogenation of the aniline moiety, yielding a ring-chlorinated product. They also found that the sulfonamide moiety of sulfamethoxazole is ruptured when free chlorine is in excess, resulting in the formation of 3-amino-5-methylisoxazole and N-chloro-*p*- benzoquinoneimine. Huber *et al.* (2005b) studied the sulfonamide antibiotics sulfamethoxazole, sulfamethazine, sulfapyridine, and sulfathiazole, which all contain the aniline moiety. Although the compounds have similar structures, they exhibited varying reactivity with chlorine dioxide, which the authors attributed to differences in speciation. For example, sulfapyridine has a pk_a of 8.4 so during the experiments it remained in its neutral form and was less reactive than sulfamethoxazole, which has a pk_a of 5.7.

In ozonation, pharmaceuticals can be oxidized by one of two mechanisms, either by ozone directly, or by $OH^{\cdot}$ radicals. Ozone spontaneously decomposes in water by chain reactions involving different free radical species [AWWA, 1999]. When applied directly, a significant amount of ozone may be lost due to decomposition in water [Staehelin and Holgne, 1982]. Ozone tends to react selectively with functional groups, while $OH^{\cdot}$ radicals are nonselective toward organic compounds [Calamari *et al.*, 2003; Haag and Yao, 1992]. Westerhoff *et al.* (2005) found that functional groups affect how efficiently a pharmaceutical is oxidized by ozone. For example, ibuprofen, which contains a propionate moiety, was not as efficiently oxidized as compounds that contain an amine functional group, such as diclofenac. Westerhoff *et al.* (2005) also compared the structural properties of compounds that reacted rapidly with both chlorine and ozone and found that those compounds usually had hydroxyl or amine functional groups along with low pk_a values. Evidence from both bench-scale and full-scale studies suggest

pharmaceuticals with a double carbon bond (C=C) or an activated aromatic ring are more susceptible to ozonation than pharmaceuticals with amide structures [Nakada *et al.*,2007].

UV or UV/H_2O_2 processes are capable of oxidizing organic contaminants, but the effectiveness of the processes depends on the absorption spectra of the molecule. Adding hydrogen peroxide (H_2O_2) helps to lower the UV dose required [Rosenfeldt and Linden, 2004]. The effectiveness of UV processes also depends on the pressure of the lamp used and the ability of absorbed radiation by the pharmaceutical to reach an excited state [Rosenfeldt and Linden, 2004]. Other factors that influence UV efficiency are background absorbance and scavenging capacity of the water matrix.

f. Factors Affecting Oxidation Rates

The degradation of pharmaceuticals during oxidation of wastewater or drinking water depends primarily on the pH of the water, the amount of oxidant present, the concentration of pharmaceutical, the available contact time, and matrix water. Table 4 shows pH effects on pharmaceuticals during chlorination studies involving sodium hypochlorite. Boyd *et al.* (2005) found the transformation of naproxen during chlorination was dependent on pH, contact time, and chlorine dose. The rate and extent of the reaction increased when a higher chlorine dose was applied and favored low pH levels.

TABLE 4. Effect of pH During Chlorination of Pharmaceuticals by Sodium Hypochlorite

Pharmaceutical	pH Studied	pH Effect	Source
Acetaminophen	6, 7.5, 9 5.5, ambient 5 – 10	Effects varied in each study	Xagoraraki *et al.*, 2008; Westerhoff *et al.*, 2005; Pinkston & Sedlak, 2004
Atenolol	5 – 10	Increased with increased pH	Pinkston & Sedlak, 2004
Carbadox	6.1, 7.6, 9.1	No effect observed	Chamberlain & Adams, 2006
Carbamazepine	5.5,ambient	Decreased with increased pH	Westerhoff *et al.*, 2005
Diazepam	5.5, ambient	Decreased with increased pH	Westerhoff *et al.*, 2005
Diclofenac	5.5, ambient	No effect observed	Westerhoff *et al.*, 2005;
Dilantin	5.5, ambient	No effect observed	Westerhoff *et al.*, 2005;
Erythromycin	6.1, 7.6, 9.1 5.5, ambient	No effect observed	Chamberlain & Adams, 2006; Westerhoff *et al.*, 2005
Estradiol	3.5 – 12 5.5, ambient	Greatest between pH 8 and 10	Deborde *et al.*, 2004; Westerhoff *et al.*, 2005
Estriol	3.5 – 12 5.5, ambient	Greatest between pH 8 and 10	Deborde *et al.*, 2004; Westerhoff *et al.*, 2005
Estrone	3.5 – 12 5.5, ambient	Greatest between pH 8 and 10	Deborde *et al.*, 2004; Westerhoff *et al.*, 2005
Ethinylestradiol	3.5 – 12 5.5, ambient	Greatest between pH 8 and 10	Deborde *et al.*, 2004; Westerhoff *et al.*, 2005
Fluoxetine	5.5, ambient	No effect observed	Westerhoff *et al.*, 2005
Gemfibrozil	5 – 10 5.5, ambient	Decreased with increased pH	Pinkston & Sedlak, 2004; Westerhoff *et al.*, 2005
Ibuprofen	5 – 10 5.5, ambient	No effect observed	Pinkston & Sedlak, 2004; Westerhoff *et al.*, 2005
Indometacine	5 – 10	Decreased with increased pH	Pinkston & Sedlak, 2004
Metoprolol	5 – 10	Increased with increased pH	Pinkston & Sedlak, 2004
Naproxen	5, 7, 9 5 – 10 5.5, ambient	Decreased with increased pH	Boyd *et al.*, 2005; Pinkston & Sedlak, 2004; Westerhoff *et al.*, 2005
Propanolol	5 – 10	Increased with increasing pH	Pinkston & Sedlak, 2004
Sulfamerazine	6.1, 7.6, 9	Decreased with increased pH	Chamberlain & Adams, 2006;
Sulfamethazine	6.1, 7.6, 9 6.6, 7.6, 8.6	Decreased with increased pH	Chamberlain & Adams, 2006; Qiang *et al.*, 2006
Sulfamethoxazole	6.1, 7.6, 9 4 – 9 6.6, 7.6, 8.6 5.5, ambient	Decreased with increased pH	Chamberlain & Adams, 2006; Dodd & Huang, 2004; Qiang *et al.*, 2006; Westerhoff *et al.*, 2005
Sulfathiazole	6.1, 7.6, 9	Decreased with increased pH	Chamberlain & Adams, 2006;
Trimethoprim	5.5, ambient	No effect observed	Westerhoff *et al.*, 2005

Pinkston and Sedlak (2004) found that the reaction rates of pharmaceuticals with free chlorine increased when the pH was reduced from 10 to 7, since free chlorine exists predominantly as HOCl below a pH of 7.5, and HOCl is more reactive than OCl^-. Dodd and Huang (2004) also found that reactions of sulfamethoxazole with chlorine were pH dependent. The reactivity of sulfamethoxazole with free chlorine decreased substantially with increasing pH. Similar results were observed by Chamberlain and Adams (2006), when they studied the removal of six different sulfonamides with chlorine; sulfonamides were readily removed from drinking water at neutral pH, but were only partially removed at pH 9. Pinkston and Sedlak (2004) observed reactions of aromatic ether- and amine-containing pharmaceuticals with free chlorine where they found that the reaction rates tended to increase with decreasing pH. Acidic pharmaceuticals, such as gemfibrozil, ketoprofen, and ibuprofen, exhibit low reactivity with chlorine-containing oxidants [Gibs *et al.*, 2007; Glassmeyer and Shoemaker, 2005; Pinkston and Sedlak, 2004; Westerhoff *et al.*, 2005]. These pharmaceuticals all have acid dissociation constants less than 5, but were studied at pH levels greater than or equal to 5.0. For acidic pharmaceuticals, the greatest reactivity with oxidants may fall at lower pH levels.

The extent that a pharmaceutical reacts with an oxidant is also largely dependent on the oxidant dose and the concentration of pharmaceutical present. When the molar ratio of oxidant to pharmaceutical is greater, a higher degree of reactivity is expected. For instance, Huber *et al.* (2005a) observed that the amount of oxidation of a pharmaceutical increased with greater ozone doses. Also, Chamberlain and Adams (2006) applied either 0.1 or 1.0 mg/L free chlorine to distilled water spiked with macrolide antibiotics. After two hours, the average removal of antibiotics for a 0.1 mg/L

Cl_2 dose was only 28%, while the average removal for a 1.0 mg/L Cl_2 dose was 85%. Adams *et al.* (2002) found that UV doses typical to water disinfection were ineffective at removing several different antibiotics. In order to achieve 50 – 80% removal of the antibiotics, the UV dose had to be increased to 3,000 mJ/cm^2. This dose was 100 times greater than those typically used in disinfection.

Oxidation rates and the formation of intermediate products are affected by the length of time a pharmaceutical is in contact with an oxidant as well. Chamberlain and Adams (2006) observed that antibiotics were removed to a greater extent as the contact time with chlorine increased, however, the time required for adequate removal varied for each antibiotic. Boyd *et al.* (2005) found that when naproxen was chlorinated, intermediate products increased over contact time, and then decreased after one hour.

Another factor affecting degradation rates of pharmaceuticals is the water matrix. In a study done by Adams *et al.*, removal times of antibiotics by free chlorine were shorter in distilled water than in surface water suggesting natural organic matter in surface water decreases reactivity (2002). Huber *et al.* (2005b) demonstrated that when chlorine dioxide is used as a disinfectant for surface waters containing a considerable amount of organic matter, the pharmaceuticals and the water matrix compete for chlorine dioxide, thereby increasing the chlorine dioxide dose necessary to oxidize the pharmaceuticals. When ozone is used as an oxidant, the oxidation rates of OH radicals with organic compounds may be limited by the rate of OH generation and by competing OH scavengers such as dissolved organic carbon [Haag and Yao, 1992]. Adams *et al.* (2002) found that reactions of ozone with antibiotics were faster in distilled water than in surface water.

g. Formation of Byproducts

Often, pharmaceuticals are said to be 'removed' by oxidation processes, when in fact they are only transformed into different compounds. It is known that chlorine reacts with dissolved natural organic matter to produce disinfection byproducts including trihalomethanes and haloaccetic acids. Deborde and von Gunten (2008) reported that 600 different disinfection byproducts have been identified. Ozonation may also produce bromate when it is applied to waters that contain bromide, and chlorine dioxide reacts with organic compounds to form chlorite. Monochloramine as a disinfectant can lead to the formation of nitrosamines, while UV irradiation may convert nitrate to nitrite.

Pharmaceuticals may react with chlorine during water treatment to form byproducts with confirmed toxicity to humans [Bedner and Maccrehan, 2006; Korshin *et al.*, 2006], or byproducts of unknown or no toxicity to humans [Andreozzi *et al.*, 2005; Bedner and Maccrehan, 2006; Dodd and Huang, 2004; Gould and Richards, 1984; McDowell *et al.*, 2005; Pinkston and Sedlak, 2004]. Similarly, ozonation of drinking water may result in the formation of byproducts as well [Alum *et al.*, 2004; Andreozzi *et al.*, 2005]. The formation of oxidation byproducts that cause adverse health effects is of particular concern in regards to human health.

Table 5 presents a summary of oxidation byproducts of pharmaceuticals and whether or not the byproducts are known to be toxic to humans. As shown in the table, the toxicity of most of the byproducts is relatively unknown, indicating more research in this area is needed. Bedner and Maccrehan (2006) discovered two byproducts of known toxicity to humans resulting from the chlorination of the common pain reliever, acetaminophen. Phenolic compounds, such as acetaminophen, react to form monochloro-

and dichloro- intermediate products from the chlorine substitution at the ortho and para positions of the ring [Brezonik, 1994]. The antibiotic, sulfamethoxazole contains an aniline ring, which rearranges to ortho-chlorinated intermediates in the presence of free chlorine [Dodd and Huang, 2004]. Depending on oxidation conditions, finished water may contain compounds with confirmed toxicity to humans or compounds of unknown toxicity. Further chemical, toxicological, and risk assessment studies are needed to determine the potential for human and environmental risk.

TABLE 5. Byproduct Formation during Pharmaceutical Oxidation

Oxidant	Pharamceutical	Byproducts	Byproduct Toxicity	Reference
NaOCl	Acetaminophen	N-Acetyl-*p*-benzoquinone imine 1,4-Benzoquinone Chloro-4-acetamindophenol Dichloro-4-acetamidophenol	Toxic Toxic Unknown Unknown	Bedner & Maccrehan, 2006
NaOCl	Estrogen	Chloroacetic acids	Toxic	Korshin *et al.*, 2006
NaOCl	Sulfamethoxazole	3-amino-5-methylisoxazole N-chloro-*p*-benzoquinoneimine	Not Toxic Possibly	Dodd and Huang, 2004
Ozone	Amoxicillin	2-amino-2-(*p*-hydroxyphenyl) - acetic acid	Unknown	Andreozzi *et al.*, 2005
Ozone	Carbamazepine	1-(2-benzaldehyde)-4-hydro-(1H, 3 H))-quinazoline-2-one 1-(2-benzaldehyde)-(1 H, 3H)-quinazoline-2,4-dione 1-(2-benzoic acid)-(1 H, 3H)-quinazoline-2,4-dione	Unknown Unknown Unknown	McDowell *et al.*, 2005

h. Quantitative Structure-Property Relationships (QSPRs)

To study how each pharmaceutical behaves during water treatment would require a great deal of time and money. Since each pharmaceutical compound has different properties (see Appendix 2), and a large number of pharmaceuticals exist. The use of QSPRs for modeling contaminants reduces the amount of experimentation required to

understand contaminant fate and transport by making predictions based on a compound's structure and chemical properties (Papa and Gramatica, 2008; Lei and Snyder, 2007; Hu *et al.*, 2000; Dai *et al.*, 1999). One of the primary assumptions of QSPR modeling is that the chemical and physical properties of a compound depend on its structure (Dai *et al.*, 1999). Chemical properties and structures are then used to form mathematical relationships that allow for prediction of contaminant fate in the environment. Statistical testing and comparison with available data determine if the developed equations are predictive of reaction rates or removal mechanisms. An approach to QSPR modeling of compounds with similar structures usually involves molecular connectivity characteristics and quantum chemical descriptors (Dai *et al.*, 1999).

Different molecular properties or descriptors may be used to predict removal by separate treatment processes. For instance, common predictors used for correlation with oxidation rate constants are oxidation potentials, σ constants in the Hammett equation, and the energy of the highest occupied molecular orbital (ε_{HOMO}) (Hu *et al.*, 2000). To model contaminant removal by free chlorine and ozone, Lei and Snyder (2007) used various geometrical properties, solubility, Henry's law constant, hexadecane/gas partition coefficient, octanol/gas partition coefficient, and water/gas partition coefficient. The study also evaluated dipole moment, electron affinity, ionization potential, molecular weight, octanol-water partition coefficient, polarizability, and number and types of functional groups. Lei and Snyder (2007) were able to determine the most important parameters for a QSPR ozonation model based on statistical testing. They found contaminant removal correlated with weakly polar surface area, number of metabolites, π surface area, number of reactive functional groups and electron affinity, with the most

important parameter being weakly polar surface area. In the same study, Lei and Snyder found functional groups were significant in determining reactivity with chlorine. For a more detailed approach to kinetic modeling, refer to Crittenden's study on contaminant degradation by advanced oxidation processes (Crittenden *et al.*, 1999).

i. Conclusions

The oxidation of a pharmaceutical is affected by the pharmaceutical's functional groups, oxidant dose, water matrix, pH of the system, and the initial pharmaceutical concentration. Ozone is capable of oxidizing more functional groups than chlorine, and this is demonstrated through comparison of the studies involving pharmaceutical oxidation by ozone or chlorine. UV is only effective at oxidizing pharmaceuticals if hydrogen peroxide is used in combination. To avoid costly and time-consuming experiments, QSARs may be employed to predict the oxidation potential of a pharmaceutical.

Conclusions and Recommendations

Drinking water utilities may be required to treat source water for pharmaceuticals if federal or state agencies decide to regulate these compounds. Currently, there is some debate within the scientific community over the relevance of pharmaceuticals in drinking water and whether they pose significant risks to human health. A question that remains is, does the ability to detect substances in water mean that it is really a human health risk? Have humans been consuming water containing pharmaceuticals for decades without realizing? Humans have used medicines since ancient times, but only recently have

detection methods been developed. Instruments today are able to detect pharmaceuticals at ng/L concentrations, but without sufficient toxicology studies involving relevant mixtures of organic compounds present in drinking water, it is very difficult to assess the risk these compounds pose to humans.

Generalized predictions for the removal or transformation of pharmaceuticals in water and wastewater utilities cannot be made since their fate depends on multiple parameters. The efficiency of an oxidant and its effects on the fate of pharmaceuticals depend on the molecular structure of the pharmaceutical, concentration of pharmaceutical, pH of the water, oxidant dose, contact time, and water matrix. For example, some compounds exhibit greater reactivity at lower pH levels and some at higher pH levels. Conventional studies of fate, transformation and removal of pharmaceuticals are important, but it is not possible to evaluate each and every pharmaceutical under all treatment processes and all operating conditions. Modeling efforts that take into account the molecular structure of pharmaceuticals, such as quantitative structure activity relationships (QSARs), and kinetic parameters, may provide significant results in this area.

The focus of research can be narrowed to more persistent and/or unpredictable compounds. These include dilantin, diclofenac, carbamazepine, fluoxetine, and ibuprofen. More research on oxidation byproducts of endocrine disruptors is also needed.

Implementation of a risk assessment is necessary to determine acceptable levels of pharmaceuticals in environmental waters and drinking water. Once levels are determined, preventative measures may be taken to reduce or remove pharmaceuticals.

More research is needed on pharmaceutical transport as it applies to the land application of biosolids. Also, the increasing development of new pharmaceuticals requires a method for predicting and identifying compounds that are not currently being monitored, or a way to predict risk of new compounds before they enter environmental waters. It may also be possible to predict mixtures of drugs that occur by region based on drug prescriptions and sales. Furthermore, there is a need for research on long term effects on humans and organisms of exposure to multiple pharmaceuticals, metabolites, and oxidation byproducts.

CHAPTER 2

LABORATORY EXPERIMENTS

Summary

To investigate further the oxidation of pharmaceuticals, bench-scale experiments involving the chlorination of acetaminophen were conducted. In total, 23 experiments were performed at room temperature using sodium hypochlorite. The initial objectives of the experiments were to study how pH, molar ratio of oxidant to pharmaceutical, and initial pharmaceutical concentration effected degradation and the formation of an oxidation byproduct. Later objectives were to determine reaction mechanisms that dominate during the chlorination of acetaminophen by developing equations that model the reaction kinetics. Acetaminophen was chosen because it is commonly used, and has been documented to produce 1,4-benzoquinone during chlorination.

The first nine experiments were conducted at pH levels of 6.0, 7.5, and 9.0 and the molar ratio of chlorine to acetaminophen was varied from about 100 to 10,000. Results indicate that acetaminophen is highly susceptible to oxidation by free chlorine, but greatest degradation occurs at pH 9.0 and a molar ratio of 10,000. The production of 1,4-benzoquinone was also effected by pH and molar ration, with the maximum amount of 1,4-benzoquinone produced at pH 6.0 and a molar ratio of 1,275.

The next fourteen experiments were conducted at pH levels of 6.0, 7.5, 9.0 and 11.0 and the initial acetaminophen concentration was lowered from 2,000 μg/L to 200 and 1,000 μg/L. Overall, acetaminophen reacts with chlorine to the greatest extent

between pH 7.5 and 9.0, and the least at pH 6.0 and 11.0. Lowering the initial acetaminophen concentration reduced the amount of degradation that occurred.

Preliminary risk assessments were also performed using literature toxicity data which suggest a relatively low level of ecological and human health risk. Currently, research on this subject by another graduate student is using the data from the acetaminophen experiments to develop a set of equations that can be computer modeled to predict reaction rates at different conditions.

Primary Experiments

a. Abstract

The concern over pharmaceuticals and their toxicity in wastewater and drinking water has grown over the past decade. In this study, the common analgesic, acetaminophen, was chlorinated with sodium hypochlorite to determine the effects of pH and chlorine-to-pharmaceutical molar ratios on the degradation of acetaminophen and the formation of the toxic byproduct 1,4-benzoquinone. Reactions were studied for pH 6.0, 7.5 and 9.0 at average molar ratios of 106 ± 6, 1,417 ± 285, and 9,789 ± 1,430 over a period of 100 minutes. The degradation of acetaminophen and the formation of 1,4-benzoquinone were monitored using liquid chromatography tandem mass spectrometry (LC/MS/MS). Results indicate that acetaminophen is most reactive with free chlorine at pH 9.0 and least reactive at pH 6.0. As pH increased, degradation of acetaminophen also increased. The formation of 1,4-benzoquinone was also affected by pH and reached a maximum of 68.7% of the initial acetaminophen concentration when the pH was at 6.0, the molar ratio at 1,275, and after a contact time of 30 minutes. At all pH values the rate

of degradation of acetaminophen was slowest at a molar ratio of about 100, and the highest at a molar ratio of about 10,000.

b. Introduction

Acetaminophen, also known as paracetamol, is a very common over-the-counter analgesic used for fever, headaches and other minor pain. In 2002, the US produced 3.6 x 10^9 g of acetaminophen (Bedner and Maccrehan, 2006). In 1998, it was estimated that 3.2×10^9 tablets were consumed in the UK alone (Bessems and Vermeulen, 2001).

Acetaminophen has been detected in surface waters, wastewater, and drinking water. In the 2002 survey of 139 U.S. streams, Kolpin *et al.* detected acetaminophen in roughly 25% of the samples tested at a median concentration of 0.11 μg/L (2002). The median concentration of acetaminophen detected in surface waters is 0.055 ± 0.051 μg/L (Bound & Voulvoulis, 2006; Gros *et al.*, 2006; Stackelberg *et al.*, 2004; Wiegel *et al.*, 2004; Boyd & Furlong, 2002; Kolpin *et al.*, 2002). In raw wastewater, acetaminophen was detected at a median concentration of 48 ± 75 μg/L (Gomez *et al.*, 2007; Gros *et al.*, 2006; Han *et al.*, 2006). The median concentration of acetaminophen detected in finished wastewater is 0.76 ± 0.96 μg/L (Gomez *et al.*, 2007; Radjenovic *et al.*, 2007; Bound & Voulvoulis, 2006; Brun *et al.*, 2006; Gros *et al.*, 2006; Han *et al.*, 2006). Table 6 summarizes the occurrence of acetaminophen and the range concentrations detected in water samples.

TABLE 6. Acetaminophen Occurrence in the Environment (μg/L)

Surface Water	Raw Wastewater	Finished Wastewater	Finished Drinking Water
<0.1 (8)	0 - 0.26 (6)	0 - 6.0 (12)	Detected at
0.11 (10)	29 - 246 (1)	0 - 0.16 (6)	low ppb levels
0 - 0.026 (9)	0.13 - 26 (5)	1.9 (4)	(11)
0 - 0.25 (5)		0 - 4.3 (1)	
0.052 – 0.56 (3)		0 - 5.99 (5)	
0.007 – 0.066 (7)		0.048 - 0.418 (2)	
		0.079 – 0.22 (3)	

(1) Gomez *et al.*, 2007; (2) Radjenovic *et al.*, 2007; (3) Bound and Voulvoulis, 2006; (4) Brun *et al.*, 2006; (5) Gros *et al.*, 2006; (6) Han *et al.*, 2006; (7) Wiegel *et al.*, 2004; (8) Stackelberg *et al.*, 2004; (9) Boyd & Furlong, 2002; (10) Kolpin *et al.*, 2002; (11) Moll *et al.*, 2001; (12) Ternes *et al.*, 1998.

The widespread use of acetaminophen raises the concern of whether or not the compound persists during treatment of wastewater and drinking water. One of the most common treatment processes in water utilities is chlorination. Chlorine is a strong electrophile, and although chlorination targets the inactivation of microorganisms, chlorine may also react with chemical compounds present in water, such as acetaminophen and other pharmaceuticals. It has been shown that acetaminophen reacts with chlorine (Pinkston and Sedlak (2004); Glassmeyer and Shoemaker (2005); Westerhoff *et al.* (2005); Bedner and Maccrehan (2006); Gibs *et al.* (2007).

Bedner and Maccrehan (2006) reported that during chlorination of acetaminophen, 11 different chlorination products were observed, including the toxic substances N-acetyl-p-benzoquinone imine (NAPQI) and 1,4-benzoquinone. Although these toxicants may exist only at very low levels in drinking water and wastewater, their presence along with multiple other pharmaceuticals deserves further consideration.

The objective of this study is to investigate the effect of pH on oxidation of acetaminophen and production of 1,4-benzoquinone during chlorination, at three molar ratios representative of chlorine-to-acetaminophen molar ratios observed in water and wastewater utilities. The actual concentrations of acetaminophen that were tested are higher than those observed in drinking water supplies and wastewater effluents and therefore the chlorine chorine doses were also higher than that those applied in practice in water and wastewater utilities.

c. Methods

i.Chlorine to Acetaminophen Molar Ratios

Minimum and maximum acetaminophen concentrations detected in raw wastewater, finished wastewater, and raw drinking water (Table 6) were combined with typical chlorine doses (5-50 mg/L for wastewater and 0.1-10 for drinking water) in order to determine target molar ratios for the experiments. Based on the range of calculated molar ratios in Table 7, the target molar ratios chosen for the experiments were 100, 1,000, and 10,000.

TABLE 7. Expected Molar Ratios of Chlorine to Acetaminophen

Type of Water	Chlorine (mg/L)	Acetaminophen (µg/L)	Acetaminophen Source	Molar Ratios
Raw Drinking Water	0.1	0.007 – 0.56	Surface Waters	384 – 30, 416
	10	0.007 – 0.56	Surface Waters	38, 363 – 3,041,650
	0.1	0.048 – 6.0	Finished Wastewater	35 – 4,436
	10	0.048 – 6.0	Finished Wastewater	3,549 – 443, 574
Finished Wastewater	5	0.048 –6.0	Finished Wastewater	1,774 – 221, 787
	50	0.048 – 6.0	Finished Wastewater	17, 743 – 2,217,870
Raw Wastewater	5	0.13 – 246	Raw Wastewater	43 – 81, 891
	50	0.13 - 246	Raw Wastewater	433 – 818, 906

ii. Chlorination Experiments

The day prior to conducting each batch chlorination experiment, 6 beakers were filled with 1500 mL distilled water, covered and allowed to reach room temperature overnight. A chlorine stock was prepared by adding 25 mL of 4-6 % sodium hypochlorite to 500 mL DI water. This stock was adjusted to a pH of 6, 7.5 or 9 with hydrochloric acid or sodium hydroxide. The concentration of free chlorine in the stock was determined using the DPD Ferrous Titrimetric Method (4500-Cl F.). Next, ascorbic acid was weighed out (1-2 g per 1 L sample) and set aside. A sodium bicarbonate buffer stock was prepared by adding 4.2 g sodium bicarbonate to 500 mL DI water in a volumetric flask.

The experiment started with recording the temperature of the water in the 6 beakers. Then, 15 mL of sodium bicarbonate buffer stock was added to each beaker and the pH was adjusted to 6, 7.5, or 9. A predetermined amount of a 1000 mg/L acetaminophen solution was added to one beaker while stirring. Next, the appropriate amount of primary chlorine stock was added to the same beaker to achieve the desired

amount of primary chlorine stock was added to the same beaker to achieve the desired molar ratio of chlorine to acetaminophen. The solution was then transferred to a 1 L amber bottle, headspace free, and a timer was started. The remaining solution was divided into two 130-mL amber bottles, headspace free, and set aside. At the end of the desired contact time, ascorbic acid was added to the 1 L bottle to stop the reaction of chlorine with acetaminophen. Also, the chlorine residual, temperature, and pH were measured using the two 130 mL samples at the end of the contact time. The addition of pharmaceutical and chlorine was repeated for the remaining 5 beakers with contact times of 0, 3, 10, 30, and 100 minutes, and one replicate contact time randomly chosen for each batch. The 1 L samples were stored in a refrigerator at 4 degrees Celsius until analysis on a LC/MS/MS.

iii. Analytical Methods for Acetaminophen

Acetaminophen was purchased from Sigma Aldrich, >99% purity. The initial acetaminophen stock solution was prepared at 1000mg/L in methanol and the stock was then diluted to 10 mg/L. A standard curve of 100, 200, 500, 1,000, and 2,000 μg/L (μg/L) was used for measuring acetaminophen concentrations. Samples were analyzed using liquid chromatography/ tandem mass spectrometry (LC/MS/MS) which a Shimadzu Prominence Liquid Chromatograph (LC-20AD) with autosampler (SIL-20A) and an Applied Biosystems API 3200 tandem mass spectrometer. An electrospray ionization (ESI) interface was used as the ionization source. The retention time on a Phenomenex Luna C18 (150 x 4.60 mm 3 micron) column was from 6.7 to 7.3 minutes. For the mobile phases, eluent A was 0.1% formic acid/5% methanol/95% distilled water

and eluent B was 01% formic acid/5% distilled water/95% methanol. Isocratic flow was used at a rate of 0.10 mL/min eluent A, and 0.17 mL/min eluent B. A volume of 10 µL of sample was injected through the LC/MS/MS system. An ESI (+) MRM scan produced a precursor ion for acetaminophen at 152 amu and two product ions at 110 and 93 amu using unit resolution. The tandem MS parameters used for analysis of acetaminophen were as follows: curtain gas (CUR) of 12 psi, collision gas (CAD) of 2 psi, ionspray voltage of 5400 V, nebulizer gas (GS1) of 55 psi, auxiliary gas (GS2) of 40 psi, and temperature of probe at 650°C. The standard curves used for quantification of acetaminophen were linear with R-squared values of 0.995 or greater.

iv. Analytical Methods for 1, 4-Benzoquinone

1, 4-Benzoquinone was purchased from Acros Organics, >98% purity. A 1000 mg/L stock was made by adding 0.100g 1,4-benzoquinone to 100 mL distilled water. This stock was diluted to 10 mg/L, from which standard curve dilutions were made. The standard curves consisted of 50, 100, 200, 500, and 1000 µg/L. Samples were analyzed using liquid chromatography/ tandem mass spectrometry (LC/MS/MS). An atmospheric pressure chemical ionization (APCI) interface was used as the ionization source. The retention time on a Phenomenex Luna C18 (150 x 4.60 mm 3 micron) column was from 6.5 to 6.9 minutes. For the mobile phases, eluent A was 0.1% formic acid/5% methanol/95% distilled water and eluent B was 01% formic acid/5% distilled water/95% methanol. Isocratic flow was used at a rate of 0.10 mL/min eluent A, and 0.17 mL/min eluent B. 10 µL of sample was injected through the LC/MS/MS system. An APCI (-) ion scan produced a precursor ion of 108.1 amu. A product ion for 1,4-benzoquinone

could not be identified. The MS parameters used for analysis of benzoquinone were as follows: curtain gas (CUR) of 10 psi, collision gas (CAD) of -5 psi, nebulizer gas (GS1) of 40 psi, auxiliary gas of 50 psi, and the temperature of the probe at 675°C. The standard curves used to quantitate 1,4-benzoquinone were linear with R-squared values greater than 0.995.

d. Results and Discussion

i. Overall Results

Nine chlorination experiments were performed at five contact times each, at room temperature (21.8 ± 2.2 °C), using buffered water. For each experiment, one contact time was run in duplicate to confirm the accuracy of the results. The average relative standard deviation (defined as the standard deviation divided by the mean times 100) in acetaminophen concentrations between replicate samples was 9.52%. The average relative standard deviation in 1,4-benzoquinone concentrations between replicate samples was 2.98%.

The experiments were conducted at pH 6.0, 7.5 and 9.0, and at molar ratios of chlorine/acetaminophen of 106 ± 6, 1,417 ± 285, and 10,454 ± 1,430. Each experiment produced an acetaminophen degradation curve and a 1,4-benzoquinone formation curve. Examples of acetaminophen and 1,4-benzoquinone curves are shown in Figures 2, 3, and 4. At a free chlorine dose of 100 mg/L and at pH 6.0 with an initial acetaminophen concentration of 2150 µg/L (molar ratio = 99), acetaminophen was only slightly degraded, and 1,4-benzoquinone was produced at a slow rate (Figure 2). When the molar ratio of chlorine-to-acetaminophen was increased to 1,745 and the pH was kept at 6.0,

produced in comparison to the 99 molar ratio (Figure 3). When the molar ratio was further increased to 10,386 and the pH was kept at 6.0, acetaminophen was degraded rapidly over time and 1,4-benzoquinone was produced within the first three minutes of chlorination, after which 1,4-benzoquinone began to slowly degrade over time as well (Figure 4). At the highest chlorine to pharmaceutical molar ratio (Figure 4), more chlorine was available to attack both acetaminophen and 1,4-benzoquinone over time. Similar graphs were produced for all conditions. The graphs showed that degradation of acetaminophen and production of 1,4-benzoquinone were dependent on pH and chlorine-to-acetaminophen molar ratios.

Rate constants were estimated for the degradation of acetaminophen and the formation of 1,4-benzoquinone. For example, in Figure 3, the rate constant for acetaminophen degradation is -0.044 min^{-1} and the rate of formation of 1,4-benzoquinone (0-30 min) is 0.077 min^{-1} using an exponential equation. In Figure 4, the rate constant for degradation of acetaminophen increased to -0.595 min^{-1} and the rate of formation of 1,4-benzoquinone (3-100 min) is 0.045 min^{-1}. The rate constants of acetaminophen degradation were not equal to the rate constants of 1,4-benzoquinone formation signifying the possible formations of other intermediate products during the chlorination of acetaminophen. This study the focuses on the formation of 1,4-benzoquinone because it is known to be toxic.

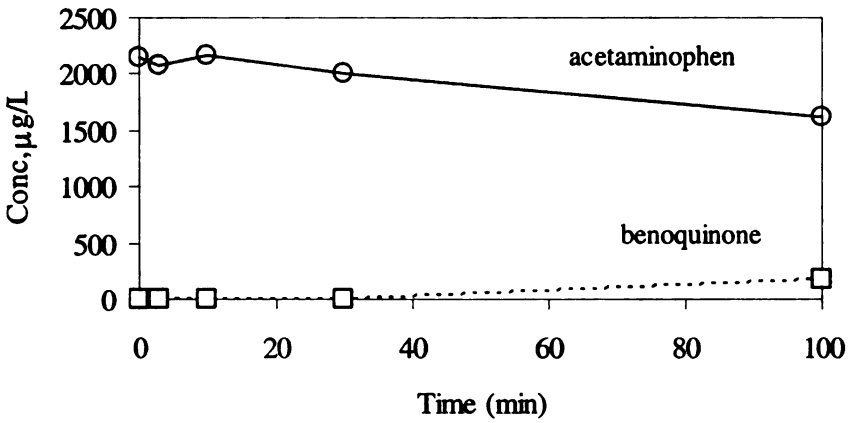


Figure 2. Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 100 mg/L, initial acetaminophen concentration of 2150 µg/L (molar ratio = 99).

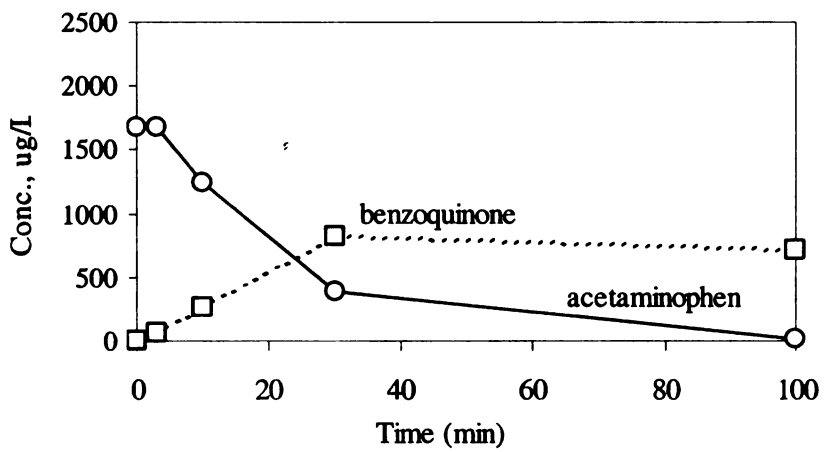


Figure 3. Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 1,000 mg/L, initial acetaminophen concentration of 1670 µg/L (molar ratio = 1,275).

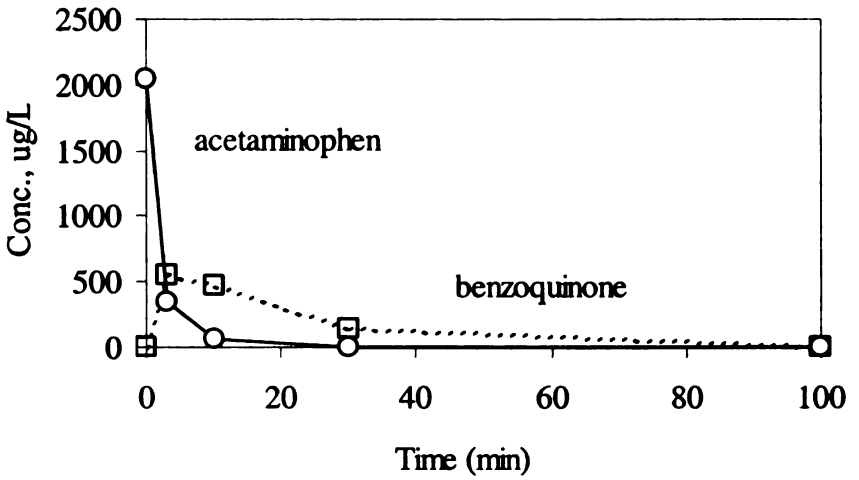


Figure 4. Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 10,000 mg/L, initial acetaminophen concentration of 2050 μg/L (molar ratio = 10,386).

ii. Effect of pH on Acetaminophen Degradation

Figures 5, 6, and 7 show the effect of pH on acetaminophen degradation at molar ratios of chlorine/acetaminophen of 106 ± 6, 1,417 ± 285, and 10,454 ± 1,430 respectively. In the figures, C/C_0 is the remaining concentration of acetaminophen after chlorination divided by the initial acetaminophen concentration. At the beginning of the experiments (0 min contact time), C/C_0 equals one since no reaction has occurred. As acetaminophen is allowed to react with chlorine, C/C_0 decreases since the concentration of acetaminophen decreases. Figure 5 reveals that at a molar ratio of 106 ± 6, the acetaminophen degradation rate was lowest at pH 6.0 and highest at pH 9.0. Estimated rate constants for the degradation of acetaminophen by free chlorine at an average molar ratio of 106 ± 6 are -0.00279, -0.0257, and -0.0577 min^{-1} for pH 6.0, 7.5, and 9.0,

respectively. For pH 6.0, 7.5, and 9.0, the percent degradation of acetaminophen after 100 minutes was 24.7, 87.0, and 94.8%, respectively.

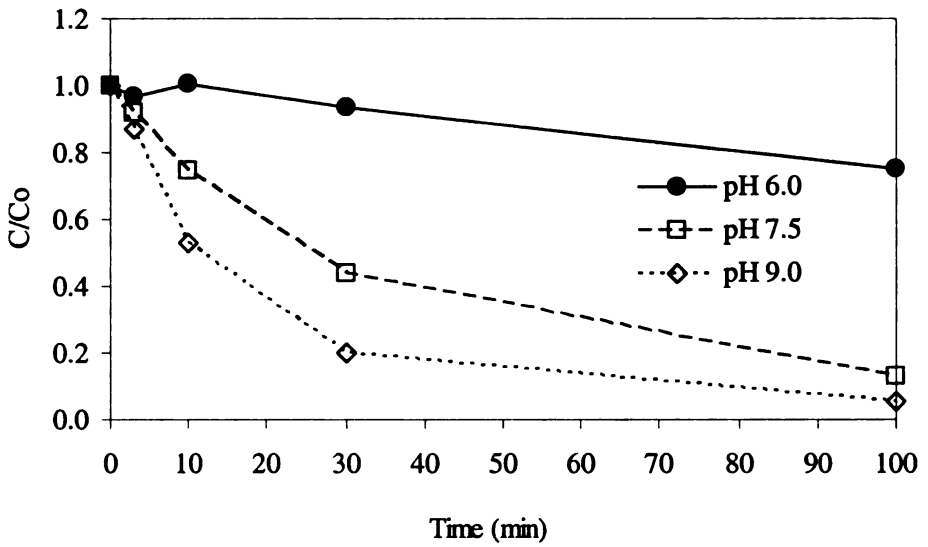


Figure 5. Effect of pH and contact time on acetaminophen for an average initial acetaminophen concentration (C_0) of 2013.33 ± 119.30 μg/L and 100 mg/L free chlorine dose (chlorine/acetaminophen molar ratio= 106 ± 6).

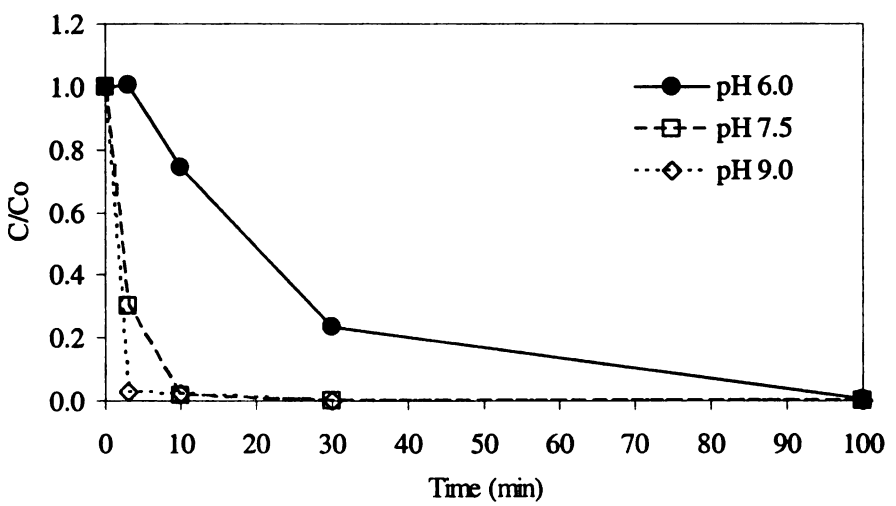


Figure 6. Effect of pH and contact time on acetaminophen degradation for an average initial acetaminophen concentration (C_0) of 1540 ± 278. 75 μg/L and 1,000 mg/L free chlorine dose (chlorine/acetaminophen molar ratio = 1,417 ± 285).

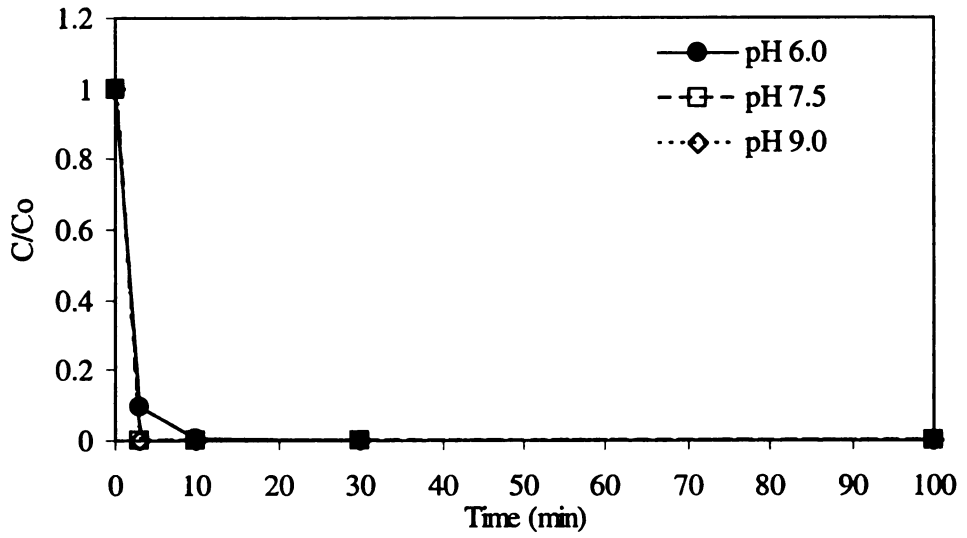


Figure 7. Effect of pH and contact time on acetaminophen degradation at an average initial acetaminophen concentration (C_0) of 2036.67 ± 270.25 μg/L and 10,000mg/L free chlorine dose (chlorine/acetaminophen molar ratio = 9789 ± 1430).

The same trends are observed for molar ratios of 1,417 ± 285 and 9,789 ± 1,430 (Figures 5 and 6). For an average molar ratio of 1,417 ± 285, the rate constants for acetaminophen degradation are -0.0435, -0.400, and -1.23 min^{-1} for pH 6.0, 7.5, and 9.0, respectively. The percent degradation of acetaminophen after 100 minutes was 99.2% for pH 6.0 and 100% for pH 7.5 and 9.0. For an average molar ratio of 9,789 ± 1,430, the estimated rate constant for pH 6.0 is -0.791 min^{-1} and -0.333 min^{-1} for pH 7.5 and 9.0. The percent degradation of acetaminophen after 100 minutes was 100% at all pH levels.

Free chlorine, which consists of hypochlorous acid (HOCl) and hypochlorite ion (OCl^-), has a pk_a of 7.5. Since the stronger oxidant, HOCl, is the dominant chlorine species at pH less than 7.5, it was expected that the acetaminophen degradation rate would be greater at pH 6.0 than at pH 9.0. At pH 9.0, the dominant chlorine species is

OCl^-, a weaker oxidant, so it was surprising to observe acetaminophen react to a greater extent at a higher pH. The results suggest that the acetaminophen molecule is more reactive with OCl^- than with HOCl.

Acetaminophen contains a phenolic functional group as well as an amide group. Amides do not react rapidly with free chlorine so the main site of the reaction is most likely the phenol. Pinkston and Sedlak (2004) stated that the main site of the reaction between acetaminophen and free chlorine would likely be between HOCl and the phenolic functional group. Depending on pH, two forms of acetaminophen are present, the protonated form (ROH) and the phenolate form (RO^-).

The ionization constant of acetaminophen is pk_a= 9.5 (Dasmalchi *et al.*, 1995). According to Pinkston and Sedlak (2004) in reactions with free chlorine, phenols tend to exhibit a maximum reaction rate between the pk_a of free chlorine (pk_a= 7.5) and that of the phenol. When determining rate constants, Pinkston and Sedlak did not consider reactions with OCl- because previous research proved substituted phenols do not react fast enough with hypochlorite. However, the results of this study indicate that acetaminophen reacts with hypochlorite at a faster rate than it reacts with hypochlorous acid.

iii. Effect of pH on Benzoquinone Production

Figures 8, 9, and 10 show the effect of pH on 1,4-benzoquinone formation at molar ratios of chlorine/acetaminophen of 106 ± 6, 1,417 ± 285, and 10,454 ± 1,430 respectively. In these figures, C_B/C_0 is the 1,4-benzoquinone molar concentration formed

from the chlorination of acetaminophen divided by the initial acetaminophen molar concentration. For an average molar ratio of 106 ± 6, 1,4-benzoquinone was produced up to 11.8, 50.5, and 24.4 % of the initial acetaminophen concentration for pH 6.0, 7.5, and 9.0, respectively. For an average molar ratio of 1,417 ± 285, 1,4-benzoquinone was produced up to 68.7, 54.3, and 33.1 % of the initial acetaminophen concentration for pH 6.0, 7.5, and 9.0, respectively. For an average molar ratio of 9,789 ± 1,430, 1,4-benzoquinone was only produced for pH 6.0 up to 38% of the initial acetaminophen concentration.

The effect of pH on 1,4-benzoquinone formation is more complex than the effect of pH on acetaminophen degradation since1,4-benzoquinone also reacts with free chlorine over time, resulting in its own degradation. Bedner and Maccrehan (2006) observed increasing 1,4–benzoquinone production over a 60 minute contact time with free chlorine at pH 7, reaching a maximum concentration of 2.5 μmol/L, or 25% of the initial acetaminophen concentration. This is lower than the 50% 1,4-benzoquinone production observed in this study for pH 7.5 and average molar ratio 106 ± 6. However, their study involved a much lower molar ratio of chlorine to acetaminophen (5.7) than those used in this study (minimum of 100).

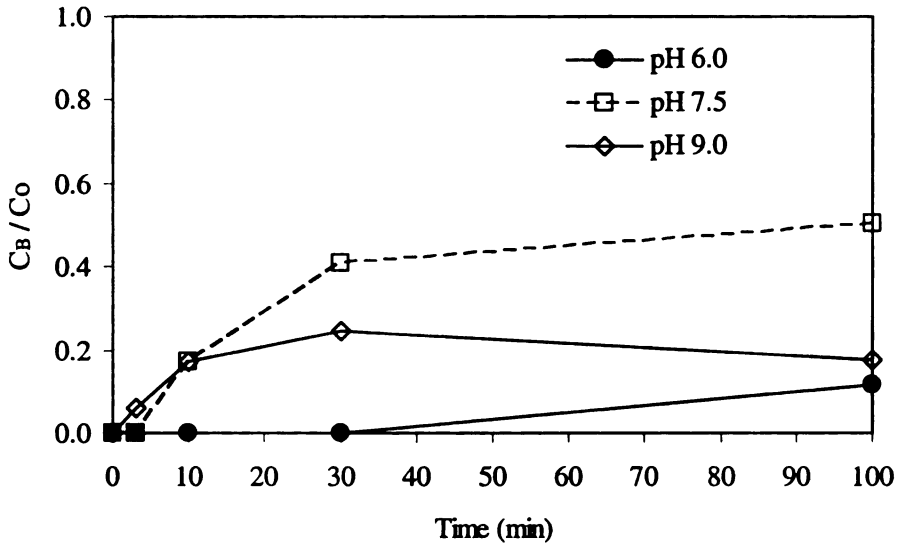


Figure 8. Effect of pH and contact time on 1,4-benzoqiunone formation (C_B) at an average initial acetaminophen concentration (C_0) of 2013.33 ± 119.30 μg/L and 100 mg/L free chlorine dose (chlorine/acetaminophen molar ratio = 106 ± 6).

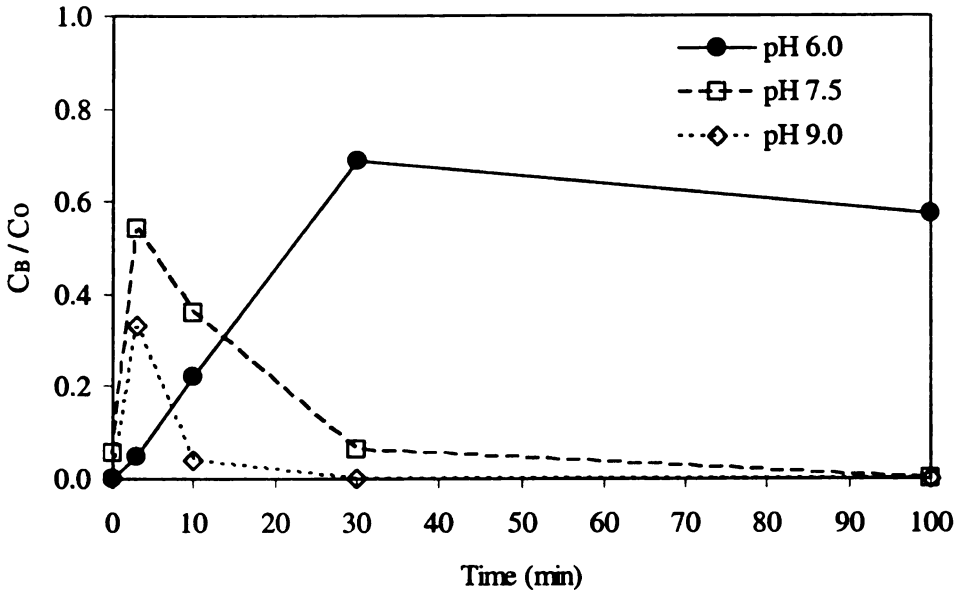


Figure 9. Effect of pH and contact time on 1,4-benzoquinone formation (C_B) at an average initial acetaminophen concentration (C_0) of 1540 ± 278. 75 μg/L and 1,000 mg/L free chlorine dose (chlorine/acetaminophen molar ratio = 1,417 ± 285).

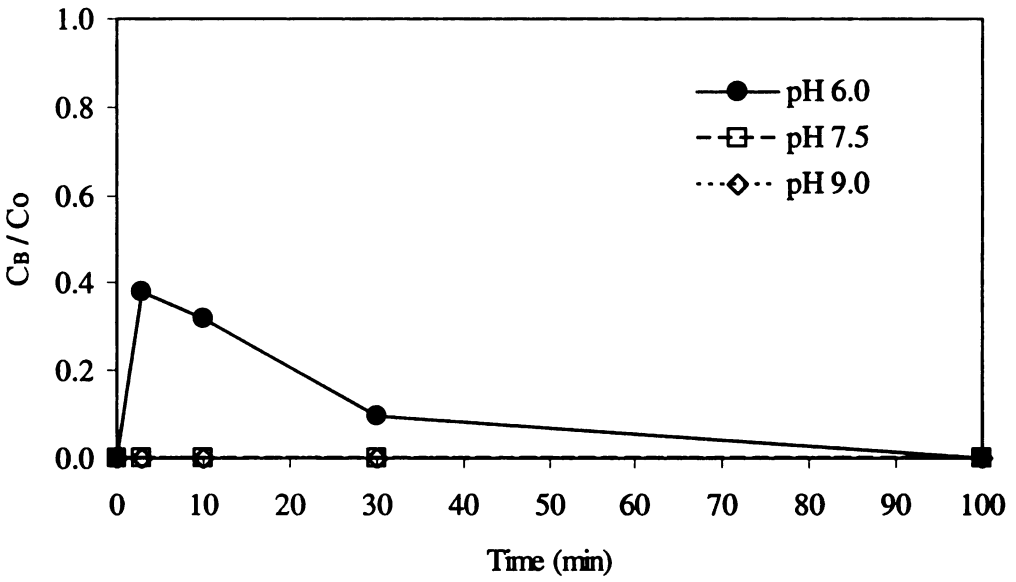


Figure 10. Effect of pH and contact time on 1,4-benzoquinone formation (C_B) at an average initial acetaminophen concentration (C_0) of 2036.67 ± 270. 25 μg/L and 10,000 mg/L free chlorine dose (chlorine/acetaminophen molar ratio = 9789 ± 1430).

iv. Effect of Molar Ratios

At all pH values the rate of degradation of acetaminophen was slowest at a molar ratio of about 100, and highest at a molar ratio of about 10,000. At pH 6.0 and a molar ratio of 100 acetaminophen is removed by only 25% after a 100 minute contact time, while at a molar ratio of 10,000, acetaminophen is removed entirely after 100 minutes. A similar trend was observed for pH 7.5 and 9.0.

At pH 6.0, 1,4-benzoquinone formation was greatest at the intermediate molar ratio of about 1,000. At pH 7.5 and 9.0, 1,4-benzoquinone formation increased steadily at the molar ratio of about 100. At the molar ratio of about 1,000, 1,4-benzoquinone was

produced rapidly after 3 minutes, but then quickly dropped. For the molar ratio of about 10,000, 1,4-benzoquinone was detected only at pH 6.0.

v. Comparison with Literature Data

The results of this study are compared with the results from previous acetaminophen chlorination work (Gibs *et al.*, 2007; Bedner and Maccrehan, 2006; Glassmeyer and Shoemaker, 2005; Westerhoff *et al.*, 2005; Pinkston and Sedlak, 2004). Table 8 summarizes experimental conditions and basic conclusions obtained from published studies and this study. Table 8 presents chemical dose, acetaminophen concentration, molar ratio, pH, and contact time conditions. All studies concluded that acetaminophen was degraded when reacting with chlorine.

One study identified chlorinated byproducts. The transformation of acetaminophen during chlorination into the toxic byproduct, 1,4-benzoquinone, first observed by Bedner and Maccrehan (2006), was confirmed in this study, and the effects of pH and molar ratios were further explored. Also, molar ratio conditions representing the whole range of ratios observed in water and wastewater engineering practices are only tested in this study.

Pinkston and Sedlak (2004) found that acetaminophen was significantly transformed by free chlorine with a half-life of 5.2 minutes. Rate constants were studied over a similar pH range, 5 - 10, and at a molar ratio of chlorine/acetaminophen of 30, which is lower than the molar ratios used in this study. Glassmeyer and Shoemaker (2005) found that acetaminophen showed definite signs of chlorination when acetaminophen-spiked water was dosed with 28.75 mg/L of free chlorine and allowed to

react for 48 hours. The primary product of the reaction was a singly chlorinated acetaminophen molecule, but other chlorinated products were also observed, and some of the acetaminophen did not react. Glassmeyer and Shoemaker (2005) did not attempt to test the effects of pH or molar ratio.

TABLE 8. Summary of Results and Comparison with Literature Data Involving the Reaction of Acetaminophen with Sodium Hypochlorite

Chemical Dose	Acetaminophen Concentration	Molar Ratio	pH	Contact Time	Acetaminophen Degradation	1,4-Benzoquinone Formation	Reference
57 µmol/L	1 µmol/L 10 µmol/L	57 5.7	7.0	2-90 min	88% of acetaminophen (10 µmol/L initial) was transformed in 1 hour	1,4-benzoquinone accounted for 25% of the initial acetaminophen concentration after 1 hour.	Bedner & Maccrehan, (2006)
405 µmol/L	NA	NA	NA	48 hrs	Definite signs of chlorination	N/A	Glassmeyer & Shoemaker, (2005)
53.5 µmol/L 49.3 µmol/L	1.98 µmol/L	27 25	5.5	24 hr.	>95% oxidized	N/A	Westerhoff *et al.*, (2005)
600 µmol/L	20 µmol/L	30	5-10	5 days	Acetaminophen was significatly transformed	N/A	Pinkston and Sedlak, (2004)
16.9 µmol/L	0.0033 µmol/L	5121	8	1-10 days	Completely degraded after 1 day in contact with free chlorine	N/A	Gibs *et al.*, (2007)
1,408.45 µmol/L	14.22 µmol/L	99	6	0-100 min	Acetaminophen was removed by 6.51 and 24.7% after 30 and 100 min, respectively.	Benzoquinone was produced up to 11.8% of the initial acetaminophen after 100 min, no amount was detected before 100 min	This study
1,408.45 µmol/L	12.97 µmol/L	109	7.5	0-100 min	Acetaminophen was removed by 56.4 and 87.0% after 30 and 100 min, respectively.	Benzoquinone was produced up to 41.1 and 50.5% of the initial acetaminophen after 30 and 100 min, respectively.	This study
1,408.45 µmol/L	12.77 µmol/L	110	9	0-100 min	Acetaminophen was removed by 80.0 and 94.8% after 30 and 100 min, respectively.	Benzoquinone was produced up to 24.4 and 17.7% of the initial acetaminophen after 30 and 100 min, respectively.	This study
14,084.5 µmol/L	11.05 µmol/L	1,275	6	0-100 min	Acetaminophen was removed by 76.8 and 99.2% after 30 and 100 min, respectively.	Benzoquinone was produced up to 68.7 and 57.3% of the initial acetaminophen after 30 and 100 min, respectively.	This study
14,084.5 µmol/L	8.07 µmol/L	1,745	7.5	0-100 min	Acetaminophen was removed by 100% after 30 and 100 min.	Benzoquinone was produced up to 54.3% of the initial acetaminophen after 3 min, no amount was detected after 100 min.	This study
14,084.5 µmol/L	11.44 µmol/L	1,231	9	0-100 min	Acetaminophen was removed by 100% after 30 and 100 min.	Benzoquinone was produced up to 33.1% of the initial acetaminophen after 3 min., no amount was detected after 100 min.	This study
140,845 µmol/L	13.56 µmol/L	10,386	6	0-100 min	Acetaminophen was removed by 100% after 30 and 100 min.	Benzoquinone was produced up to 38.0% of the initial acetaminophen after 3 min., no amount was detected after 100 min.	This study
140,845 µmol/L	15.21 µmol/L	9,257	7.5	0-100 min	Acetaminophen was removed by 100% after 30 and 100 min.	Benzoquinone was not detected in any of the samples.	This study
140,845 µmol/L	11.51 µmol/L	12,237	9	0-100 min	Acetaminophen was removed by 100% after 30 and 100 min.	Benzoquinone was not detected in any of the samples.	This study

Westerhoff et al. (2005) added 3.5-3.8 mg/L free chlorine to surface water spiked with 1.98 μmol/L of acetaminophen at pH 5.5. After a 24 hour contact time, greater than 95% of acetaminophen was oxidized, indicating a high degree of reactivity with chlorine. The effects of pH and molar ratio were not tested in this study either, but different water matrices were studied.

Bedner and Maccrehan (2006) monitored the reaction of free chlorine with acetaminophen over 90 minutes at pH 7 and at molar ratios of 5.7 and 57. At an initial concentration of 1 μmol/L, acetaminophen reacted to a greater extent than at an initial concentration of 10 μmol/L due to the greater molar ratio of free chlorine to acetaminophen (molar ratio of 57) at the lower initial concentration. Similarly, in this study degradation of acetaminophen increased with increasing chlorine-to-acetaminophen molar ratios. In this study a wide range of molar ratios was evaluated. Bedner and Maccrehan also found that acetaminophen exhibited a high degree of reactivity with hypochlorite at a neutral pH.

Gibs *et al.* (2007) analyzed chlorinated samples of drinking water over 10 days and found that acetaminophen reacted completely with residual chlorine within one day at pH 8 and at a molar ratio of free chlorine to acetaminophen of 5121.

e. Conclusions

This study found that acetaminophen was degraded and transformed by free chlorine. The rate of degradation was affected by pH and chlorine/acetaminophen molar ratio. The highest degradation rates were observed at pH 9.0, and the lowest degradation rates were observed at pH 6.0. Acetaminophen degradation was also greatest at molar

ratios of approximately 10,000, and lowest at molar ratios of approximately 100. Acetaminophen was transformed by free chlorine to form the toxic byproduct, 1,4 – benzoquinone. The formation of 1,4 – benzoquinone was also affected by pH, and chlorine/acetaminophen molar ratio. Depending on the applied molar ratios, up to 68.7 % of acetaminophen may be converted into the toxic byproduct, 1,4- benzoquinone. The effects of varying pH and chlorine/acetaminophen molar ratios are significant in drinking water and wastewater treatment plants since those parameters can be slightly modified by water utility professionals. Water chlorination conditions affect the potential of acetaminophen transformation to toxic 1,4-benzoquinone and further affect the potential of human exposure to toxic substances.

Additional Experiments and Continuing Research

a. Additional Experiments

For the additional 14 experiments, initial acetaminophen concentrations of 200, 1,000, and 2,000μg/L were tested. These concentrations are not typically observed in environmental waters, but were necessary to quantify the formation of 1,4-benzoquinone. Therefore, chlorine doses used in the experiments are also greater than those typical of water treatment plants. To achieve the desired molar ratios of chlorine to acetaminophen, chlorine doses of 10, 50, 100, 500, 1,000, and 10,000 were applied. The pH levels tested were 6, 7.5, 9, and 11. Table 9 shows the conditions tested in each experiment. Chlorination experiments were conducted in buffered, distilled water using 1.5 L beakers (method details are given in Xagoraraki *et al.*, 2008).

TABLE 9. Conditions tested in this study.

Initial Acetaminophen Concentration (μg/L)	Chlorine Dose (mg/L)	Molar Ratio Chlorine/Acetaminophen	pH
188 ± 42	10 100 1,000	99.5 ± 3.04 995 ± 121 15,705 ± 489	6, 7.5, 9 6, 7.5, 9 6, 7.5, 9
908 ± 158	50 500	134 1,044	7.5 6
1,950 ± 352	100 1,000 10,000	107 ± 5 1,325 ± 285 9,722 ± 1,727	11 (6, 7.5, 9) 11 (6, 7.5, 9) 11 (6, 7.5, 9)

Note: pH levels in parentheses were tested in previous study, Xagoraraki *et al.*, 2008.

b. Analytical Procedures

Samples were analyzed using liquid chromatography/tandem mass spectrometry (LC/MS/MS). The instrumentation consisted of a Shimadzu Prominence Liquid Chromatograph (LC-20AD) with autosampler (SIL-20A) and an Applied Biosystems API 3200 tandem mass spectrometer. A Phenomenex Luna C18 (150 x 4.60 mm 3 micron) column was used. Refer to previous publication for specific analytical method details (Xagoraraki *et al.*, 2008).

c. Determination of pk_a

Knowledge of the acid dissociation constant, or pk_a, of acetaminophen is important for predicting speciation at different pH levels. Since previous studies on the determination of acetaminophen pk_a could not be obtained, the reported pk_a of 9.38 was verified by spectrophotometric method. This method consisted of preparing two 100 ppm solutions of acetaminophen in distilled water. One solution was adjusted to pH 3 with hydrochloric acid and the other solution was adjusted to pH 12 with sodium

hydroxide. Each solution was diluted to 1, 5, 10, and 25 ppm, and absorbance measurements for each dilution were obtained at wavelengths (λ) 241 and 255.5 nm. A plot of absorbance versus acetaminophen concentration produced linear absorbance curves for each pH, and the slopes of the lines (a_1, a_2) were used to calculate ratios of ROH (protonated acetaminophen) and RO- (unprotonated acetaminophen) at known pH values. The mixture composition of ROH and RO- was calculated from measured absorbancies (A_1, A_2) at λ_1=241 nm and λ_2=255.5 nm,

$$A_1 = a_1(ROH) + a_1(RO-) \quad (1)$$

$$A_2 = a_2(ROH) + a_2(RO-) \quad (2)$$

For acetaminophen solutions ranging from pH 7-11, a pH 9.47 solution resulted in approximately equal amounts of ROH and RO-, verifying the reported pk_a of 9.38 (Dasmalchi *et al.*, 1995).

d. Overall Results

Fourteen chlorination experiments were performed at five contact times each, at room temperature using buffered, distilled water. Each experiment included a duplicate contact time to confirm the accuracy of the results. The average relative standard deviation, defined as the standard deviation divided by the mean times 100, in acetaminophen concentrations between replicate samples was 10.9%. The average relative standard deviation in 1,4-benzoquinone concentrations between replicate samples

was 28.3%. This value is high due to the low concentrations of 1,4-benzoquinone produced and the poor sensitivity of the instrumentation at low concentrations. Furthermore, only five of the fourteen experiments could be analyzed for 1,4-benzoquinone due to the low initial acetaminophen concentration of the other nine experiments. For initial and final temperature, the average relative standard deviation between replicates was 0.2 and 0.3%, respectively. For initial and final pH, the average relative standard deviation between replicates was 0.5 and 0.7%, respectively. The average relative standard deviation for final measured chlorine in replicates was 16%, indicating some variability in the rate of chlorine consumption during the experiments.

One experiment was performed without the addition of acetaminophen at pH 7.5 and chlorine dose 1,000 mg/L. This was to ensure that chlorine was not reacting with any other compounds than acetaminophen during the original experiments. Chlorine was added to each beaker at a dose of 1,000 mg/L, and the pH was adjusted to 7.5. Samples were collected after 0, 3, 10, 30, and 100 minutes and analyzed for residual chlorine concentration. The experiment where no acetaminophen was added resulted in no reduction of residual chlorine, indicating that chlorine was not reacting with any other compounds.

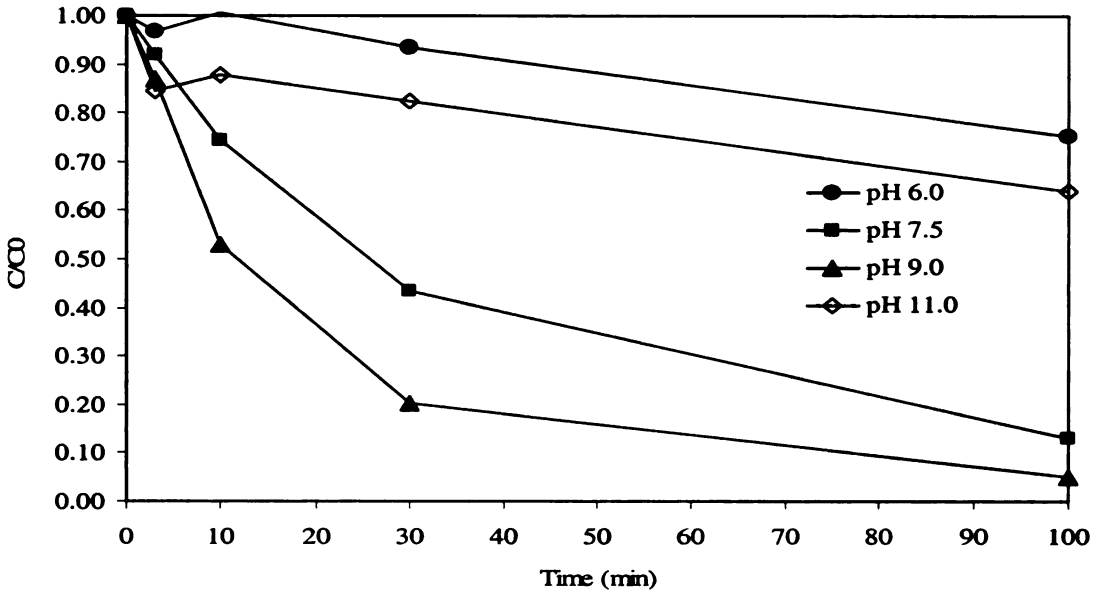
The experiments were conducted at pH 6.0, 7.5, 9.0, and 11.0. At pH 11.0, molar ratios of 109, 1,049, and 8,035 were tested only at an initial acetaminophen concentration of 2,000 μg/L, to supplement previous experiments (see Xagoraraki *et al.*, 2008). At an initial acetaminophen concentration of 200 μg/L, molar ratios of 99.5 ± 3, 995 ± 121, and 15,705 ± 489 were tested for pH 6.0, 7.5, and 9.0. Two experiments were performed at an initial acetaminophen concentration of 1,000 μg/L. One was performed at pH 7.5,

molar ratio 134, and the other at pH 6.0, molar ratio 1,044. Each experiment produced an acetaminophen degradation curve and a 1,4-benzoquinone formation/degradation curve. 1,4-benzoquinone is targeted in this study since it is a toxic compound.

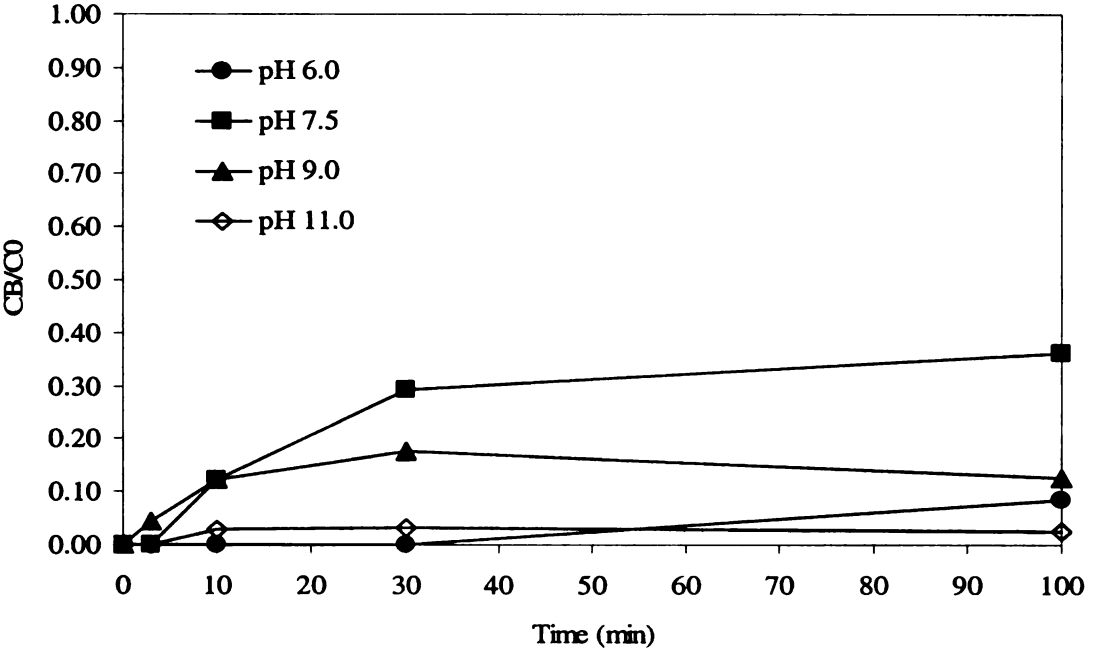
e. Effect of pH

Figure 11a shows the effect of pH on acetaminophen degradation at an average molar ratio of chlorine to acetaminophen of 107 ± 5. In the figure, C/C_0 is the concentration of acetaminophen after each contact time with free chlorine divided by the initial acetaminophen concentration. Before free chlorine is added, C/C_0 equals one since no reaction has occurred. Figure 11a shows that acetaminophen degradation is faster at pH 7.5 and 9.0 than at pH 6.0 and 11.0.

Figure 11b shows the effect of pH on detected 1,4-benzoquinone concentration at an average molar ratio of chlorine to acetaminophen of 107 ± 5. In the figure, C_B/C_0 is the concentration of 1,4-benzoquinone after each contact time of acetaminophen with free chlorine divided by the initial acetaminophen concentration. Before free chlorine is added C_B/C_0 equals zero since no 1,4-benzoquinone has formed. Figure 11b shows that the highest 1,4-benzoquinone concentration is detected at pH 9.



(a)



(b)

FIGURE 11. (a) Effect of pH on acetaminophen degradation and (b) 1,4-benzoquinone formation for an average initial acetaminophen concentration of 13.2 ± 0.68 μmol/L (average molar ratio 107 ± 5).

Different species of free chlorine and acetaminophen are expected to be dominant in solution at different pH levels. Free chlorine, which consists of hypochlorous acid (HOCl) and hypochlorite ion (OCl-), has a pk_a of 7.5. Therefore, at pH 6.0 it is assumed that majority of chlorine is in HOCl form, and at pH 9.0 and 11.0 the majority of chlorine is in OCl- form. Similarly, acetaminophen consists of a protonated form (ROH) and an unprotonated form (RO-) that are in equilibrium at the pk_a of 9.4. Therefore, it is assumed that at pH 6.0 and 7.5 the majority of acetaminophen is in the ROH form, and at pH 11.0 the majority of acetaminophen is in the RO- form. Table 10 shows which species of acetaminophen and chlorine are dominant at the pH levels studied. The lowest extent of acetaminophen degradation is observed at pH 6.0, when HOCl reacts with ROH, and at pH 11, when OCl- reacts with RO-. The highest degradation is observed at pH 7.5 and pH 9.0, when different forms of acetaminophen and chlorine coexist. Similar results are observed at all molar ratios.

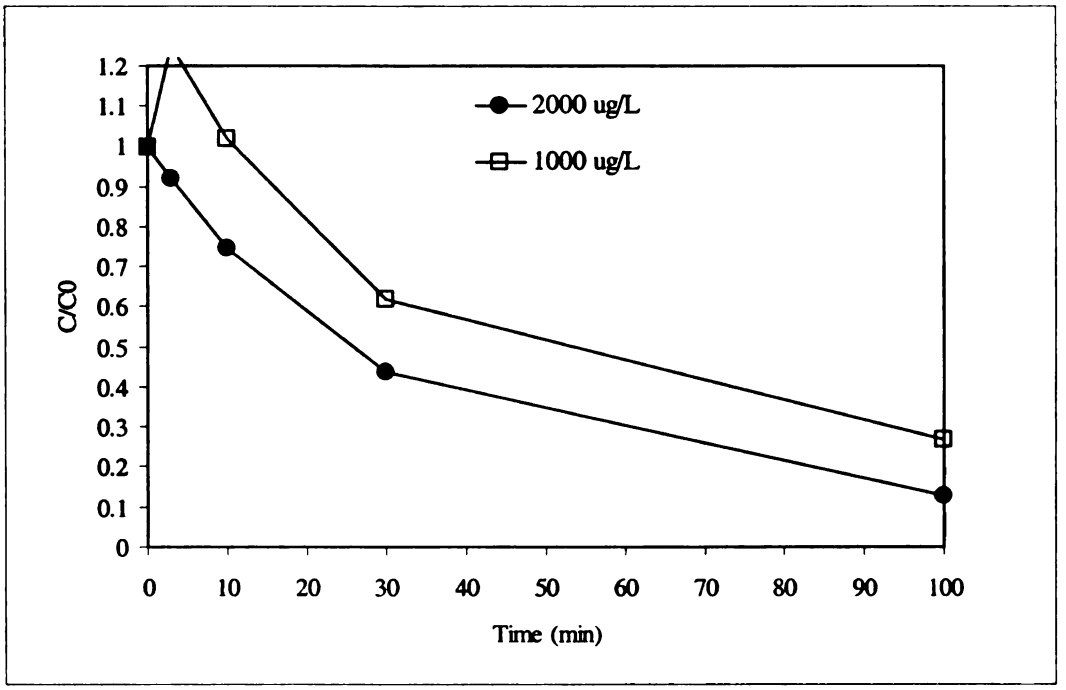
TABLE 10. Acetaminophen and chlorine species composition at each pH tested.

pH	6.0	7.5	9.0	11.0
Dominant Chlorine Species	HOCl	(HOCl + OCl-)	OCl-	OCl-
Dominant Acetaminophen Species	ROH	ROH	(ROH + RO-)	RO-
Pseudo first-order Reaction Rate*	0.044 min^{-1}	0.4 min^{-1}	1.23 min^{-1}	0.06 min^{-1}

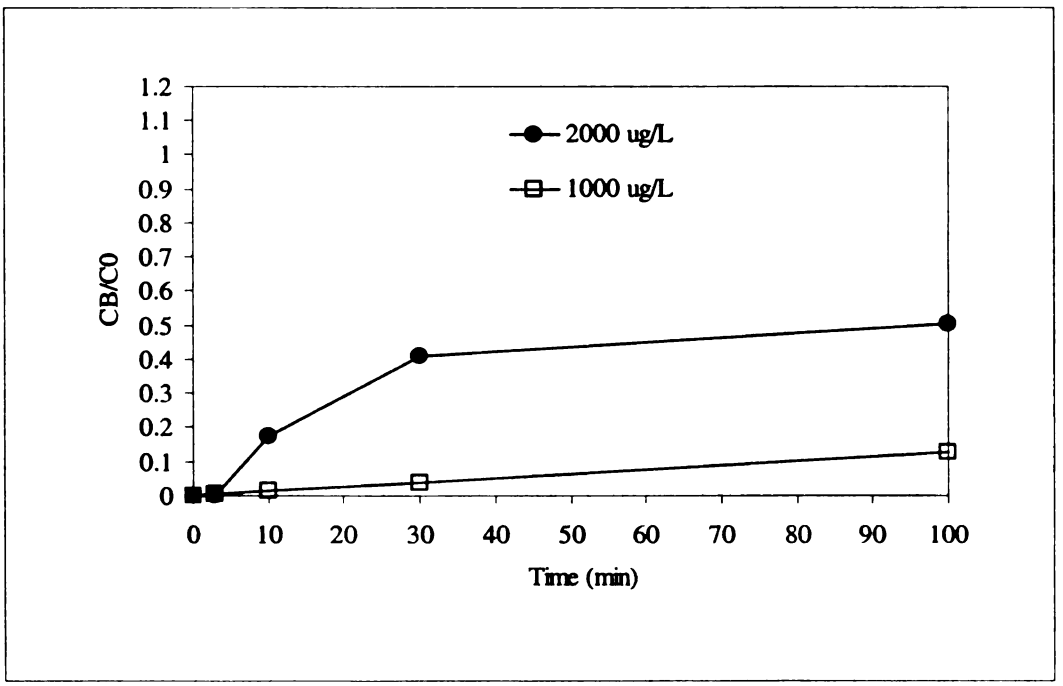
*Reaction rates are for experiments at molar ratio 1,325 ± 285 and initial acetaminophen concentration of 1,663 ± 334 μg/L.

f. Effect of Initial Concentration

Figures 12 and 13 show the effect of initial acetaminophen concentration on acetaminophen degradation and 1,4-benzoquinone formation over contact time with free chlorine. Figures 12a and 13a show that slightly less degradation of acetaminophen occurs at the lower initial concentration of 1,000 μg/L than at 2,000 μg/L. Figures 12b and 13b show that more 1,4-benzoquinone is formed at the higher initial acetaminophen concentration of 2,000 μg/L than at 1,000 μg/L.

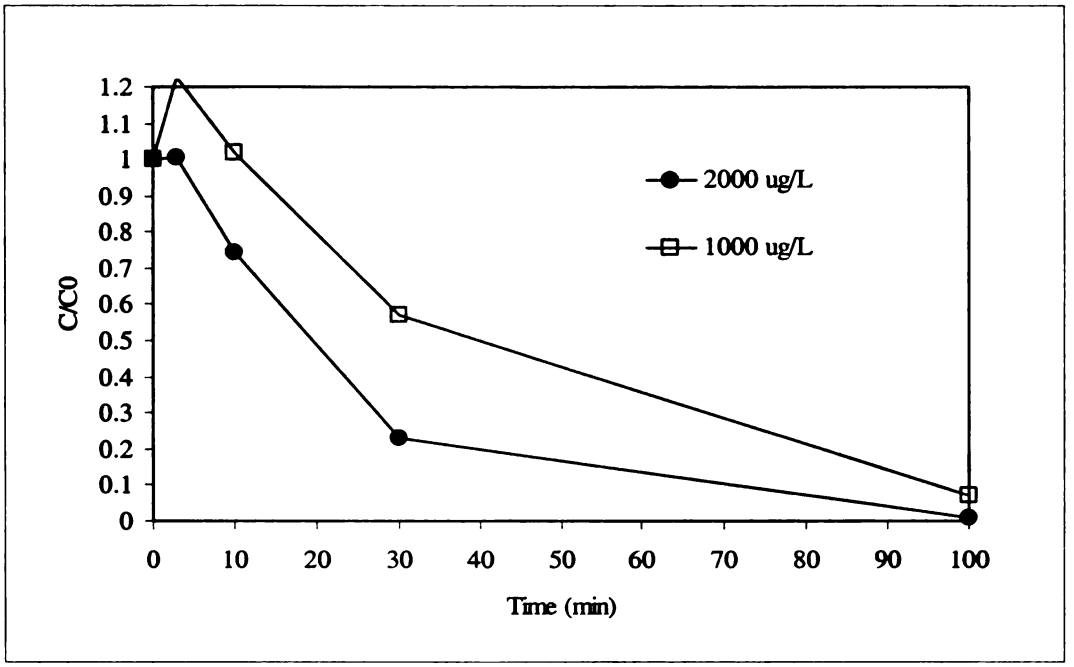


(a)

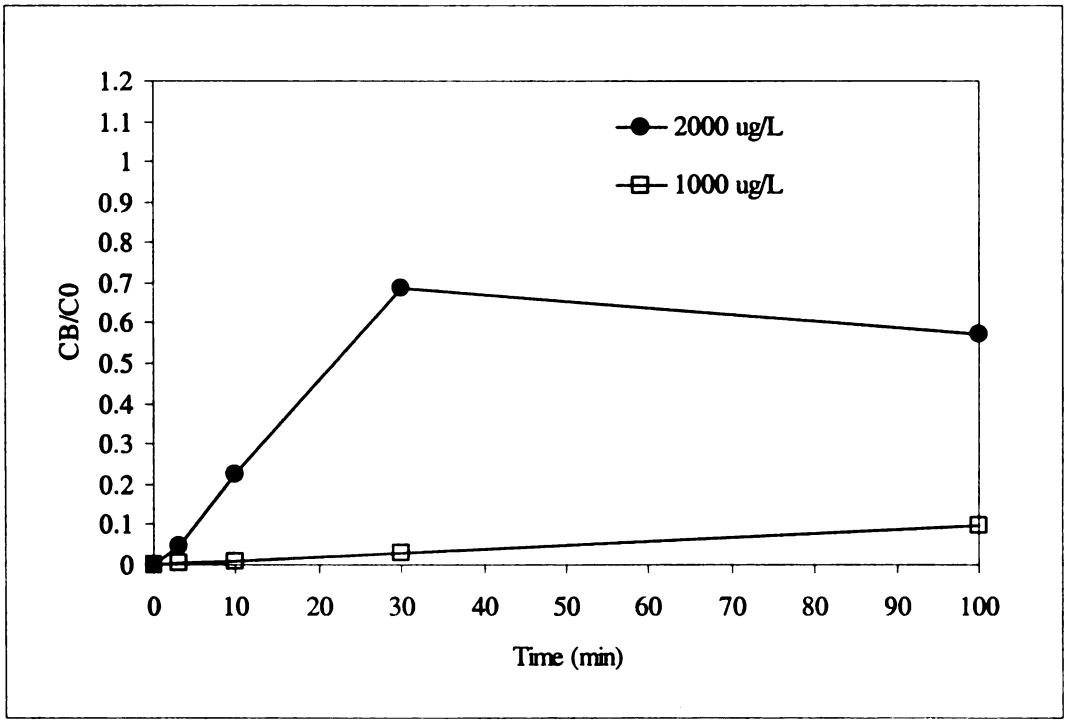


(b)

FIGURE 12. (a) Effect of initial acetaminophen concentration on acetaminophen degradation and (b) 1,4-benzoquinone formation (average molar ratio 121 ± 18, pH 7.5).



(a)



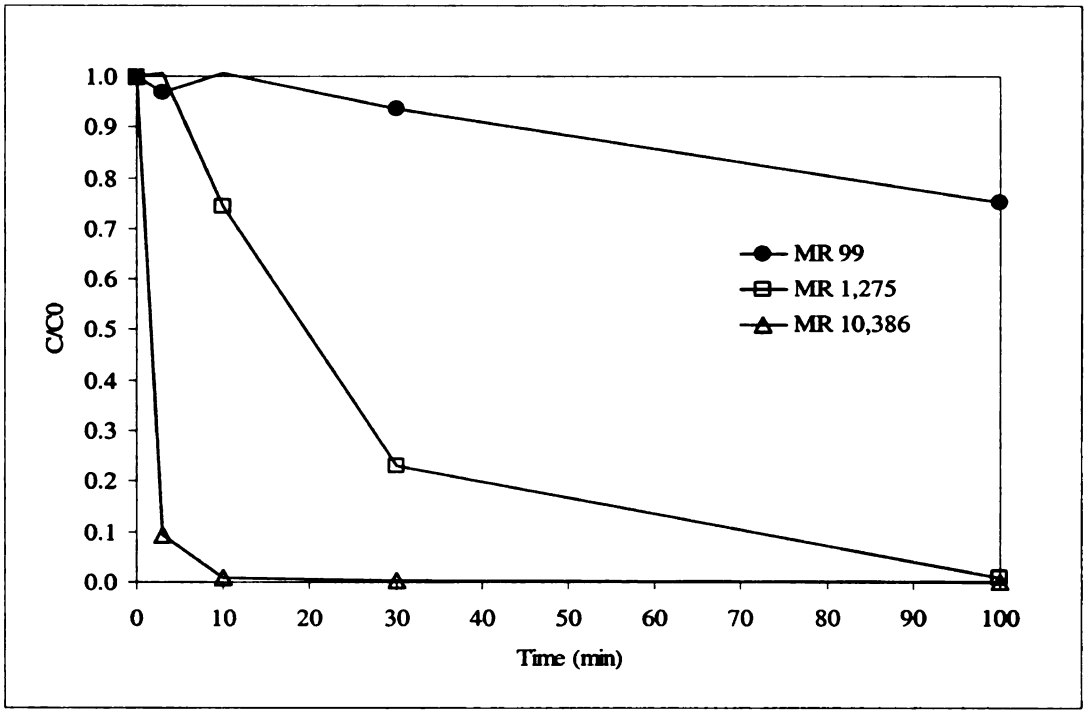
(b)

FIGURE 13. (a) Effect of initial acetaminophen concentration on acetaminophen degradation and (b) 1,4-benzoquinone formation (average molar ratio 1,159 ± 164, pH 6.0).

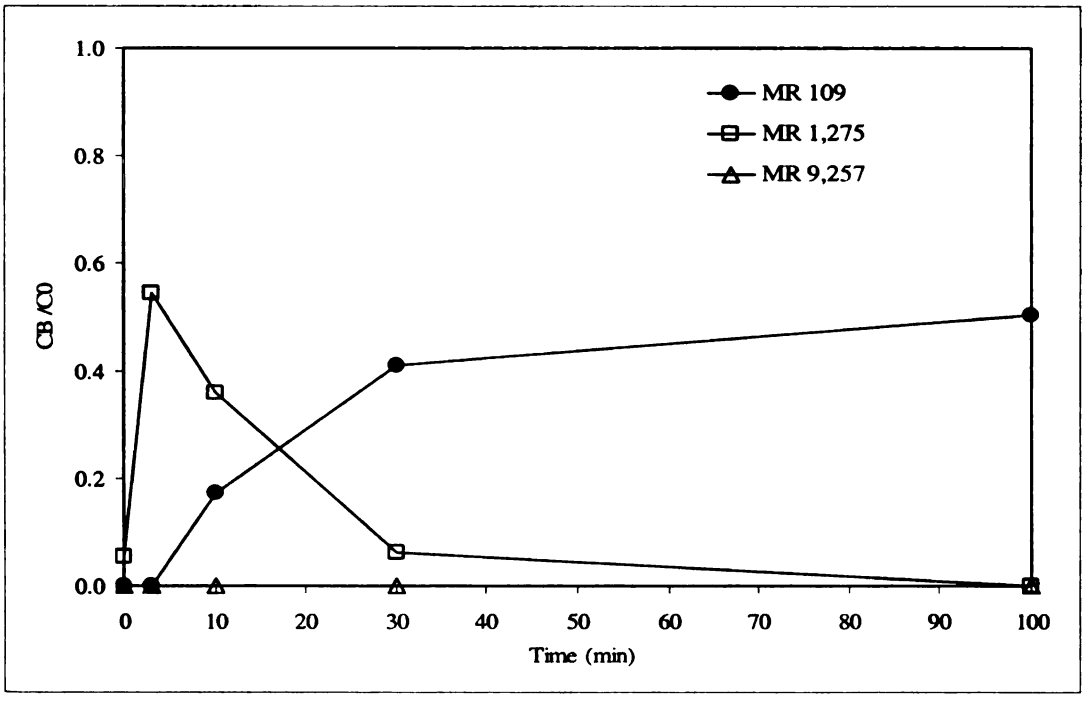
g. Effect of Molar Ratio and Contact Time

Acetaminophen underwent greater degradation with increasing oxidant dose and increasing contact time with free chlorine. Figure 14a shows the effect of molar ratio of chlorine to acetaminophen on acetaminophen degradation at pH 6.0. Degradation increases with increasing molar ratio. Similar trends are observed at all pH values.

Figure 14b shows the effect of molar ratio of chlorine to acetaminophen on 1,4-benzoquinone formation at pH 6.0. At the lower molar ratio of 109, 1,4-benzoquinone formed after ten minutes then remained at a steady concentration. When the molar ratio increased to 1,049, 1,4-benzoquinone peaked at three minutes then began to degrade with longer contact time with free chlorine. At the highest molar ratio of 8,035, a small amount of 1,4-benzoquinone formed after three minutes, after which none could be detected.



(a)



(b)

FIGURE 14. Effect of molar ratio on (a) acetaminophen degradation and (b) 1,4-benzoquinone formation for an average initial acetaminophen concentration (C_0) of 12.9 ± 1.7 μmol/L (pH 6).

The greatest amount of 1,4-benzoquinone formed at pH 6, molar ratio 1,275, with 69% of acetaminophen converted to 1,4-benzoquinone (initial acetaminophen concentration 2,000μg/L). At pH 7.5, molar ratio 109 and molar ratio 1,745, 50.5% and 54.3% of acetaminophen was converted to 1,4-benzoquinone, respectively. Significant amounts of 1,4-benzoquinone also formed at pH 6.0, molar ratio 10,386, with 38% of acetaminophen converted to 1,4-benzoquinone, and at pH 9, molar ratio 1,231, where 33.1% was converted.

h. Continuing Research

The experimental results are being used to evaluate the reaction rate order of the reaction between acetaminophen and chlorine. The reaction mechanisms are being investigated by calculating reaction rates from a set of equations. The equations are being evaluated using a computer modeling program. Also, these reaction rates are being compared to those reported in previous literature for both chlorination and oxidation studies. Preliminary results suggest that the reaction is second-order, and that ozonation is expected to oxidize acetaminophen more efficiently than chlorination.

Conclusions

The concern over pharmaceuticals in drinking water is spurring research at all levels of drinking water treatment processes. The above reported experiments evaluated the chlorination of acetaminophen by free chlorine. Results indicate at which conditions greatest degradation of acetaminophen will occur, as well as the conditions at which the greatest amount of 1,4-benzoquinone may be produced as a byproduct. Although the

experiments only evaluated one compound, the research may be applied to other compounds in terms of the effect pH, molar ratios, and initial pharmaceutical concentration have on a pharmaceutical. Furthermore, the continuing research on reaction rates and mechanisms may be used as a model for investigating other pharmaceuticals.

Appendix 1. Pharmaceutical Chemical Properties*

Pharmaceutical	Formula	Molecular Weight (g/mol)	Log K_{OW}	pK_a
Acetaminophen	C8H9NO2	151.2	0.46	9.4
Atenolol	C14H22N2O3	266.3	0.5	-
Carbadox	C17H15N3O6	262.2	1.3	-
Carbamazepine	C15H12N2O	236.3	2.5	<2
Diazepam	C16H13ClN2O	284.8	2.9	3.4
Diclofenac	C14H11Cl2NO2	296.2	3.9	4.2
Dilantin	C15H12N2O2	252.3	2.2	8.3
Erythromycin	C37H67NO13	734	3.1	8.8
Estradiol	C18H24O2	272.2	4.0	10.4
Estriol	C18H24O2	288.4	2.5	10.4
Estrone	C18H22O2	270.2	3.1	10.3
Ethinylestradiol	C20H24O2	296.2	4.7	10.5
Fluoxetine	C17H18F3NO	309.3	4.6	-
Gemfibrozil	C15H22O3	250.2	3.4	9.4
Ibuprofen	C13H18O2	206.1	3.6	4.5
Indometacine	C19H16ClNO4	357.8	3.4	4.5
Metoprolol	C15H25NO3	267.4	1.6	-
Naproxen	C14H14O3	230.1	2.8	4.2
Progesterone	C21H30O2	314.2	3.9	-
Propanolol	C16H21NO2	259.3	3	-
Sulfamerazine	C11H12N4O2S	264.3	0.14	-
Sulfamethazine	C12H14N4O2S	278.3	0.89	-
Sulfamethoxazole	C10H11N3O3S	253.1	2.1	2.1
Sulfathiazole	C9H10N4O2S	270.3	0.9	-
Trimethoprim	C14H18N4O3	290.1	0.6	6.3

*Chemical data obtained from www.DrugBank.com (Wishart et al., 2006)

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