Effect of pH on degradation of acetaminophen and production of 1,4-benzoquinone in water chlorination

Irene Xagoraraki, Rebecca Hullman, Wenlu Song, Hui Li and Thomas Voice

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 its concentration 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 highest at a molar ratio of about 10,000.

Key words | acetaminophen, benzoquinone, byproducts, chlorination, oxidation, pharmaceutical

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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 3.6×10^9 g of acetaminophen (Bedner & Maccrehan 2006). In 1998, it was estimated that 3.2×10^9 tablets were consumed in the UK alone (Bessems & Vermeulen 2001).

Acetaminophen has been detected in surface waters, wastewater, and drinking water. In a 2002 survey of 139 U.S. streams, Kolpin *et al.* detected acetaminophen in roughly 25% of the samples tested at a median concentration of $0.11\ \mu g L^{-1}$ (Kolpin *et al.* 2002). The median concentration of acetaminophen detected in surface waters is $0.055 \pm 0.051\ \mu g L^{-1}$ (Boyd & Furlong 2002; Kolpin *et al.* 2002; Stackelberg *et al.* 2004; Wiegel *et al.* 2004; Bound & Voulvoulis 2006; Gros *et al.* 2006). In raw wastewater, acetaminophen was detected at a median concentration of $48 \pm 75\ \mu g L^{-1}$ (Gros *et al.* 2006; Han *et al.* 2006; Gomez *et al.* 2007). The median concentration of acetaminophen detected in finished wastewater is $0.76 \pm 0.96\ \mu g L^{-1}$ (Bound & Voulvoulis 2006; Brun *et al.* 2006; Gros *et al.* 2006; Han *et al.* 2006; Gomez *et al.* 2007; Radjenovic *et al.* 2007). Table 1 summarizes the occurrence of acetaminophen and the range of concentrations detected in water samples.

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,

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Table 1 | Acetaminophen occurrence in the environment ($\mu g L^{-1}$)

Surface water	Raw wastewater	Finished wastewater	Finished drinking water
<0.1 (8)	0–0.26 (6)	0–6.0 (12)	low ppb levels (11)
0.11 (10)	29–246 (1)	0–0.16 (6)	
0–0.026 (9)	0.13–26 (5)	1.9 (4)	
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 & 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 1998

such as acetaminophen and other pharmaceuticals. It has been shown that acetaminophen reacts with chlorine (Pinkston & Sedlak 2004; Glassmeyer & Shoemaker 2005; Westerhoff *et al.* 2005; Bedner & Maccrehan 2006; Gibs *et al.* 2007).

Bedner & 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 tested are higher than those observed in drinking water supplies and wastewater effluents and therefore the chlorine doses were also higher than those applied in practice in water and wastewater utilities.

METHODS

Chlorine to acetaminophen molar ratios

Minimum and maximum acetaminophen concentrations detected in raw wastewater, finished wastewater, and raw drinking water (Table 1) were combined with typical chlorine doses (5–50 $mg L^{-1}$ 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 2, the target molar ratios chosen for the experiments were 100, 1,000 and 10,000.

Chlorination experiments

The day prior to conducting each batch chlorination experiment, 6 beakers were filled with 1,500 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

Table 2 | Expected molar ratios of chlorine to acetaminophen

Type of water where ratio may occur	Chlorine ($mg L^{-1}$)	Acetaminophen ($\mu g L^{-1}$)	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

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 1,000 mgL^{-1} 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 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.

Analytical methods for acetaminophen

Acetaminophen was purchased from Sigma Aldrich, $>99\%$ purity. The initial acetaminophen stock solution was prepared at 1,000 mgL^{-1} in methanol and the stock was then diluted to 10 mgL^{-1}. A standard curve of 100, 200, 500, 1,000 and 2,000 μgL^{-1} was used for measuring acetaminophen concentrations. Samples were analyzed using liquid chromatography/ tandem mass spectrometry (LC/MS/MS) using a Shimadzu Prominence Liquid Chromatograph (LC-20AD) with autosampler (SIL-20A) and an Applied Biosystems API 3,200 tandem mass spectrometer. An electrospray ionization (ESI) interface was used as the ionization source. The retention time on a Phenomenex Luna C18 (150 × 4.60 mm 3 micron) column was from 6.7 to 7.3 minutes. For the mobile phase, eluent A was 0.1% formic acid/5% methanol/95% water and eluent B was 01% formic acid/5% water/95% methanol. Isocratic flow was used at a rate of 0.10 $mlmin^{-1}$ A, and 0.17 $mlmin^{-1}$ 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 5,400 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.

Analytical methods for 1,4-benzoquinone

1,4-Benzoquinone was purchased from Acros Organics, $>98\%$ purity. A 1,000 mgL^{-1} stock was made by adding 0.100g 1,4-benzoquinone to 100 ml distilled water. This stock was diluted to 10 mgL^{-1}, from which standard curve dilutions were made. The standard curves consisted of 50, 100, 200, 500 and 1,000 μgL^{-1}. 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 × 4.60 mm 3 micron) column was 6.5 minutes. For the mobile phase, eluent A was 0.1% formic acid/5% methanol/95% water and eluent B was 01% formic acid/5% water/95% methanol. Isocratic flow was used at a rate of 0.10 $mlmin^{-1}$ eluent A, and 0.17 $mlmin^{-1}$ 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.

RESULTS AND DISCUSSION

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 1, 2 and 3. At a free chlorine dose of 100 mgL^{-1} and at pH 6.0 with an initial acetaminophen concentration of 2,150 μgL^{-1} (molar ratio = 99), acetaminophen was only slightly degraded, and 1,4-benzoquinone was produced at a slow rate (Figure 1). When the molar ratio of chlorine-to-acetaminophen was increased to 1,745 and the pH was kept at 6.0, acetaminophen was degraded over time at a faster rate

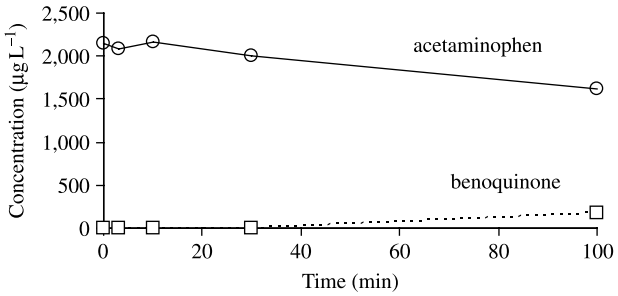

Figure 1 | Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 100 mgL^{-1}, initial acetaminophen concentration of 2,150 μgL^{-1} (molar ratio = 99).

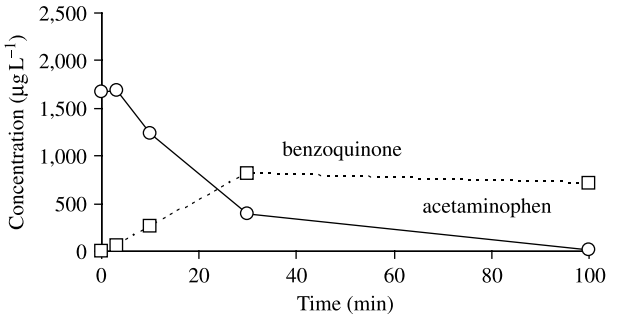

Figure 2 | Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 1,000 mgL^{-1}, initial acetaminophen concentration of 1,670 μgL^{-1} (molar ratio = 1,275).

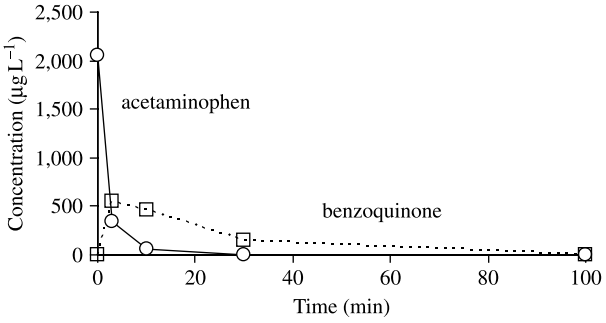

Figure 3 | Degradation of acetaminophen and formation of 1,4-benzoquinone at pH 6.0 over a 100-minute contact time, with a free chlorine dose of 10,000 mgL^{-1}, initial acetaminophen concentration of 2,050 μgL^{-1} (molar ratio = 10,386).

and more 1,4-benzoquinone was produced in comparison to the 99 molar ratio (Figure 2). 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 3). At the highest chlorine to pharmaceutical molar ratio (Figure 3), 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 2, 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. 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 focuses on the formation of 1,4-benzoquinone because it is known to be toxic.

Effect of pH on acetaminophen degradation

Figures 4, 5 and 6 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 acetamino-

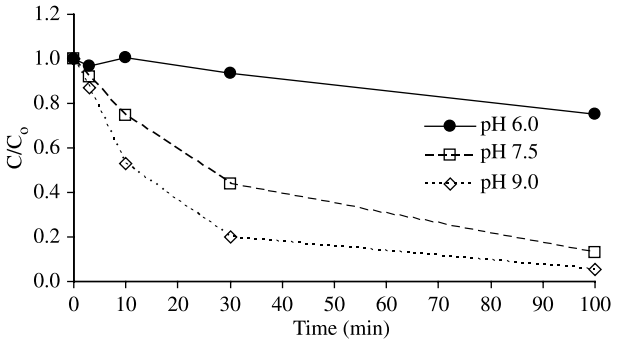

Figure 4 | Effect of pH and contact time on acetaminophen for an average initial acetaminophen concentration (C_0) of 2013.33 ± 119.30 μgL^{-1} and 100 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 106 ± 6).

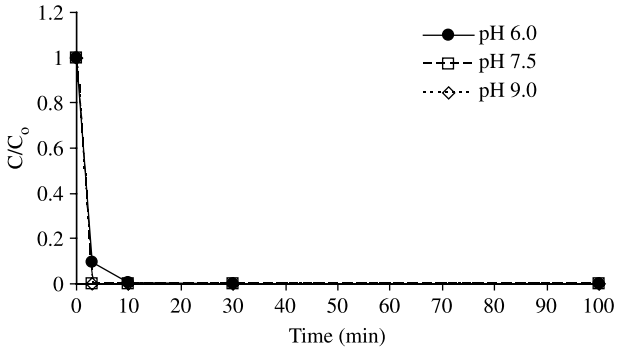

Figure 6 | Effect of pH and contact time on acetaminophen degradation at an average initial acetaminophen concentration (C_0) of 2036.67 ± 270.25 μgL^{-1} and 10,000 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 9789 ± 1430).

phen 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 4 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.

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 were −0.0435, −0.400 and

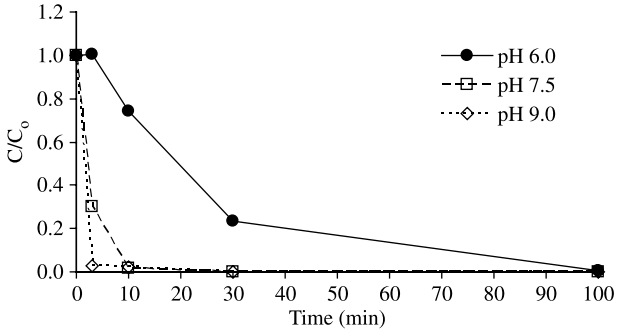

Figure 5 | Effect of pH and contact time on acetaminophen degradation for an average initial acetaminophen concentration (C_0) of 1540 ± 278. 75 μgL^{-1} and 1,000 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 1,417 ± 285).

−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 & 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 & 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.

Effect of pH on benzoquinone production

Figures 7, 8 and 9 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.

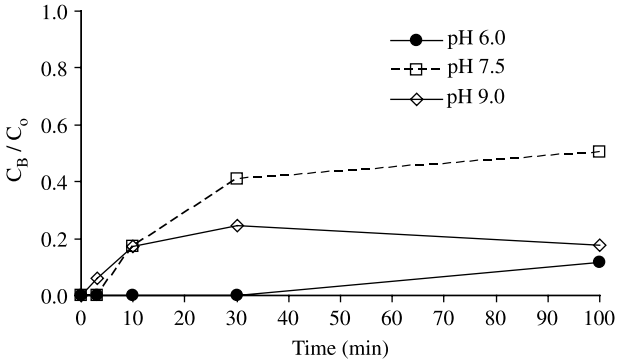

Figure 7 | Effect of pH and contact time on 1,4-benzoqiunone formation (C_B) at an average initial acetaminophen concentration (C_0) of 2013.33 ± 119.30 μgL^{-1} and 100 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 106 ± 6).

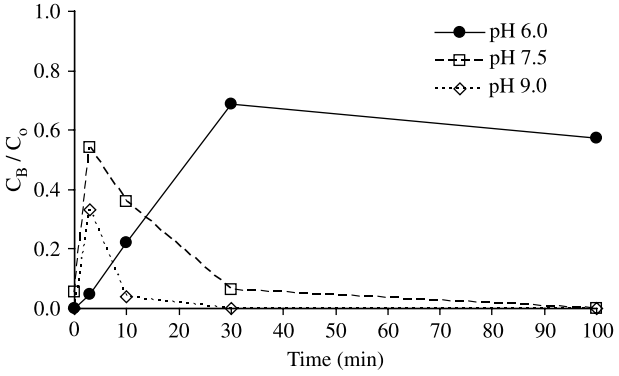

Figure 8 | Effect of pH and contact time on 1,4-benzoquinone formation (C_B) at an average initial acetaminophen concentration (C_0) of 1540 ± 278. 75 μgL^{-1} and 1,000 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 1,417 ± 285).

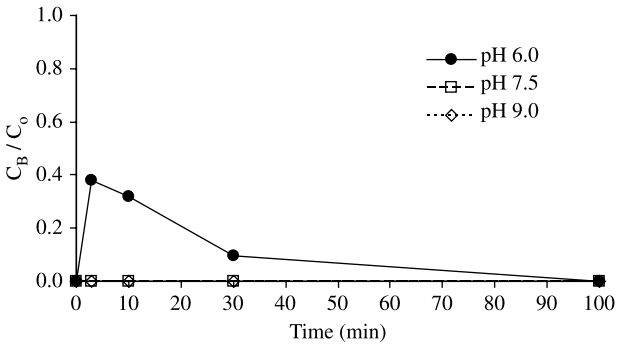

Figure 9 | Effect of pH and contact time on 1,4-benzoquinone formation (C_B) at an average initial acetaminophen concentration (C_0) of 2036.67 ± 270. 25 μgL^{-1} and 10,000 mgL^{-1} free chlorine dose (chlorine/acetaminophen molar ratio = 9789 ± 1430).

The effect of pH on 1,4-benzoquinone formation is more complex than the effect of pH on acetaminophen degradation since 1,4-benzoquinone also reacts with free chlorine over time, resulting in its own degradation. Bedner & 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 $\mu molL^{-1}$, 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).

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,

Table 3 | Summary of results and comparison with literature data involving the reaction of acetaminophen with sodium hypochlorite

Type of water	Chlorine dose	Acetaminophen concentration	Molar ratio	pH	Contact time	Acetaminophen degradation	1,4-Benzoquinone formation	Reference
Pure water	57 $\mu molL^{-1}$	1–10 $\mu molL^{-1}$	5.7–57	7.0	0–90 min	88% of acetaminophen (10 $\mu molL^{-1}$ initial) was transformed in 1 hour	1,4-benzoquinone accounted for 25% of the initial acetaminophen concentration after 1 hour.	Bedner & Maccrehan (2006)
Milli-Q water	405 $\mu molL^{-1}$	NA	NA	NA	48 hrs	Definite signs of chlorination	N/A	Glassmeyer & Shoemaker (2005)
Surface water	49–54 $\mu molL^{-1}$	0.0002 $\mu molL^{-1}$	245,000–270,000	5.5	24 hr.	>95% oxidized	N/A	Westerhoff *et al.* (2005)
Nanopure water	600 $\mu molL^{-1}$	20 $\mu molL^{-1}$	30	5–10	5 days	Acetaminophen was significatly transformed	N/A	Pinkston and Sedlak (2004)
Drinking water	16.9 $\mu molL^{-1}$	0.0033 $\mu molL^{-1}$	5121	8	1–10 days	Completely degraded after 1 day in contact with free chlorine.	N/A	Gibs *et al.* (2007)
Buffered, distilled water	1,408.45 $\mu molL^{-1}$	14.22 $\mu molL^{-1}$	99	6	0–100 min	6.51 and 24.7% acetaminophen degradation 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
Buffered, distilled water	1,408.45 $\mu molL^{-1}$	12.97 $\mu molL^{-1}$	109	7.5	0–100 min	56.4 and 87.0% acetaminophen degradation 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
Buffered, disillied M water	1,408.45 $\mu molL^{-1}$	12.77 $\mu molL^{-1}$	110	9	0–100 min	80.0 and 94.8% acetaminophen degradation 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
Buffered, distilled water	14,084.5 $\mu molL^{-1}$	11.05 $\mu molL^{-1}$	1,275	6	0–100 min	76.8 and 99.2% acetaminophen degradation 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
Buffered, distilled water	14,084.5 $\mu molL^{-1}$	8.07 $\mu molL^{-1}$	1,745	7.5	0–100 min	100% acetaminophen degradation after 30 and 100 min.	Benzoquinone was produced up to 54.3% of the initial acetamino phen after 3 min, no amount was detected after 100 min.	This study
Buffered, distilled water	14,084.5 $\mu molL^{-1}$	11.44 $\mu molL^{-1}$	1,231	9	0–100 min	100% acetaminophen degradation after 30 and 100 min.	Benzoquinone was produced up to 33.1% of the initial acetamino phen after 3 min, no amount was detected after 100 min.	This study

Table 3 | (continued)

Type of water	Chlorine dose	Acetaminophen concentration	Molar ratio	pH	Contact time	Acetaminophen degradation	1,4-Benzoquinone formation	Reference
Buffered, distilled water	140,845 μmolL^{-1}	13.56 μmolL^{-1}	10,386	6	0–100 min	100% acetaminophen degradation 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
Buffered, distilled water	140,845 μmolL^{-1}	15.21 μmolL^{-1}	9,257	7.5	0–100 min	100% acetaminophen degradation after 30 and 100 min.	Benzoquinone was not detected in any of the samples.	This study
Buffered, distilled water	140,845 μmolL^{-1}	11.51 μmolL^{-1}	12,237	9	0–100 min	100% acetaminophen degradation after 30 and 100 min.	Benzoquinone was not detected in any of the samples.	This study

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.

Comparison with literature data

The results of this study are compared with the results from previous acetaminophen chlorination work (Pinkston & Sedlak 2004; Glassmeyer & Shoemaker 2005; Westerhoff *et al.* 2005; Bedner & Maccrehan 2006; Gibs *et al.* 2007). Table 3 summarizes experimental conditions and basic conclusions obtained from published studies and this study. Table 3 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 & 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 & 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 & Shoemaker (2005) found that acetaminophen showed definite signs of chlorination when acetaminophen-spiked water was dosed with 28.75 mgL^{-1} 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 & Shoemaker (2005) did not attempt to test the effects of pH or molar ratio.

Westerhoff *et al.* (2005) added 3.5–3.8 mgL^{-1} free chlorine to surface water spiked with 0.0002 $\mu molL^{-1}$ 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 that study either, but different water matrices were studied.

Bedner & 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 $\mu molL^{-1}$, acetaminophen reacted to a greater extent than at an initial concentration of 10 $\mu molL^{-1}$ 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. 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.

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.

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REFERENCES

Bedner, M. & Maccrehan, W. A. 2006 Transformation of Acetaminophen by Chlorination Produces the Toxicants 1,4-Benzoquinone and N-Acetyl-p-benzoquinone Imine. *Environ. Sci. Technol.* **40**, 516–522.

Bessems, J. G. M. & Vermeulen, N. P. E. 2001 Paracetamol (acetaminophen)–induced toxicity: molecular and biochemical mechanisms, analogues and protective approached. *Crit. Rev. Toxicol.* **31**, 55–138.

Bound, J. P. & Voulvoulis, N. 2006 Predicted and measured concentrations for selected pharmaceuticals in UK rivers: implications for risk assessment. *Water Res.* **40**, 2885–2892.

Boyd, R. A. & Furlong, E. T. 2002 *Human-Health Pharmaceutical Compounds in Lake Mead, Nevada and Arizona, and Las Vegas Wash, Nevada, October 2000–August 2001*. US Geological Survey, Reston, VA, pp. 1–18.

Brun, G. L., Bernier, M., Losier, R., Doe, K., Jackman, P. & Lee, H. B. 2006 Pharmaceutically active compounds in Atlantic Canadian sewage treatment plant effluents and receiving waters, and potential for environmental effects as measured by acute and chronic aquatic toxicity. *Environ. Toxicol. Chem.* **25**(8), 2163–2176.

Dasmalchi, S., Rashidi, M. & Rassi, M. 1995 Simultaneous determination of the pKa and octanol/water partition coefficient (P_m) of acetaminophen. *J. School. Pharm. Med. Sci. Tehran Univ.* **4**, 7–14.

Gibs, J., Stackelberg, P. E., Furlong, E. T., Meyer, M., Zaugg, S. D. & Lippincott, R. L. 2007 Persistence of pharmaceuticals and other organic compounds in chlorinated drinking water as a function of time. *Sci. Total Environ.* **373**, 240–249.

Glassmeyer, S. T. & Shoemaker, J. A. 2005 Effects of Chlorination on the Persistence of Pharmaceuticals in the Environment. *Bull. Environ. Contam. Toxicol.* **74**, 24–31.

Gomez, M. J., Bueno, M. J. M., Lacorte, S., Fernandez-Alba, A. R. & Aguera, A. 2007 Pilot survey monitoring pharmaceuticals and related compounds in a sewage treatment plant located on the Mediterranean coast. *Chemosphere* **66**(6), 993–1002.

Gros, M., Petrovic, M. & Barcelo, D. 2006 Development of a multi-residue analytical methodology based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters. *Talanta* **70**, 678–690.

Han, G. H., Hur, H. G. & Kim, S. D. 2006 Ecotoxicological risk of pharmaceuticals from wastewater treatment plants in Korea: Occurrence and toxicity to Daphnia magna. *Environ. Toxicol. Chem.* **25**(1), 265–271.

Kolpin, D. W., Furlong, E. T., Meyer, M. T., Thurman, E. M., Zaugg, S. D., Barber, L. B. & Buxton, H. T. 2002 Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams 1999–2000: a national reconnaissance. *Environ. Sci. Technol.* **36**(6), 1202–1211.

Moll, D. M., Frick, E. A., Henderson, A. K., Furlong, E. T. & Meyer, M. T. 2001 Presence of pharmaceuticals in treated wastewater effluent and surface water supply systems, metropolitan Atlanta, Georgia, July–September 1999. In: *Proceedings of the 2001 Georgia Water Resources Conference*. Universtiy of Georgia, Athens, Georgia.

Pinkston, K. E. & Sedlak, D. L. 2004 Transformation of aromatic ether- and amine-containing pharmaceuticals during chlorine disinfection. *Environ. Sci. Technol.* **38**, 4019–4025.

Radjenovic, J., Petrovic, M. & Barcelo, D. 2007 Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. *Anal. Bioanal. Chem.* **387**, 1365–1377.

Stackelberg, P. E., Furlong, E. T., Meyer, M. T., Zaugg, S. D., Henderson, A. K. & Reissman, D. B. 2004 Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking water treatment plant. *Sci. Total Environ.* **329**, 99–113.

Ternes, T. A. 1998 Occurrence of drugs in German sewage treatment plants and rivers. *Water Res.* **32**, 3245–3260.

Westerhoff, P., Yoon, Y., Shane, S. & Wert, E. 2005 Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environ. Sci. Technol.* **39**, 6649–6663.

Wiegel, S., Aulinger, A., Brockmeyer, R., Harms, H., Loffler, J., Reincke, H., Schmidt, R., Stachel, B., von Tumpling, W. & Wanke, A. 2004 Pharmaceuticals in the river Elbe and its tributaries. *Chemosphere* **57**, 107–126.

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