Print version

CEE 690K

ENVIRONMENTAL REACTION KINETICS

Lecture #10

Special Topics: Pharmaceuticals in Water I

Primary Literature (e.g., Westerhoff et al., 2005)

David A. Reckhow | Introduction

Boston Globe

March 10, 2008; page 2

...urgency about climate change even within groups that once dismissed assertions of an overheating planet as a liberal ruse. The president of the Southern Baptist Convention was among the signers. (AP)

MICHIGAN

Paper ties mayor's friend to contracts

DETROIT — Companies headed by a friend of Mayor Kwame Kilpatrick won millions of dollars in city contracts while the friend secretly consulted with the mayor's chief of staff about bidding strategies, the Detroit Free Press reported yesterday. The paper said Bobby Ferguson and companies he partnered collected at least $45 million. Ferguson, the city, and a lawyer for former chief of staff Christine Beatty denied wrongdoing. (AP)

FLORIDA

Shuttle cleared for launch with new lab

CAPE CANAVERAL — NASA cleared the space shuttle Endeavour yesterday for launch early tomorrow to begin attaching a Japanese laboratory to the International Space Station and install Canadian-built robot arms. Liftoff from the Kennedy Space Center is scheduled for 2:28 a.m. Meteorologists predicted a 90 percent chance that weather conditions would be suitable for the rare night launch. (Reuters)

Bus, pickup collide, killing woman

FORT LAUDERDALE — A tour

Pharmaceuticals found in US drinking water

Trace quantities could endanger wildlife, humans

By Jeff Donn
ASSOCIATED PRESS

EPA ADDRESSING THE ISSUE

'We recognize it is a growing concern, and we're taking it very seriously,' said Benjamin Grumbles, assistant administrator for water at the federal EPA.

NEW YORK — An array of pharmaceuticals — including antibiotics, anticonvulsants, mood stabilizers, and sex hormones — have been found in the drinking water supplies of at least 41 million Americans, an Associated Press investigation found.

The concentrations of these pharmaceuticals are tiny, measured in quantities of parts per billion or trillion, far below the levels of a medical dose. And utilities insist that their water is safe.

But the presence of so many prescription drugs — and over-the-counter medicines like acetaminophen and ibuprofen — in so much of our drinking water is heightening worries among scientists of long-term consequences to human health.

In the course of a five-month inquiry, the AP discovered that drugs have been detected in the drinking water supplies of 24 major metropolitan areas — from southern California to northern New Jersey, from Detroit to Louisville, Ky.

Water providers rarely disclose results of pharmaceutical screenings, unless pressed, the Associated Press found.

For example, the head of a group representing major California suppliers said the public "doesn't know how to interpret the information" and might be unduly alarmed.

When people take pills, their bodies absorb some of the medication, but the rest of it passes through and is flushed down the toilet. The wastewater is treated before it is discharged into reservoirs, rivers, or lakes.

Then, some of the water is cleansed again at drinking water treatment plants and piped to consumers. But most treatments do not remove all drug residue.

While researchers do not yet understand the exact risks from decades of persistent exposure to random combinations of low levels of pharmaceuticals, recent studies, which have gone virtually unnoticed by the public, have found alarming effects on human cells and wildlife.

"We recognize it is a growing concern, and we're taking it very seriously," said Benjamin H. Grumbles, assistant administrator for water at the US Environmental Protection Agency.

The Associated Press reviewed hundreds of scientific reports, analyzed federal drinking water databases, visited environmental study sites, and treatment plants and interviewed more than 230 officials, academics, and scientists.

They also surveyed the nation's 50 largest cities and a dozen other major water providers, as well as smaller community water providers in all 50 states.

Here are some of the key test results:

- Officials in Philadelphia said testing discovered 56 pharmaceuticals or byproducts in treated drinking water, including medicines for pain, infection, high cholesterol, asthma, epilepsy, mental illness, and heart problems. Sixty-three pharmaceuticals or byproducts were found in the city's watersheds.
- Antiepileptic and antianxiety medications were detected in a portion of the treated drinking water for 18.5 million people in southern California.
- Researchers at the US Geological Survey analyzed a Passaic Valley Water Commission drinking water treatment plant, which serves 850,000 people in northern New Jersey, and found a metabolized angina medicine and the mood-stabilizing carbamazepine in drinking water.
- A sex hormone was detected in San Francisco's drinking water.
- The drinking water for Washington, D.C., and surrounding areas tested positive for six pharmaceuticals.

The federal government doesn't require any testing and hasn't set safety limits for drugs in water. Some providers screen only for one or two pharmaceuticals, leaving open the possibility that others are present.

Of the 62 major water providers contacted, the drinking water for 28 was tested. Boston is among the 34 that haven't been tested, along with Baltimore, Chicago, Houston, Miami, New York, and Phoenix.

The investigation also indicates that watersheds, the natural sources of most of the nation's water supply, also are contaminated. Tests were conducted in the watersheds of 35 of the 62 major providers surveyed by the Associated Press and pharmaceuticals were detected in 28.

Yet officials in six of those 28 metropolitan areas said they did not go on to test their drinking water: Fairfax, Va.; Montgomery County in Maryland; Omaha; Oklahoma City; Santa Clara, Calif.; and New York City.

Of the 28 major metropolitan areas where tests were performed on drinking water supplies, only Albuquerque; Austin, Texas; and Virginia Beach, Va., said tests were negative.

Calif. dunes lure off-road enthusiasts, smugglers

By Richard Marosi
LOS ANGELES TIMES

of fortification that they hope will cut down on incursions.

the Department of Homeland Security seems willing to flex its

EDCs and PPCPs

3

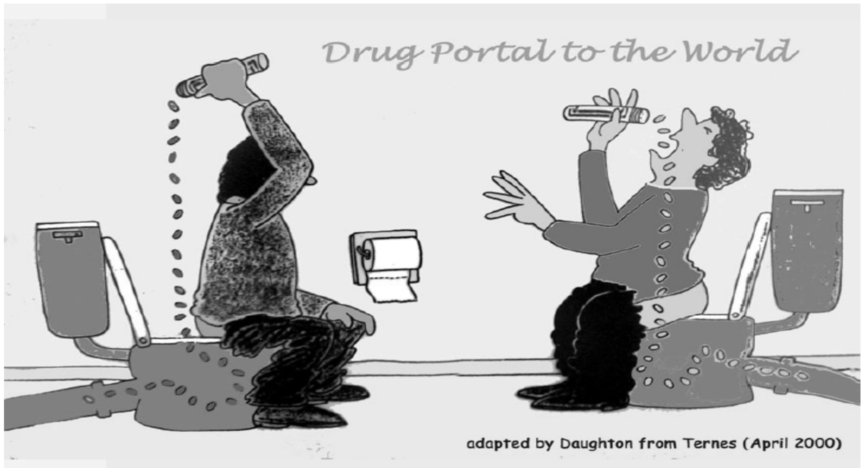
- Why study these?
  - Direct impacts on human health
    - Maybe not the most important?
  - Public perception
    - Becoming a very sensitive issue
  - Direct impacts on ecological health
    - Well documented: feminization of fish, etc.
  - Tracers of wastewater contamination
  - Indicators & promoters of antibiotic resistance
  - Precursors to more Hazardous DBPs

WW Tracers

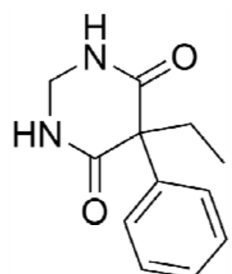
4

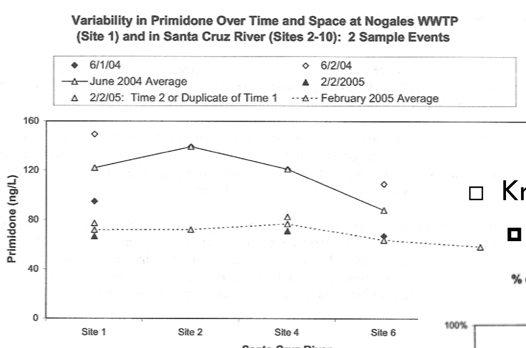
- WW contributions: Near conservative PPCP tracers
  - Primidone
  - Others? Carbamazepine, caffeine, etc.
- Raw vs Treated: Chiral PPCPs
  - Racemic mixtures that undergo enantioselective biodegradation
  - Analysis of enantiomeric fractions may permit discrimination between raw and treated WW contributions
    - Propranolol example: Fono & Sedlak, 2005 [ES&T]

Sources (2)

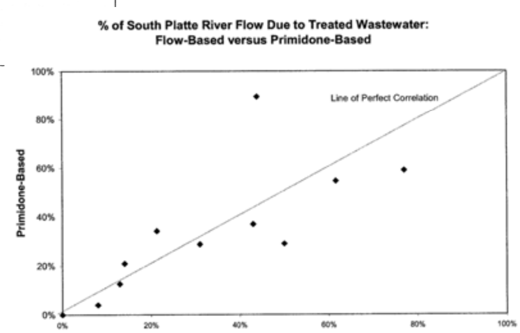


Primidone





- Krasner et al., 2006
  - WQTC



Antibiotic Resistance

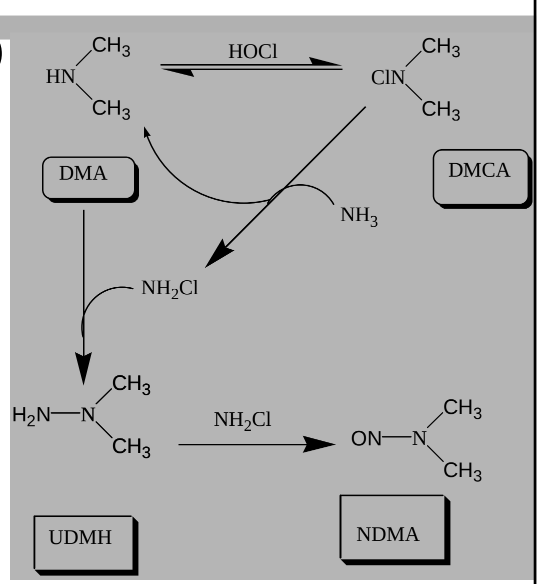
7

- One of the most critical human health challenges of the 21st century (WHO report)
  - >1,000,000 Americans infected each year
  - 14,000 deaths annually
- Cause: antibiotics are everywhere
  - Up to 95% of antibiotics in US are excreted in an unaltered state
  - Over prescription in humans
  - Heavy use in agriculture
- Result: Antibiotic resistant genes (ARGs) are ubiquitous in the aquatic environment
  - e.g., Pruden et al., 2006 [ES&T]

Precursors to NDMA??

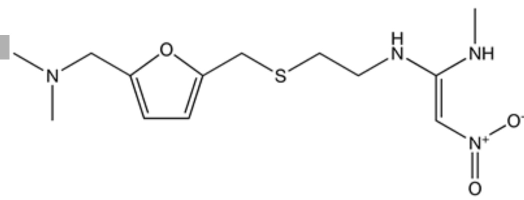
8

- NDMA (nitrosodimethylamine) is a very potent probable human carcinogen
- Formation of NDMA from chloramination of dimethylamine (DMA)
  - Not enough DMA to account for anything much
- NDMA formation is **<u>much</u>** higher in municipal WW than in pristine natural waters
- Major precursor is not natural???



The Unnatural Precursor?

9

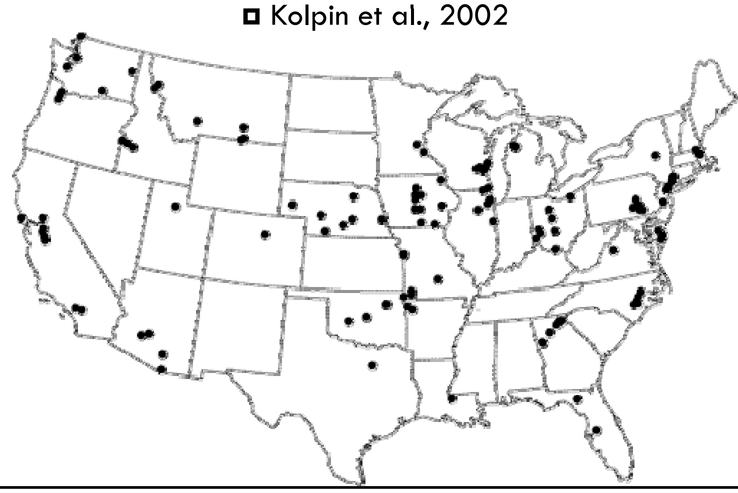


- Ranitidine (Zantac)
  - 63% conversion to NDMA
    - Schmidt et al., 2006 [WQTC]
  - Introduced in 1981, largest selling prescription drug by 1988
    - Stomach ulcers and esophageal reflux
  - Mean concentration of 3000 ng/L estimated for raw municipal WW (national average)
    - Sedlak 2005 AWWARF report
  - 450 ng/L formation in raw WW expected
  - Unknowns: how much does this persist in treatment and in the environment?

USGS Survey

10

- 138 stream sampling sites
  - Kolpin et al., 2002



Removal by coagulation & disinfection/oxidation

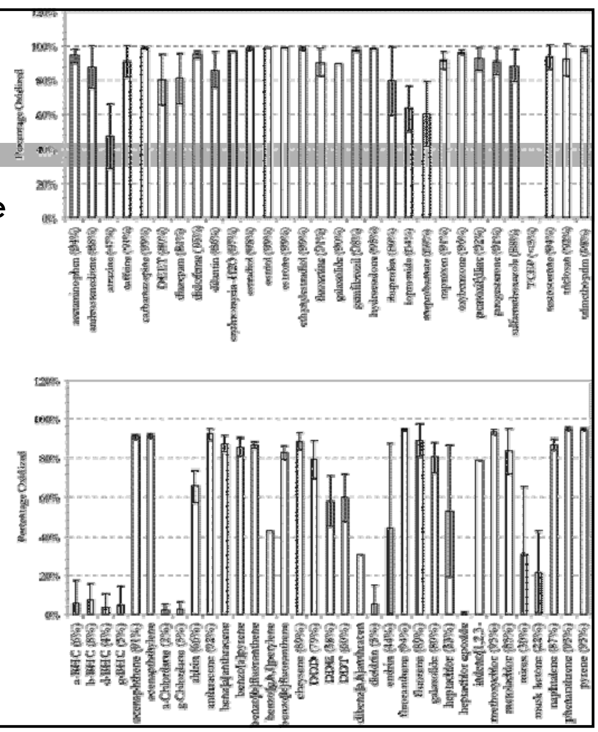
11

- Coagulation
  - Generally no
    - Nearly all EDCs and PPCPs are too small or too low in functional group density to be susceptible
- Oxidation/Disinfection
  - Yes to some
  - Chlorination: primary amines and activated aromatics (especially phenolics) and activated aliphatics
  - Ozonation: Many aromatics; aliphatics if hydroxyl radicals are formed
- Oxidation & Biofiltration
  - Almost nothing is known

Ozonation

12

- Removal by ozone



Westerhoff et al., 2005 [EST 39:17:6649]

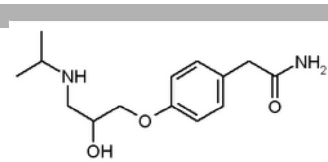
Selected Compounds

13

EDC	PhAC	WW associated
17β-estradiol	Atorvastatin or Gemfibrozil	Nitrosodimethylamine
Estriol	Naproxen	
Estrone	Sulfamethoxazole	
17α-ethinylestradiol	Trimethoprim	
Perchlorate	Atenolol	
	Ranitidine	
	Primidone?	

Beta-Blockers: Atenolol

14

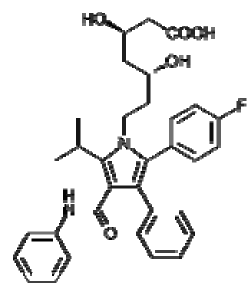


- Atenolol is a representative of the group of Beta-blockers, for treating cardiovascular disease.
- This particular drug has been in use since 1976.
- Sedlak and co-workers (2005) estimate a nationwide average raw municipal wastewater concentration of about 1500 ng/L.
- This compound is rather unreactive with free chlorine, as it lacks activated aromatic structures as well as reactive nitrogen sites.
- It does not appear to have been tested for reaction with ozone
- May be used as an indicator of treated vs raw WW as propranolol was by Fono & Sedlak

Statins: Atorvastatin

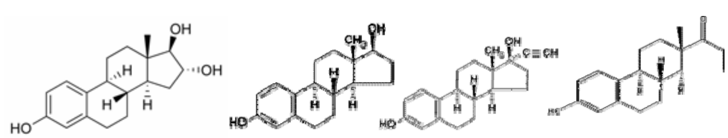
15

- This compound is more commonly known as Lipitor, and it is representative of a larger group of cholesterol-reducing drugs called statins.
- It does not appear to have been tested for removal by coagulation or reaction with either chlorine or ozone.
- Based on its structure, we would expect it to be slightly reactive with ozone, but little affected by the other treatments



Reproductive Hormones: 17b-estradiol, 17a-ethinylestradiol, Estrone, Estriol

16

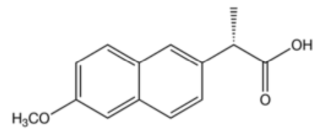


Estriol 17β-Estradiol Ethynylestradiol Estrone

- Three of these four (17b-estradiol, Estrone, Estriol) are naturally occurring human estrogens. Ethinylestradiol is the estrogen component of oral contraceptives.
  - All four of these compounds have the fundamental steroid skeleton, with many similarities in positioning of the functional groups.
- All of these compounds are rapidly destroyed by free chlorine
  - (Westerhoff et al., 2005; Deborde et al., 2004). It's quite likely that the phenolic "A" ring is the initial site of attack and the most reactive structure within each of these compounds.
- Reaction with chlorine should result in large fragments that are partially oxygenated or even halogenated.
  - Estradiol has been found to produce at least 7 daughter products that persist in treated waters (Irmak et la., 2005; Hu et al., 2003)

Non-steroidal anti-inflammatory: Naproxen

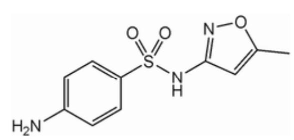
17



- Naproxen is a common arthritis treatment, intended to reduce pain and inflammation.
- Its mean concentration in US wastewaters has been estimated to be about 2400 ng/L (Sedlak et al., 2006). Limited occurrence data has centered around 300 ng/L in US wastewaters
- It is quite reactive with ozone, and surprisingly reactive with chlorine too.
- Probably many daughter products

Sulfonamide Antibiotic: Sulfamethoxazole

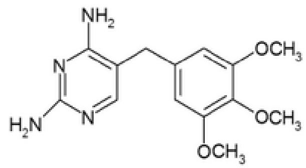
18



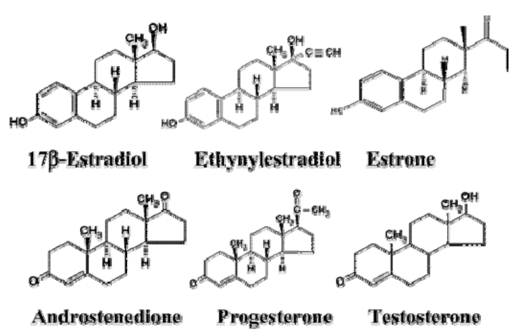
- This antibiotic is a major component of Bactrim.
- Its median concentration in treated wastewaters has been mesured at 1400 ng/L, a value quite close to its nationwide estimated level of 3200 ng/L.
- This compound is moderately reactive with free chlorine and ozone

Bacteriostatic Antibiotic: Trimethoprim

19

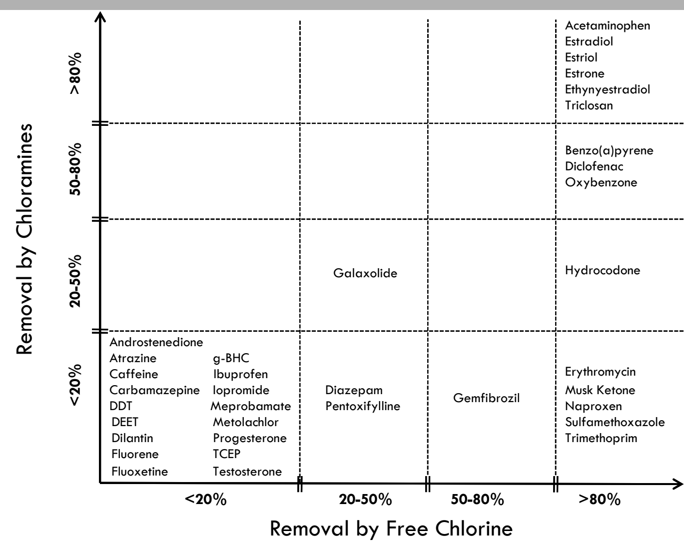


- This particular antibiotic is widely used for treatment or urinary tract infections. It is also a member of the group of dihydrofolate reductase inhibitors.
- It is quite prevalent in US wastewaters (500 ng/L median; 1500 ng/L estimated nationwide).
- It is extremely reactive with free chlorine, as would be expected from its structure. It is quite likely that the molecule is extensively degraded and oxidized by chlorine or ozone treatments.



Removal by Residual Disinfectants

Snyder et al., 2007 [AwwaRF report]



- Rates
  - Pinkston & Sedlak, 2004

TABLE 2. Rate Constants for the Reaction of Pharmaceuticals and Model Compounds with Chlorine

	k_1 ($M^{-1}s^{-1}$)	k_2 ($M^{-1}s^{-1}$)	k_3 ($M^{-1}s^{-1}$)	k_{H^-} ($M^{-2}s^{-1}$)	k_{mono} ($M^{-1}s^{-1}$)	half-life (min), HOCl/OCl$^-$ [a]	half-life (min), monochloramine[a]
Pharmaceuticals							
acetaminophen	3.1×10^0	7.0×10^3			$<1.3 \times 10^{-3}$	5.2×10^0	$>6.2 \times 10^4$
atenolol			1.7×10^{-2}	0.0×10^0	$<3.0 \times 10^{-2}$	6.3×10^3	$>2.7 \times 10^3$
gemfibrozil			7.3×10^{-1}	4.2×10^6	$<8.0 \times 10^{-4}$	9.3×10^1	$>1.0 \times 10^5$
indometacine			6.7×10^1	6.9×10^7	$<1.5 \times 10^{-2}$	1.4×10^0	$>5.4 \times 10^3$
metoprolol			1.7×10^{-2}	1.1×10^4	$<3.0 \times 10^{-2}$	5.9×10^3	$>2.7 \times 10^3$
nadolol			1.8×10^{-1}	1.3×10^6	$<4.0 \times 10^{-4}$	3.4×10^2	$>2.0 \times 10^5$
naproxen			2.4×10^0	8.7×10^6	$<8.0 \times 10^{-4}$	3.3×10^1	$>1.0 \times 10^5$
propranolol			7.5×10^0	6.6×10^6	$<3.0 \times 10^{-2}$	1.3×10^1	$>2.7 \times 10^3$
Model Compounds							
anisole			1.9×10^{-2}	1.9×10^4			
butyl phenyl ether			2.5×10^{-2}	8.2×10^4			
1-methoxynaphthalene			3.5×10^{-1}	2.4×10^7			
3-methylanisole			3.3×10^{-1}	1.2×10^6			
4-methylanisole			3.2×10^{-2}	4.7×10^4			
1-phenoxy-2-propanol			1.4×10^{-2}	2.5×10^4			

[a] The half-lives were calculated assuming a total chlorine concentration of 10 mg/L and a pH value of 7.

Aromatic EDCs

- Rates
  - Deborde et al., 2004
    - Env. Sci Technol. 38:5577

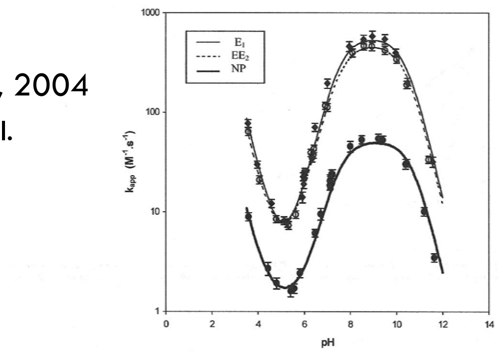


FIGURE 2. pH-dependence of the apparent-second-order rate constants of nonylphenol, ethinylestradiol, and estrone chlorination at 20 ± 2 °C. Symbols represent measured data and lines represent the model calculations.

Aromatic EDCs (cont.)

- Rates
  - Deborde et al., 2004

TABLE 2. Second-Order Rate Constants Calculated for the ED Chlorination Mechanism (20 ± 2 °C, 3.5−12.0 pH Range)

compounds	k_1' (±σ) (M^{-1} s^{-1})	k_1 (±σ) (M^{-2} s^{-1})	k_2 (±σ) (M^{-1} s^{-1})	k_3 (±σ) (M^{-1} s^{-1})
4-*n*-nonylphenol	3.02 (0.34) × 10^7	3.02 (0.34) × 10^4	1.31 (0.13)	7.5 (0.27) × 10^4
17α-ethinylestradiol	2.04 (0.16) × 10^8	2.04 (0.16) × 10^5	4.33 (0.53)	3.52 (0.10) × 10^5
β-estradiol	2.24 (0.17) × 10^8	2.24 (0.17) × 10^5	3.78 (0.42)	3.64 (0.11) × 10^5
estrone	2.62 (0.18) × 10^8	2.62 (0.18) × 10^5	3.74 (0.57)	4.15 (0.17) × 10^5
estriol	1.82 (0.15) × 10^8	1.82 (0.15) × 10^5	4.82 (0.50)	3.56 (0.12) × 10^5

$$EDC + HOCl + H^+ \xrightarrow{k_1} products$$

$$EDC + HOCl \xrightarrow{k_2} products$$

$$EDC^- + HOCl \xrightarrow{k_3} products$$

TABLE 3. Apparent-Second-Order Rate Constants and Half-Life Times Calculated at pH 7, 20 °C for Total Chlorine Doses Ranging from 0.1 to 1 mg/L

compounds	k_{app} (M^{-1} s^{-1})	$t_{1/2}$ (min) chlorine concn 0.1 mg/L	chlorine concn 0.5 mg/L	chlorine concn 1 mg/L
4-*n*-nonylphenol	12.6	651	130	65.1
17α-ethinylestradiol	112.1	73.2	14.6	7.3
β-estradiol	115.2	71.2	14.2	7.1
estrone	131.1	62.6	12.5	6.3
estriol	113.6	72.2	14.4	7.2

25

- To next lecture