

Oxidation of Pharmaceuticals in Drinking Water Utilities

Rebecca Hullman

Irene Xagorarakis, Sponsoring Professor

September 2009



MICHIGAN STATE
UNIVERSITY

Part I: Background

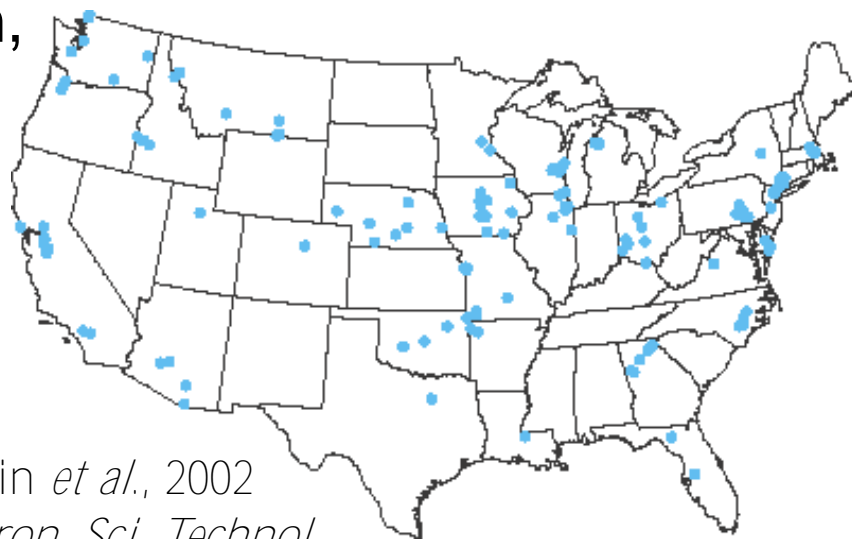
- Occurrence and Sources of Pharmaceuticals in the Environment
- Fate of Pharmaceuticals in Drinking Water Utilities
- Oxidation of Pharmaceuticals
- Conclusions and Recommendations



Occurrence

Organic wastewater contaminants were detected in 80% of 139 U.S. streams sampled in 1999 and 2000 (Kolpin et al., 2002).

Most frequently detected pharmaceuticals included trimethoprim, acetaminophen, erythromycin, estriol, lincomycin, and sulfamethoxazole.



Kolpin *et al.*, 2002
Environ. Sci. Technol.

Occurrence

Typical Concentrations and Compounds

■ Wastewater

- <10 to >100 $\mu\text{g/L}$
- beta-blockers, analgesics, antibiotics

■ Surface Water

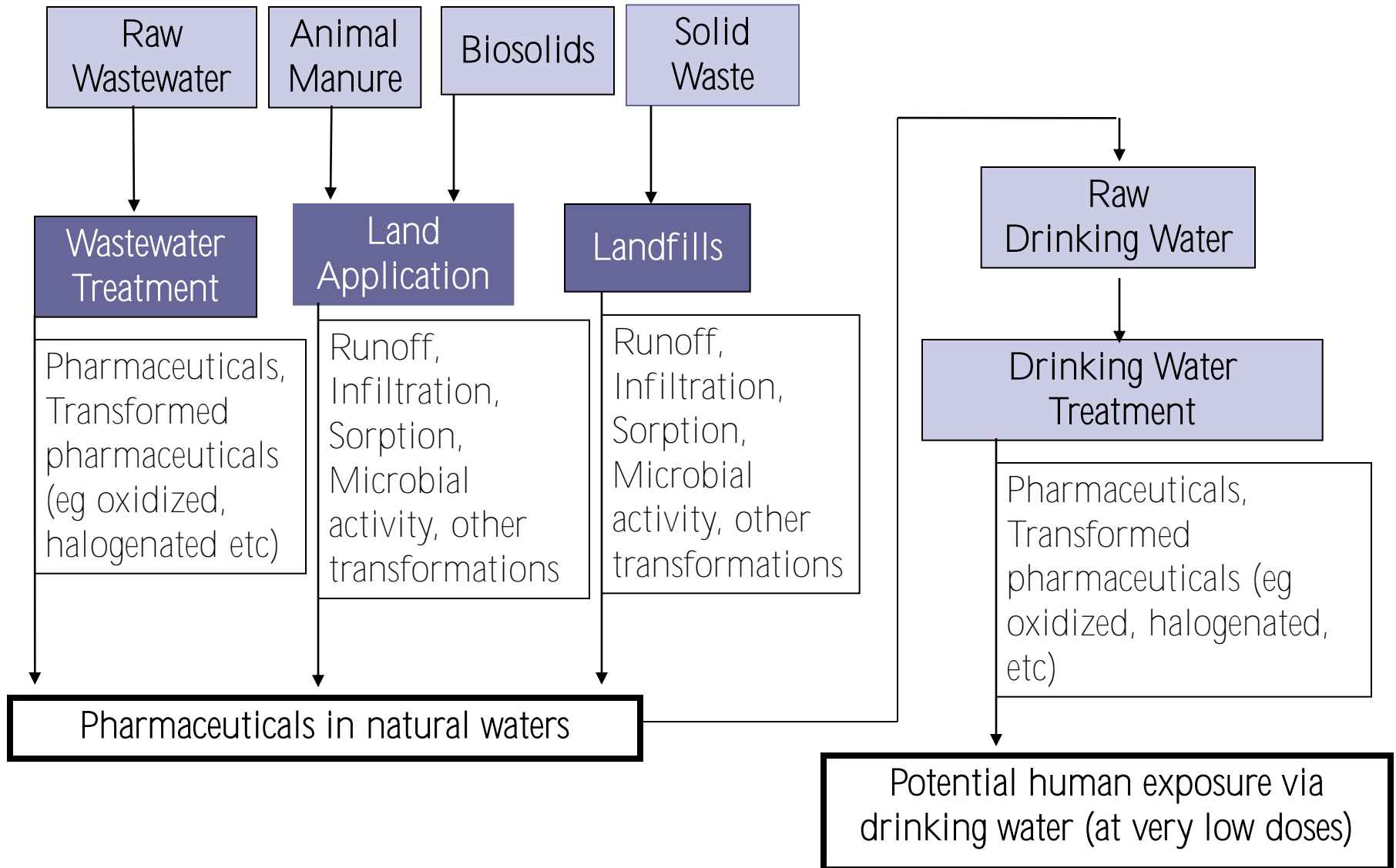
- < 1 $\mu\text{g/L}$
- analgesics,
carbamazepine

■ Drinking Water

- < 1 $\mu\text{g/L}$
- ibuprofen, sulfonamides, carbamazepine



Sources





Fate in Drinking Water Utilities

- Few studies exist
- Treatment trains for existing studies:
 - Stackelberg et al., 2007: screening, clarification, 1^e chlorine disinfection, sand/GAC filtration, 2^e chlorine disinfection
 - Boyd et al., 2003: PAC addition, coagulation, flocculation, sedimentation, chlorination, filtration, chloramination
 - Ternes et al., 2002: pre-ozonation, flocculation, main ozonation, multiple-layer filtration, GAC filtration

Overall Removal in Drinking Water Utilities

Pharmaceutical	Influent Conc. (ng/L)	Overall Removal (%)	Reference
Acetaminophen	15 ^a	98	Stackelberg et al.(2007)
Carbamazepine	80 ^b – 200 ^{ab}	36.7 ^a – 100 ^c	Stackelberg et al.(2004, 2007), Ternes et al. (2002)
Bezafibrate	80 ^b	100 ^c	Ternes et al. (2002)
Clofibric Acid	10 ^b	100 ^c	Ternes et al. (2002)
Diclofenac	65 ^b	100 ^c	Ternes et al. (2002)
Erythromycin	10 ^a	100	Stackelberg et al. (2007)
Naproxen	63 – 65	100	Boyd et al., 2003
Sulfamethoxazole	30 ^a	100	Stackelberg et al., 2007

^a Value represents average; ^b Approximated from figure;

^c Removal calculated by authors

Percent Removal During Individual Process at Drinking Water Utilities

Pharmaceutical	Primary Treatment	Filtration	Main Disinfection	Reference
Acetaminophen	60^b	98	100^b (NaOCl)	Stackelberg et al. (2007)
Carbamazepine	0 – 60^{ab}	0 - >90^{ab}	0 – 20^{ab} (NaOCl) >99 (Ozone)	Stackelberg et al. (2004, 2007), Ternes et al. (2002)
Bezafibrate	8.8^b	>95^b	Not measured	Ternes et al. (2002)
Clofibric Acid	0^b	50^b	77 (Ozone)	Ternes et al. (2002)
Diclofenac	7.7^b	>95^b	>99 (Ozone)	Ternes et al. (2002)
Erythromycin	47^b	100^b	92^b (NaOCl)	Stackelberg et al. (2007)
Naproxen	0^b	NA	100^b (NaOCl)	Boyd et al. (2003)
Sulfamethoxazole	33^b	NA	100^b (NaOCl)	Stackelberg et al. (2007)

^a Value represents average; ^b Removal calculated by authors

Comparison of Oxidants

Pharmaceutical	Sodium Hypochlorite	Chlorine Dioxide	Mono-chloramine	Ozone	UV Irradiation
Naproxen	High reactivity	Some reactivity	No reactivity	High reactivity	NA
17 α -ethinylestradiol	High reactivity	High reactivity	Low reactivity	High reactivity	High reactivity (w/ UV/H ₂ O ₂)
Carbamazepine	Some or no reactivity	No reactivity	NA	High reactivity	High reactivity (w/ UV/H ₂ O ₂)
Sulfamethazine	Some reactivity	Some reactivity	Some reactivity	High reactivity	Some reactivity
Erythromycin	Some, high, or no reactivity	Some reactivity	Some reactivity	High reactivity	NA

Sources: Adams et al., 2002; Alum et al., 2004; Deborde et al., 2004; Pinkston & Sedlak, 2004; Rosenfeldt & Linden, 2004; Boyd et al., 2005; Huber et al., 2005ab; Westerhoff et al., 2005; Chamberlain & Adams, 2006; Qiang et al., 2006; Rosenfeldt et al., 2007; Gibs et al., 2007; Lee et al., 2008



Factors Affecting Oxidation of Pharmaceuticals

- pH
- Contact time
- Oxidant Dose
- Pharmaceutical Concentration
- Water Matrix
- Functional groups of pharmaceutical

pH Trends During Chlorination

Pharmaceutical	pH Studied	pH Effect	Source
Acetaminophen	6, 7.5, 9 5.5, ambient 5 – 10	Effects varied in each study	Xagorarakis <i>et al.</i> , 2008; Westerhoff <i>et al.</i> , 2005; Pinkston & Sedlak, 2004
Carbamazepine	5.5, ambient	Decreased with increased pH	Westerhoff <i>et al.</i> , 2005
Erythromycin	6.1, 7.6, 9.1 5.5, ambient	No effect observed	Chamberlain & Adams, 2006; Westerhoff <i>et al.</i> , 2005
Estradiol	3.5 – 12 5.5, ambient	Greatest between pH 8 and 10	Deborde <i>et al.</i> , 2004; Westerhoff <i>et al.</i> , 2005
Ibuprofen	5 – 10 5.5, ambient	No effect observed	Pinkston & Sedlak, 2004; Westerhoff <i>et al.</i> , 2005
Naproxen	5, 7, 9 5 – 10 5.5, ambient	Decreased with increased pH	Boyd <i>et al.</i> , 2005; Pinkston & Sedlak, 2004; Westerhoff <i>et al.</i> , 2005
Propranolol	5 – 10	Increased with increasing pH	Pinkston & Sedlak, 2004
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 <i>et al.</i> , 2006; Westerhoff <i>et al.</i> , 2005
Trimethoprim	5.5, ambient	No effect observed	Westerhoff <i>et al.</i> , 2005

Oxidation Byproducts

Oxidant	Pharmaceutical	Byproducts	Human Toxicity
NaOCl	Acetaminophen	<ul style="list-style-type: none"> ▪ N-Acetyl-p-benzoquinone imine ▪ 1,4-benzoquinone ▪ Chloro-4-acetamidophenol ▪ Dichloro-4-acetamidophenol 	Toxic Toxic Unknown Unknown
NaOCl	Estrogen	<ul style="list-style-type: none"> ▪ Chloroacetic acids 	Toxic
NaOCl	Sulfamethoxazole	<ul style="list-style-type: none"> ▪ 3-amino-5-methylisoxazole ▪ N-chloro-p-benzoquinoneimine 	Not toxic Possibly toxic
Ozone	Amoxicillin	<ul style="list-style-type: none"> ▪ 2-amino-2(p-hydroxyphenyl) acetic acid 	Unknown
Ozone	Carbamazepine	<ul style="list-style-type: none"> ▪ 1(2-benzaldehyde)-4-hydroquinazoline-2-one ▪ 1(2-benzaldehyde)-4-hydroquinazoline-2,4-dione ▪ 1(2-benzoic acid)-4-hydroquinazoline-2,4-dione 	Unknown Unknown Unknown

Sources: Bedner & Maccrehan, 2006; Korshin et al., 2006; Andreozzi et al., 2005; McDowell et al., 2005

Conclusions



- Each pharmaceutical behaves differently during water treatment
- Factors affecting removal include the combination of processes used, process design, and the compound's chemical properties
- Oxidation is affected by pH, water matrix, dosage, initial concentration, and the compound's chemical properties
- Ozone appears to be the most effective oxidant for reducing pharmaceuticals in drinking water

What is the risk to humans?

- Most existing toxicity data is for therapeutic doses which are much greater than environmental concentrations
- Recent risk assessments suggest exposure to trace amounts is insignificant
- Risk from long-term exposure, mixtures, compounded effects (food, air, etc.) is unknown

For more information:

Snyder S. *et al.* 2008. State of Knowledge of Endocrine Disruptors and Pharmaceuticals in Drinking Water. AWWA Research Foundation.

Recommendations



- Develop models to predict how a pharmaceutical will react with oxidants
- Narrow the focus of research to more persistent, unpredictable compounds
- Identify oxidation byproducts of high-risk compounds
- Evaluate effects of antibiotics on microbial systems
- Study pharmaceutical transport after land application of biosolids
- Evaluate long-term effects of human exposure to mixtures of pharmaceutically-active compounds

Part II:

Laboratory Experiments

- Chlorination of Acetaminophen
- Conclusions
- Human and Ecological Health Risks
- Continuing Research and Recommendations



Experimental Design

- Acetaminophen chosen due to widespread use, frequency of detection, and a previous study by Bedner & Maccrehan (2006) which observed the formation of chlorination byproducts toxic to humans.

- Objectives

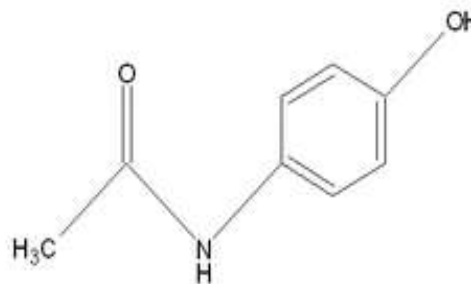
- Study effect of

- pH

- Molar Ratio

- Initial acetaminophen concentration

- Monitor formation of 1,4-benzoquinone



Acetaminophen
MW = 151.2 g/mol
Log K_{ow} = 0.46
 pK_a = 9.4

Acetaminophen Occurrence ($\mu\text{g/L}$)

Surface Water	Raw Wastewater	Finished Wastewater	Finished Drinking Water
<0.1 (8)	0 - 0.26 (6)	0 - 6.0 (12)	Detected at 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 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

Expected Molar Ratios

Type of Water	Cl ₂ Dose (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 Waste-water	5	0.048-6.0	Finished Wastewater	1,774 - 221,787
	50	0.048-6.0	Finished Wastewater	17,743 - 2,217,870
Raw Waste-water	5	0.13-246	Raw Wastewater	43 - 81,891
	50	0.13-246	Raw Wastewater	433 - 818,906

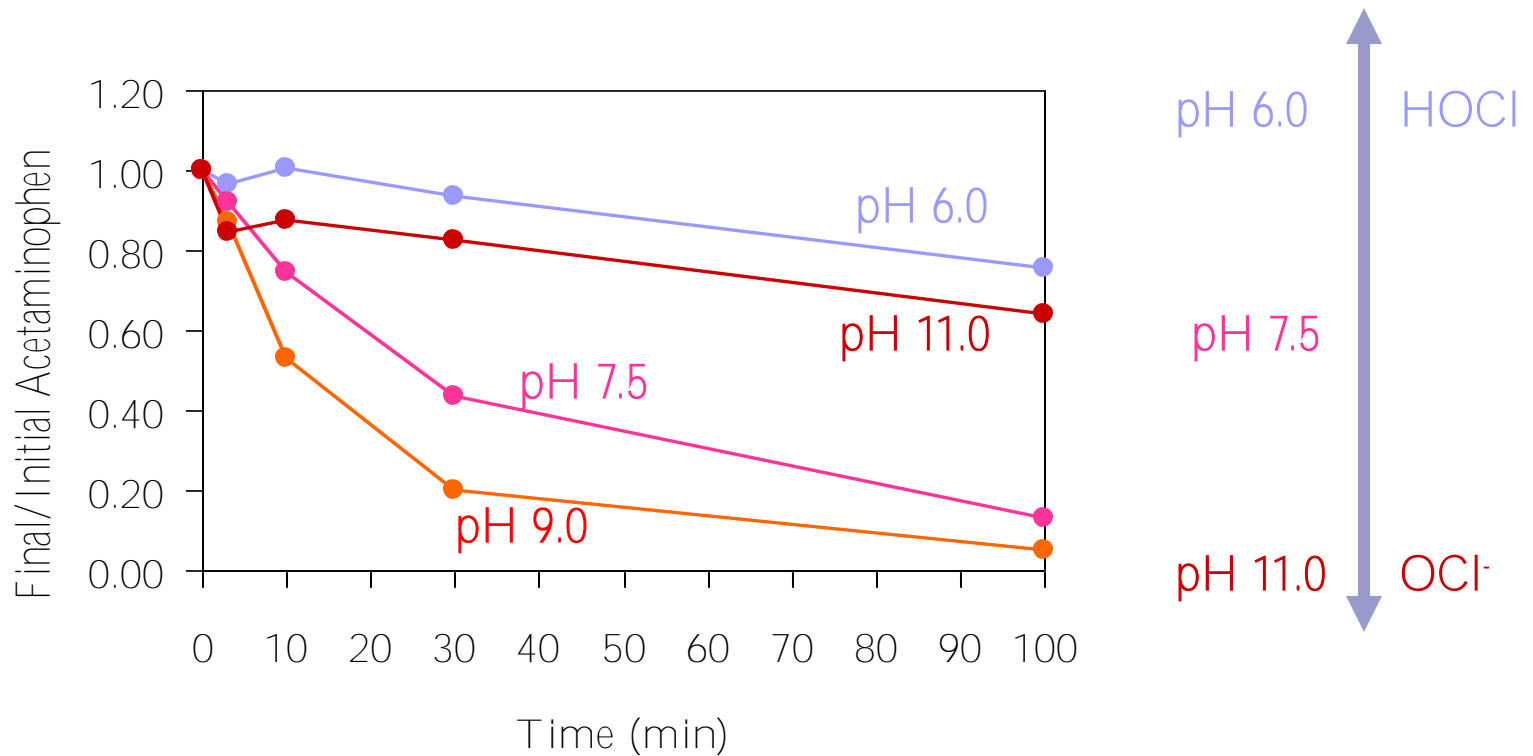
Target Molar Ratios: 100, 1,000, and 10,000

Experiments

- Independent parameters
 - pH (6.0, 7.5, 9.0, 11.0)
 - Molar ratio (100, 1,000, 10,000)
- Dependent variables
 - Acetaminophen concentration
 - 1,4- Benzoquinone concentration
- Constant
 - Temperature
 - Initial acetaminophen concentration
 - 200 $\mu\text{g/L}$
 - 1,000 $\mu\text{g/L}$
 - 2,000 $\mu\text{g/L}$

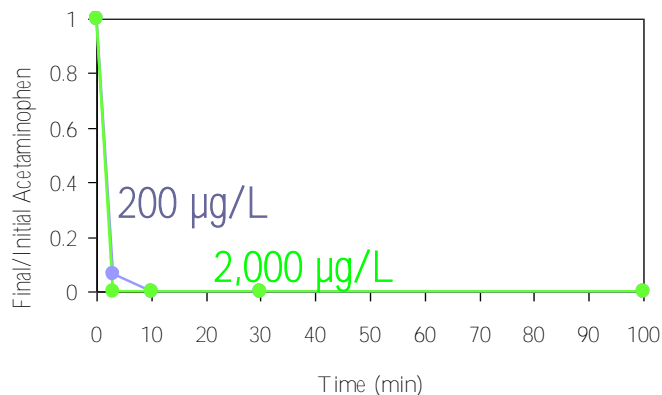
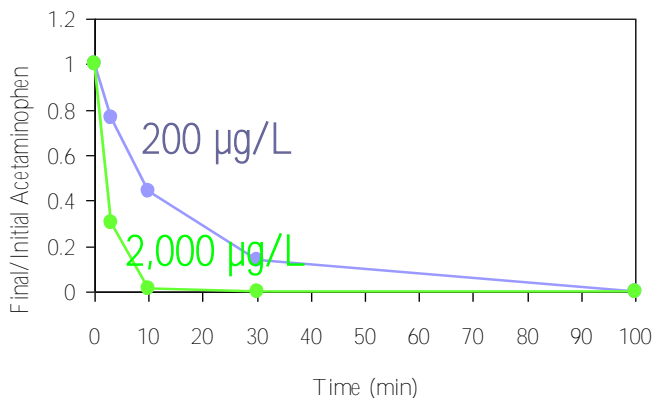
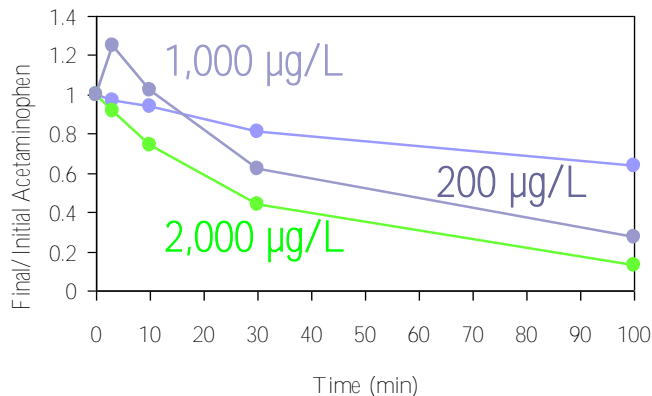


Effect of pH



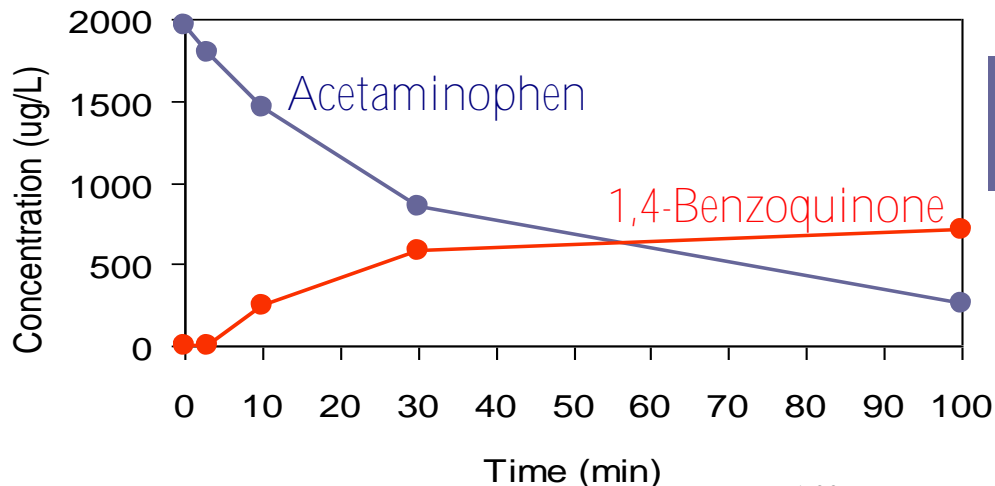
Chlorine to Pharmaceutical Average Molar Ratio = 107 ± 5
 1998 ± 102 $\mu\text{g/L}$ Acetaminophen and 100 mg/L Cl_2

Effect of Molar Ratio and Initial Acetaminophen Concentration



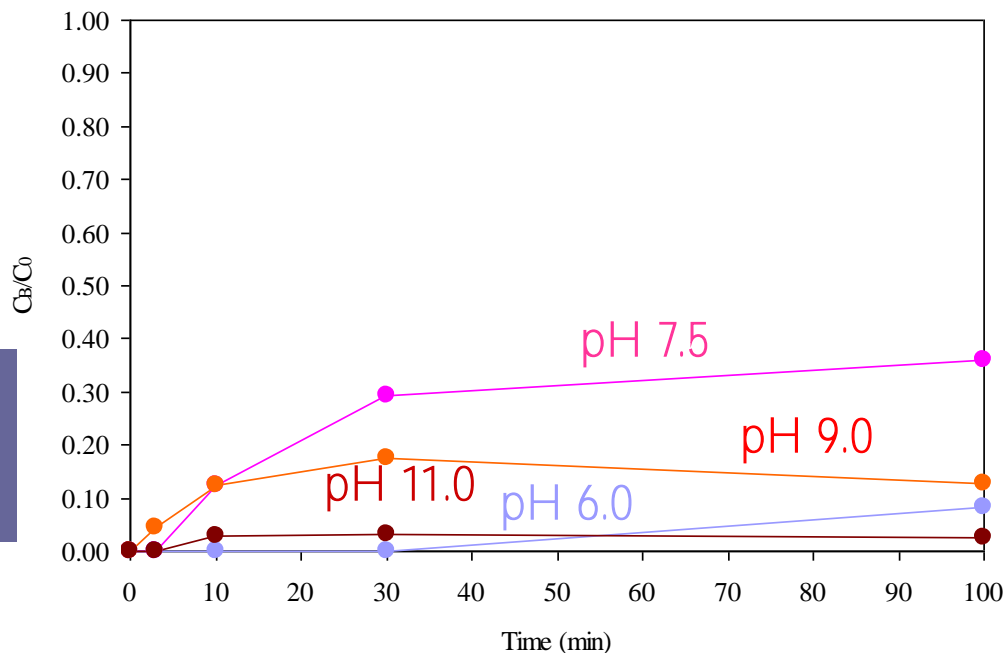
pH 7.5

1,4-Benzoquinone Formation



Example of Results
(pH 7.5, Molar Ratio = 109)

Effect of pH
(Average Molar Ratio = 107 ± 5
Acetaminophen = $1998 \pm 102 \mu\text{g/L}$)



Conclusions

- Acetaminophen reacted with free chlorine to the greatest extent at pH 9.0
- 1,4-Benzoquinone formation reached a maximum of 68.7% of initial acetaminophen (pH 6.0, molar ratio =1,275)
- Increased molar ratio resulted in greater degradation of acetaminophen and 1,4-benzoquinone
- Less degradation of acetaminophen and formation of 1,4-benzoquinone occurs at lower initial acetaminophen concentration

Human and Ecological Health Risks



■ Acetaminophen

- For humans, PNEC (predicted no effect concentration) = 5,000 $\mu\text{g/L}$ (Schwab et al., 2005)
- For aquatic organisms, PNEC = 9.2 $\mu\text{g/L}$ (Kim et al., 2007)

■ 1,4-Benzoquinone

- For humans, very little data exists. LC_{50} for mice = 25 mg/kg (MSDS).
- For aquatic organisms, LC_{50} for minnows = 0.045 mg/L and 0.125 mg/L for rainbow trout.

Even in worst case scenario (6 $\mu\text{g/L}$ acetaminophen with 69% converted to 1,4-BQ) risk is insignificant.

Continuing Research

$$\frac{d[\text{acetaminophen}]}{dt} = -k_{\text{HOCl}}[\text{acetaminophen}][\text{HOCl}] - k_{\text{OCl}^-}[\text{acetaminophen}][\text{OCl}^-] = -k_1[\text{ROH}][\text{HOCl}] - k_2[\text{RO}^-][\text{HOCl}] - k_3[\text{ROH}][\text{OCl}^-] - k_4[\text{RO}^-][\text{OCl}^-]$$

- Determination of reaction mechanism between chlorine and acetaminophen
 - Development of a mathematical model to predict reaction rates and identify reaction mechanism
- Evaluation of reaction between ozone and acetaminophen



Recommendations

- Analyze drinking water samples from various locations for 1,4-benzoquinone
- Conduct toxicity studies for 1,4-benzoquinone
- Use mathematical model to predict oxidation reaction mechanisms and byproducts for other pharmaceuticals



Acknowledgements

AWWA, Michigan Section

Irene Xagorarakis
Assistant Professor, CEE Dept. MSU

Hui Li
Professor, CSS Dept. MSU

Tom Voice
Professor, CEE Dept. MSU

Phanikumar Mantha
Professor, CEE Dept. MSU

Wenlu Song, PhD

A background image of a sunset over the ocean. The sun is low on the horizon, casting a bright orange glow across the sky and reflecting on the water. The sky is filled with soft, wispy clouds in shades of orange, yellow, and blue. The water in the foreground is dark and calm.