An informatic approach to estimating ecological risks posed by pharmaceutical use:

Human prescription pharmaceuticals

Mitch Kostich and Jim Lazorchak

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Overview

Motivation + needs

Long-term plan

The model

Example data

Next steps

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Motivation

Over 2000 prescription products currently in use

Many excreted as parent or active metabolites

Many found at ppt->ppb levels in the environment

Designed to be potent in part to minimize side effects

Some have lab effects at relevant concentrations

Similar to troubling phenomena seen in field

Concern about human exposure (swim, fish, drink)

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Motivation

Occurrence and effects data still too limited

- cannot reliably identify and quantify risks
- reflects scope and complexity of problem
- drugs vary in chemical and biological properties
- toxicity and potency in most non-humans unknown
- sensitivities can vary greatly across species

Many chemicals to look for

- 1000's of drugs, metabolites, degradates, etc.
- slow, difficult, and expensive with current technology

Many places to look

- what is relative concentration in different compartments?
  - influents, effluents, sludge, surface water,
  - ground water, sediments, run-off, tissues, etc.
- WWTP effluents a pretty good choice:
  - hi conc; cleaner than influent; can model downstream

Motivation

How much do concentrations vary and why?

many variables:

demographics, technology, hydrology, season, etc.

how well can one reading predict another?

Effects data often based on older testing paradigms

end points not reflective of drug action (i.e. LD50)

duration of exposure too short (i.e. days v. months)

concentrations often not environmentally relevant

Interesting anecdotal cases:

ethinyl estradiol and fish reproduction

SSRIs and amphibian metamorphosis

both seen with chronic low-level exposure

toxicity related to therapeutic mechanism of action

both may involve developmental 'windows of vulnerability'

Some unmet research needs

Occurrence data being gathered world-wide

Are we looking for the right things?
- the largest threats
- the right molecules (active metabolites?)

What is the significance of the occurrence data?
- what is the likelihood of toxicity?
- who or what is likely to be affected?
- what form of toxicity might result?

A conceptual framework and quantitative model
- source-to-sink mechanistic model
- for estimating ecological and human risks
- for estimating effectiveness of proposed mitigation

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Long-term plan:

Use available data to rank most likely threats

'reasonable worst case' scenario
estimate WWTP effluent concentration
rank based on ratio of a predicted concentration
divided by a predicted no-effect concentration
ratio also serves as 1st order risk estimate

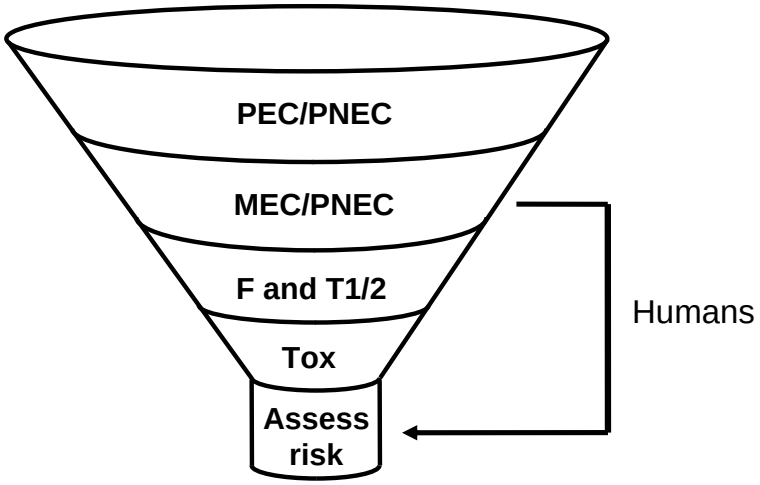
Measure concentrations for as many as possible

use ranking to prioritize measurements
characterize variability - for use in risk assessment
refine ranking by replacing predicted concentrations

Perform chronic toxicity testing

use updated ranking to prioritize measurements
upper end of measured environmental concentrations
organism and endpoint choice guided by known actions
update ranking and finalize risk assessment

Long-term plan



Mitigation

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The model: worst case estimation

Cannot produce an answer on its own

- too many uncertainties; too broad an error bar
- aim is to guide measurements, not replace them

By skewing error towards a 'reasonable worst case'

- can approach the problem with the available data
- data gaps filled with 'worst case' dummy values
- can answer: likelihood of 'an effect' is no worse than X
- for some drugs, X is worrisome
  - can be a result of model skew and data gaps
  - approach refines thru subsequent measurements
- for many others, even 'worst case' does not look too bad
  - narrows scope of problem significantly

Real 'worst case':

- **a**ssumptions about 'reasonable worst case' may be wrong

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The model: sources of medication

Only source = human prescriptions from 2004
- no OTC, no manufacturing, no grey market,
- no pets, no agriculture, no etc.

Two varieties of data:
- **dollar value sold**
  - divide by cost per unit to determine amount
  - used cheapest price found = 'worst case'
- **scripts written**
  - multiply by script size
  - used largest customary script size = 'worst case'
- **both are 'freebie' lists, limited in scope + quality**
  - incomplete active ingredient and formulation listing
  - gaps filled with 'worst case' dummy values

Model estimate = lower of these two over-estimates

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The model: sources of medication

Fraction 'wasted' thru disposal + wash off:

5% for chronic administration
15% for acute administration
33% for topical meds
'right numbers' not known

Rest assumed to pass thru human body

often know how much gets inactivated
if not, assume all stays active = 'worst case'

Not considered:

en route, in wwtp, and subsequent degradation
partitioning, and post-wwtp dilution
all these lower aqueous concentration - 'worst case' ok

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The model: expressing concentration

Metabolites complicate things

- many medicines converted to 'metabolites' in body
- excreted metabolites can have biological activity
- parent compound can also be excreted intact
- implications for excreted activity: must add up activities
- implications for chemistry: ideal analyte not always obvious

Complex mixture of actives often excreted

- parent + variety of metabolites often excreted together
- different metabolites have different potencies
- potency can be expressed in terms of parent potency
- can express net activity by assuming additive effects
- express net activity as equivalent amount of parent
- single number simplifies risk rankings and assessment

More than one molecule may be behind one number!!!

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The model: toxicity and potency

Pharmaceuticals are unusually well studied pollutants

human physiological effects extensively studied
absorption, metabolism and excretion parameters known
relationship between blood levels and effects known
chronic toxicity and developmental effects known
molecular target frequently known/suspected
mechanisms of inactivation and clearance often known

For humans, intake rates are primary unknown

if exposures are known, risk estimates can be made
typically express exposure in terms of days/dose

For non-humans, not as clear

toxin sensitivities can differ dramatically across species
tend to be close between mammals (usually well within 100x)
can be much larger between classes (i.e. fish v. mammal)

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The model: toxicity and potency

Simplifying assumptions for non-humans

- assume mechanism of toxicity related to mechanism of human therapeutic action
- assume human potency related to potency in non-humans
- assumptions consistent with scant evidence
- use what's known about pathway to guide toxicity testing
- phylogenetic distribution suggests species of concern

A 'worst case' for non-humans

- many known 'peculiar sensitivities' due to extended half-life
- sensitive critter cannot clear medicines like humans
- 'worst case' would usually be equilibration with environment
  - absence of any active clearance/concentration processes
  - plasma concentration = environmental concentration
  - tissue concentrations then fugacity driven
- can estimate significance of this case if assume similar intrinsic potency between human and non-human

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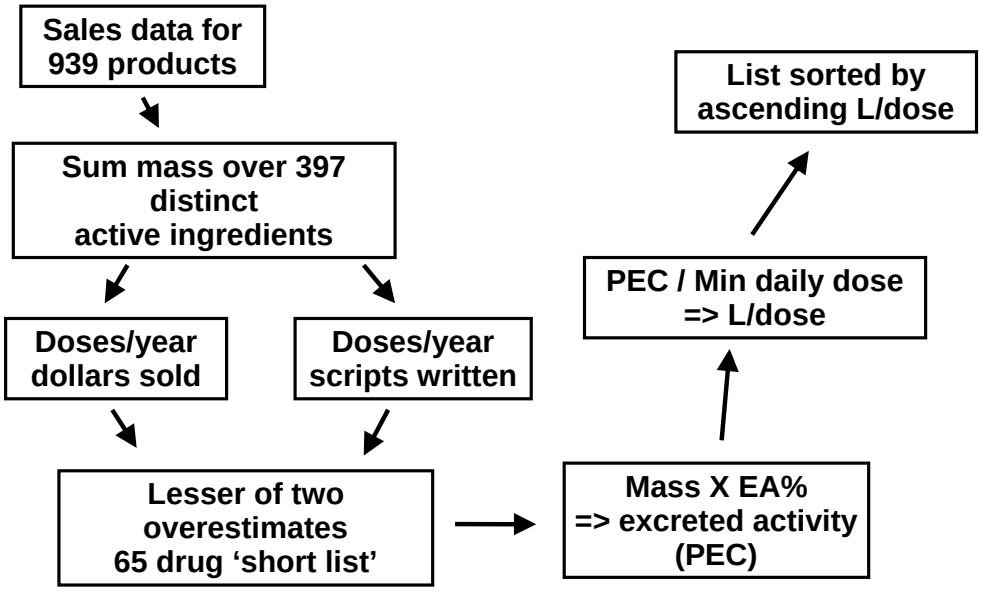
The model: data flow



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The model: sneak peak at some data

These are preliminary data based on $ sales only

script written data will narrow uncertainties + reorder a bit

Tend to dramatically overestimate in some cases

if large number of products with the ingredient
if many products small sellers – not listed in marketing data
if wide price range – lowest not very representative
'worst case' fudge factors used for imputing sales data
sum of fudge factors over many products -> large error
hydrochlorothiazide a good example

'*' indicates drug is OTC also, but only scripts counted

List does not include:

vitamins, minerals, electrolytes, x-ray contrast media

Mass dispensed per year

Active Ingredient	Lo kg/yr	Hi kg/yr	DD (mg)
acetaminophen*	9372331	20872932	300
hydrochlorothiazide	3160273	23049235	12.5
ibuprofen*	2931677	5799611	200
amoxicillin	2198734	3952621	750
metformin	1516572	2470512	250
gabapentin	1071705	1115608	900
...	...	...	...
carbamazepine	64841	972622	200
conjugated estrogens	2732	2983	0.15
estradiol	733	67641	0.5
ethinyl estradiol	75	463	0.02
...	...	...	...
calcitriol	0.0128	0.0996	0.00025

Liters / daily dose

Active Ingredient	EA %	Disp %	PEC Hi (ppt)	PEC Hi /Cmax	L/dose Hi
hydrochlorothiazide	100	5	338959	3.9784	37
levothyroxine	3-35	5	39	1.6360	318
estradiol	37-55	5	569	474.5631	878
acetaminophen	89	15	278255	0.0348	1078
nitroglycerin	0-10	5	250	0.4633	1200
hydrocortisone	3-10	33	8093	8.1585	1236
promethazine	1-100	15	10547	12.9571	1778
hydrocodone	23-98	15	3616	0.4834	2074
prednisolone	15-80	33	2342	0.1018	2135
prednisone	13-90	15	2007	0.0669	2491

Predicted effluent concentration / intrinsic potency (Cmax free)

Active Ingredient	EA %	Disp %	PEC Hi (ppt)	PEC Hi /Cmax	L/dose Hi
estradiol	37-55	5	569	474.5	878
promethazine	1-100	15	10547	12.9	1778
atorvastatin	1-100	5	2906	10.7	3441
hydrocortisone	3-10	33	8093	8.1	1236
simvastatin	3-36	5	641	6.4	7801
hydrochlorothiazide	100	5	338959	3.9	37
ethinyl estradiol	43-80	5	6	3.6	3626
sertraline	14-23	5	615	2.0	40619
levothyroxine	3-35	5	39	1.6	318

Mechanisms of action

CORTICOSTEROIDS
prednisone
fluticasone
hydrocortisone
betamethasone
prednisolone
methylprednisolone
triamcinolone

OPIOIDS
oxycodone
hydrocodone
codeine
fentanyl
morphine
propoxyphene
diphenoxylate

CNS MONOAMINE AGONISTS
sertraline
amphetamine
paroxetine
amitriptyline
venlafaxine
phentermine

BENZODIAZEPINES
alprazolam
clonazepam
diazepam
lorazepam

DIURETICS
spironolactone*
hydrochlorothiazide
triamterene
furosemide

***Also an anti-androgen**

Mechanisms of action

BETA-BLOCKERS
atenolol
metoprolol
propranolol
carvedilol

ANTI-DIABETICS
metformin
insulin
glipizide
glyburide

ESTROGENS
conjugated estrogens
ethinyl estradiol
estradiol

ANGIOTENSIN ANTAGONISTS
lisinopril
ramipril
valsartan

H1 ANTIHISTAMINES
cetirizine
promethazine
meclizine

STATINS
simvastatin
atorvastatin
rosuvastatin

NO AGONISTS
nitroglycerin
isosorbide mononitrate

TRANSPEPTIDASE INHIBITORS
amoxicillin
penicillin v

Mechanisms of action

clonidine	**alpha-adrenergic agonist**
terazosin	**alpha-adrenergic antagonist**
acetaminophen	**analgesic/antipyretic (cox2 inhibitor?)**
warfarin	**anti-coagulant (vitamin K pathway)**
albuterol	**beta-2-adrenergic agonist**
digoxin	**Na/K-ATPase inhibitor**
ibuprofen	**NSAID (cox1 and cox2 inhibitor)**
theophylline	**PDE III and IV inhibitor**
norethindrone	**progestin**
lansoprazole	**proton pump inhibitor**
amlodipine	**slow calcium channel blocker**
levothyroxine	**thyroid hormone**
allopurinol	**xanthine oxidase inhibitor**

Pilot summary*: molecular targets

							84	78	80	79
azithromycin	B	prok 50S subunit	NA	NA	NA	NA	NA	NA	NA	NA
zolpidem	B	GABRA1	100	100	97	90	50	ND	ND	ND
escitalopram	C	SLC6A4	97	91	?	82	70	60	ND	ND
lansoprazole	B	ATP4A	100	90	85	88	85	83	ND	ND

***Based on an analysis of 200 name brand products**

Poster presented at Setac-Baltimore, November 2005

Currently, have 121 molecular targets mapped onto 34 taxon bins

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Major uncertainties

Marketing data!!!

Chemical stability en route + in WWTP

Potency in non-mammals

Spatial and temporal variability

- in the works: part of literature review

Uncounted sources

OTC, agriculture, manufacture, pets
natural excretion – in the works

Future directions: in silico

Compare published data to model

- characterize variability in occurrence
- iteratively improve model

Model improvements

- natural excretion – corticosteroid, repro, thyroid
- parameters for en route stability
- parameters for WWTP/activated sludge stability
- partitioning between matrices
- better PK modeling -> BCF + biomagnification
- include data on known active uptake systems

Better data sources

- more complete for ingredients of concern
- 2006 data
- OTC? non-human?

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Future directions: at the bench

What analytes need to be measured?
- coordination with others (underway)
- method development (underway)
- monitoring

Source identification

Internal dose
- plasma concentration
- 'omics response

Chronic toxicity testing

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Identifying Chemical Compounds from Wastewater Discharges

Susan T. Glassmeyer[1], Edward T. Furlong[2], and Dana W. Kolpin[3]

[1]U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, Cincinnati, Ohio

[2]U.S. Geological Survey, National Water Quality Laboratory, Denver, Colorado

[3]U.S. Geological Survey, Iowa City, Iowa

Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.

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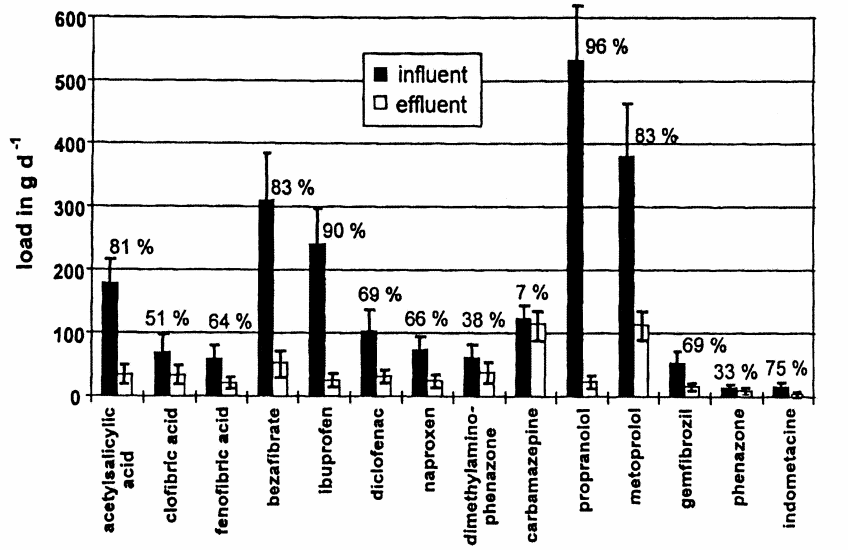
Presentation Outline

- Bench scale studies of effects of chlorination on pharmaceuticals
- Field study of persistence of pharmaceuticals and other wastewater chemicals downstream from wastewater treatment plants (WWTPs)
- Any correlation between lab predictions and observed concentrations?

Pharmaceutical Elimination from a Sewage Treatment Plant

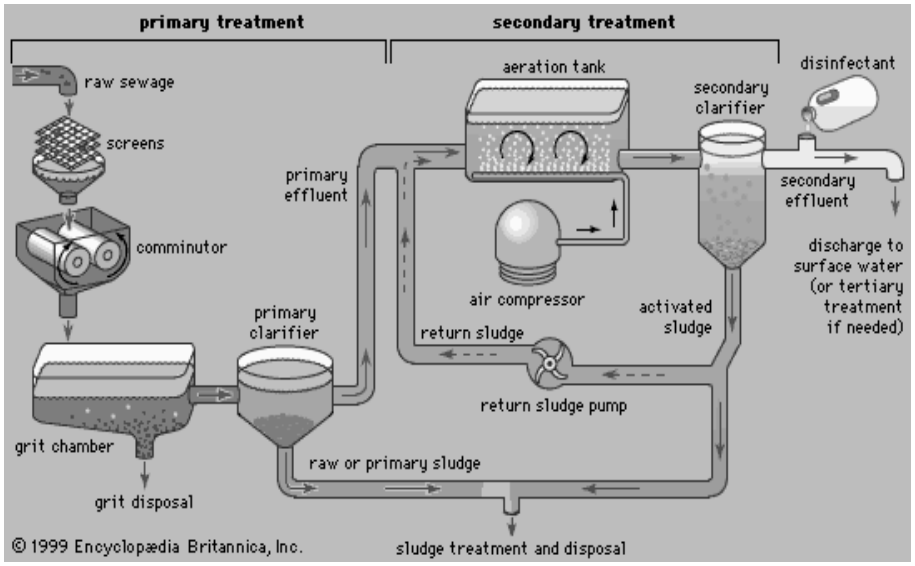


From: Ternes, T.A. **1998** Occurrence of Drugs in German Sewage Treatment Plants and Rivers. *Water Research* 32:3245-3260.

Other WWTP removal studies

- Lee, H. B.; Peart, T. E.; Svoboda, M. L. Determination of endocrine-disrupting phenols, acidic pharmaceuticals, and personal-care products in sewage by solid-phase extraction and gas chromatography-mass spectrometry Journal of Chromatography A 2005, 1094, 122-129.
- Gros, M.; Petrovic, M.; Barcelo, D. Multi-residue analytical methods using LC-tandem MS for the determination of pharmaceuticals in environmental and wastewater samples: a review Analytical and Bioanalytical Chemistry 2006.
- Quintana, J. B.; Reemtsma, T. Sensitive determination of acidic drugs and triclosan in surface and wastewater by ion-pair reverse-phase liquid chromatography/tandem mass spectrometry Rapid Communications in Mass Spectrometry 2004, 18, 765-774.
- Quintana, J. B.; Weiss, S.; Reemtsma, T. Pathway's and metabolites of microbial degradation of selected acidic pharmaceutical and their occurrence in municipal wastewater treated by a membrane bioreactor Water Research 2005, 39, 2654-2664.
- Vieno, N. M.; Tuhkanen, T.; Kronberg, L. Seasonal variation in the occurrence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water Environmental Science & Technology 2005, 39, 8220-8226.
- Clara, M.; Strenn, B.; Gans, O.; Martinez, E.; Kreuzinger, N.; Kroiss, H. Removal of selected pharmaceuticals, fragrances and endocrine disrupting compounds in a membrane bioreactor and conventional wastewater treatment plants Water Research 2005, 39, 4797-4807.
- Bendz, D.; Paxeus, N. A.; Ginn, T. R.; Loge, F. J. Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hoje River in Sweden Journal of Hazardous Materials 2005, 122, 195-204.
- Roberts, P. H.; Thomas, K. V. The occurrence of selected pharmaceuticals in wastewater effluent and surface waters of the lower Tyne catchment Science of the Total Environment 2006, 356, 143-153.
- Lishman, L.; Smyth, S. A.; Sarafin, K.; Kleywegt, S.; Toito, J.; Peart, T.; Lee, B.; Servos, M.; Beland, M.; Seto, P. Occurrence and reductions of pharmaceuticals and personal care products and estrogens by municipal wastewater treatment plants in Ontario, Canada Science of the Total Environment 2006, 367, 544-558.

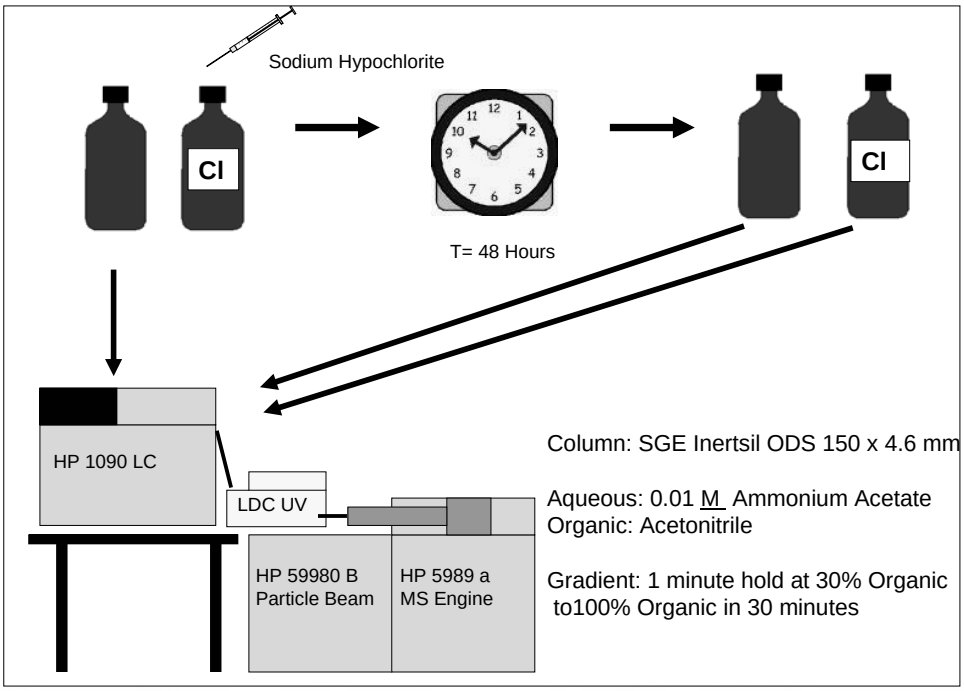
Sewage Treatment



From: www.britannica.com

So, what is happening to pharmaceuticals during sewage treatment?

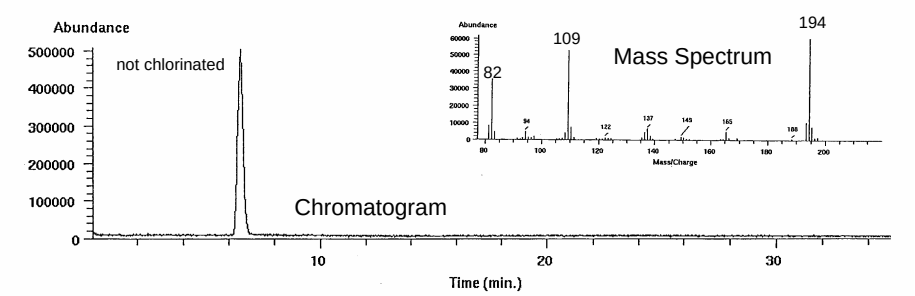
1. Sorbed to particulate matter- removed as sludge
2. Chlorinated during disinfection process
3. Destroyed (oxidized) during disinfection process
4. Degradation not related to disinfection (microbial, photolysis, etc)
5. Nothing- they pass through the system


Sodium Hypochlorite
Cl
T= 48 Hours
Cl
HP 1090 LC
LDC UV
HP 59980 B
Particle Beam
HP 5989 a
MS Engine
Column: SGE Inertsil ODS 150 x 4.6 mm
Aqueous: 0.01 M Ammonium Acetate
Organic: Acetonitrile
Gradient: 1 minute hold at 30% Organic
to100% Organic in 30 minutes

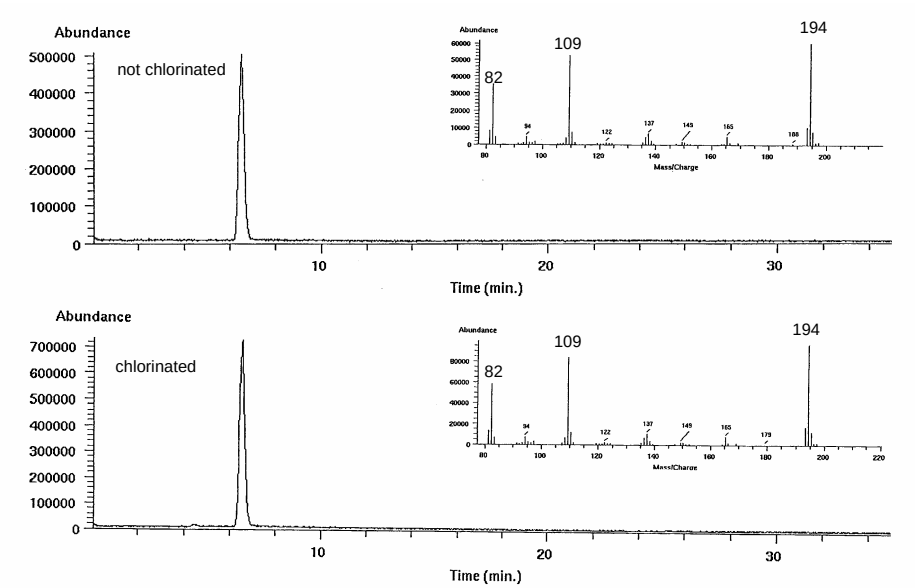
Particle Beam Pros and Cons

- Produces (mostly) complete EI spectra
  - Allows better elucidation of structural information
  - Able to use conventional spectral libraries for identification
- Solvent interferences prohibit scanning lower masses; difficult to see higher masses
- Calibration curves are neither linear nor stable
- Poor sensitivity (mg/ L)

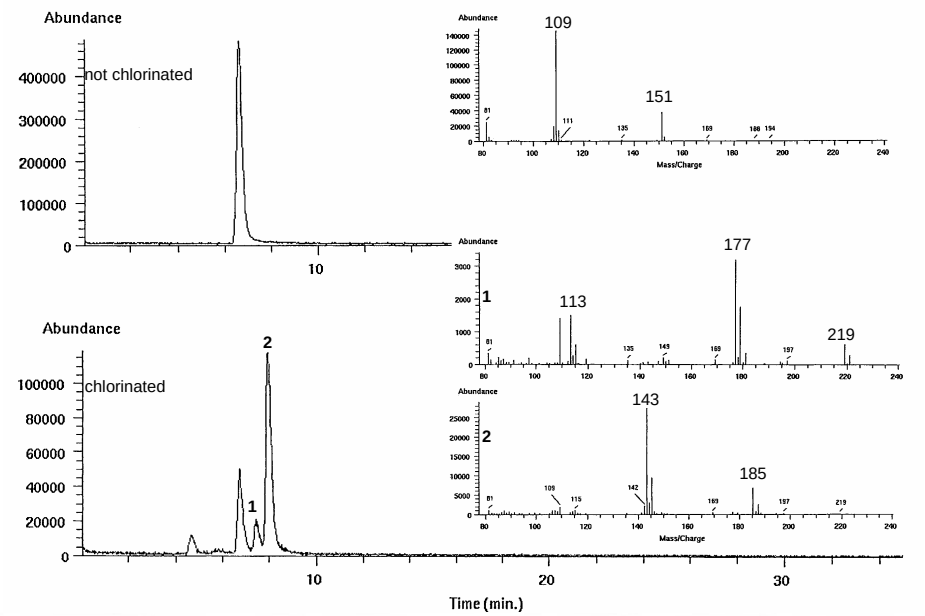
Caffeine (MW= 194.19)



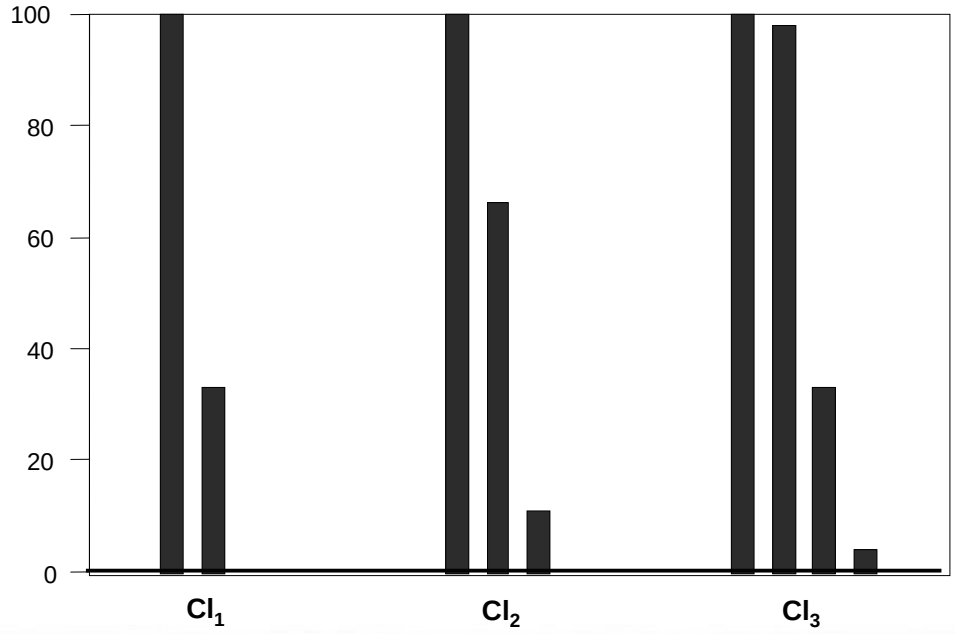
Caffeine (MW= 194.19)



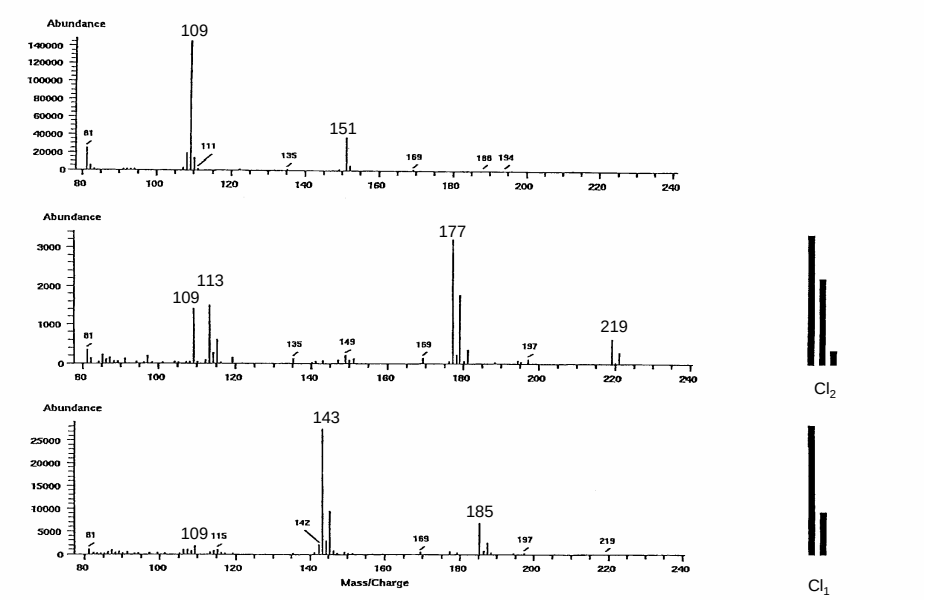
Acetaminophen (MW = 151.17)



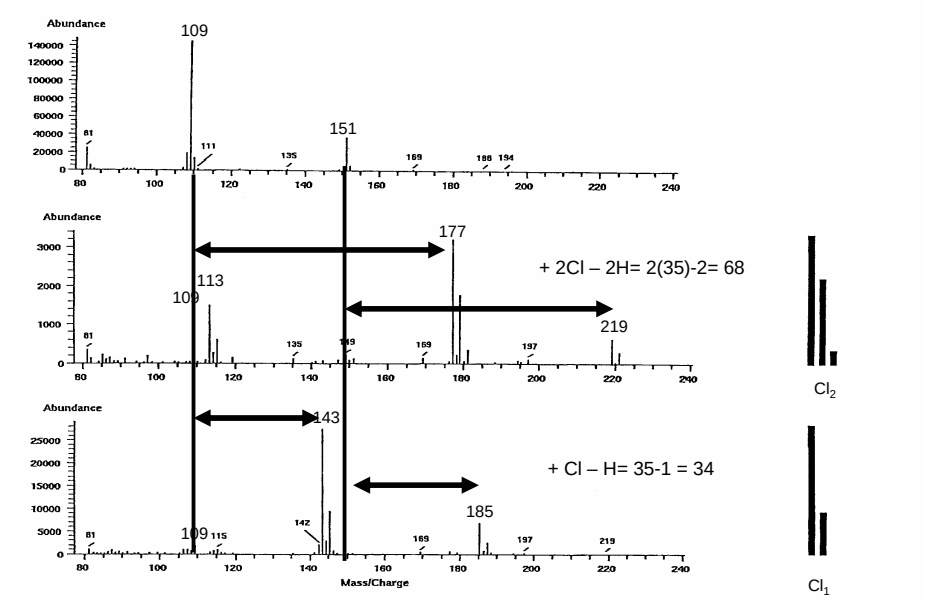
Mass Spectrometry 101: Chlorine Isotope Patterns



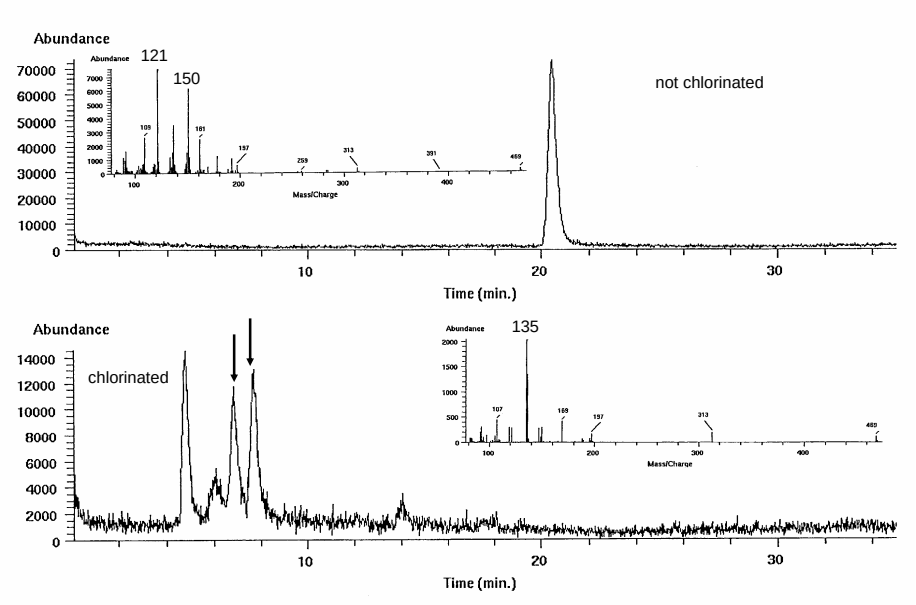
Acetaminophen Chlorination Patterns



Acetaminophen Chlorination Patterns



Diltiazem (MW = 414.53)



Data Summary

No Change	Chlorinated	Oxidized
aspirin	acetaminophen	amoxicillin
aspartame	gemfibrozil	cephalexin
caffeine		cimetidine
cotinine		diltiazem
1,7-dimethylxanthine		trimethoprim
6α-methyl-17α-hydroxy progesterone acetate		warfarin

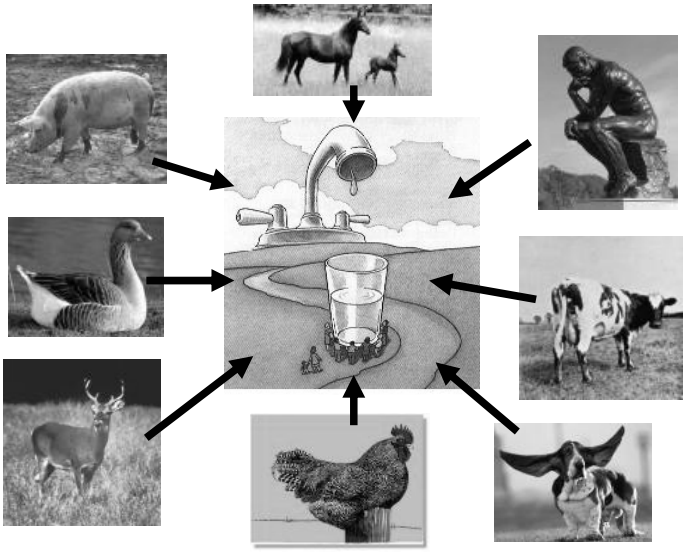
Lessons Learned

- Disinfection is one route for the removal of pharmaceuticals from water
- The addition of chlorine to the molecule is not common (at least not as seen by particle beam)
- Ramification on environmental occurrence?
- Glassmeyer, S.T.; Shoemaker, J.A. Effects of Chlorination on the Persistence of Pharmaceuticals in the Environment Bulletin of Environmental Contamination and Toxicology. 2005, 74, 24-31.
- Bedner, M.; Maccrehan, W. A. Transformation of acetaminophen by chlorination produces the toxicants 1,4-benzoquinone and N-acetyl-p-benzoquinone imine Environmental Science & Technology 2006, 40, 516-522.

Research Application:

Can pharmaceuticals (and other wastewater compounds) be used as indicators of human fecal contamination?

Sources of Fecal Pollution



Weakness of Current Microbial Indicators

- Biological assays require 18- 48 hours to grow and be visualized
- Lack specificity
  - Human v. animal
  - Fecal v. non-fecal
- May not always effectively protect against pathogens
  - Cryptosporidia outbreaks in Texas, Pennsylvania, Wisconsin, and Nevada when the water quality met Federal Standards using current microbial indicators
  - In 12% of the waterborne disease outbreaks in 1997-1998, neither total nor fecal coliform detected.

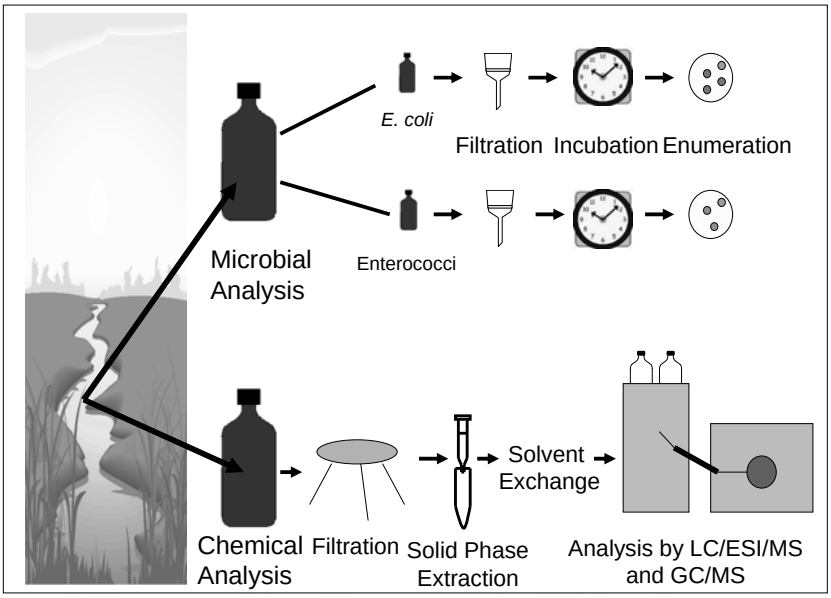
Why use Chemical Indicators?

- Rapid analysis times
- Able to discriminate human from animal fecal material
- Suite of compounds with various physical/ chemical properties may be more impervious to hydrological diversity
- However, must make sure they are persistent enough to survive wastewater treatment, but not so recalcitrant that they become ubiquitous
- "Transport of Chemical and Microbial Compounds from Known Wastewater Discharges: Potential for Use as Indicators of Human Fecal Contamination" *ES&T* 2005, 39, 5157-5169

Sampling Locations - 2002

- Focus on wastewater treatment plants
  - One Upstream
  - One Effluent
  - Two Downstream
- Two Background Locations

Experimental Approach

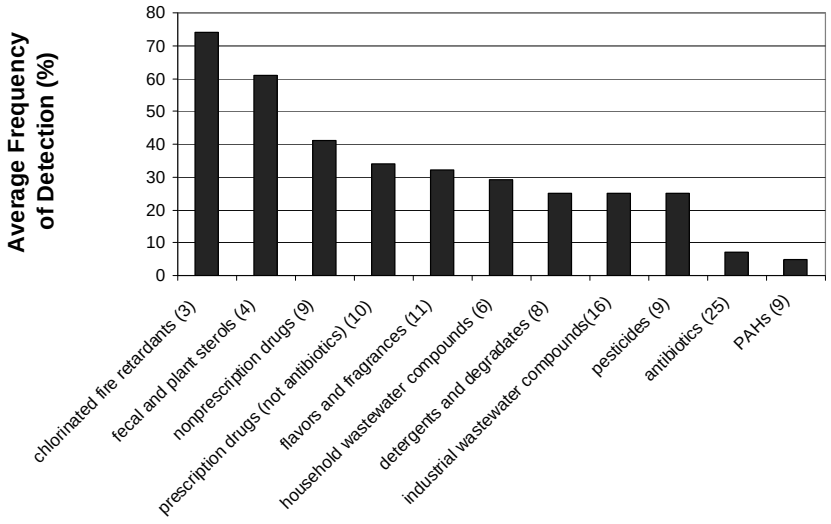


Overview of Results

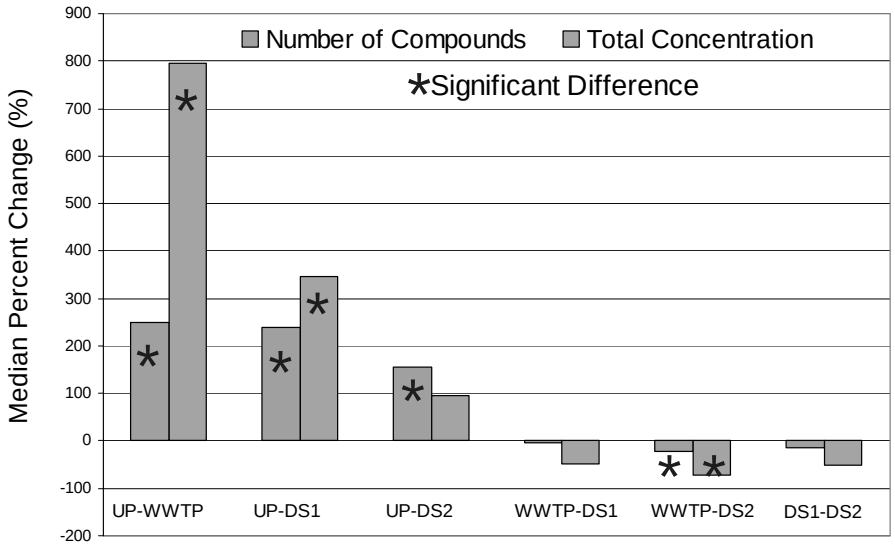
- Bacteria concentrations tended to be lower in the WWTP effluent samples, due to disinfection processes.
- Both bacteria detected at both of the reference locations. Enterococci at Montana (373 cfu/ 100 mL) exceeded guidelines.

- 78 out of 110 chemicals were found in at least one sample.
- 6 chemicals were found in at least 75 % of the samples.
- Median numbers of detections by sample type: Upstream, 10; WWTP effluent, 35; 1st Downstream, 32; 2nd Downstream, 24.
- At the reference locations, 3 chemicals with a total concentration of 0.0326 µg/ L were found in Michigan; no detects in Montana.

Frequency of Detection by Use Classification



Instream Variability

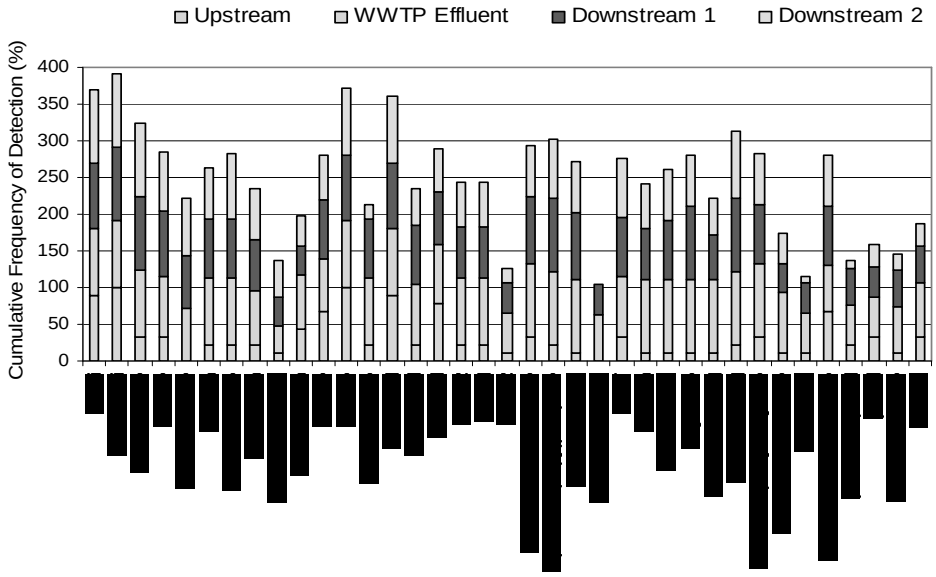


35 Most Frequently Detected Compounds

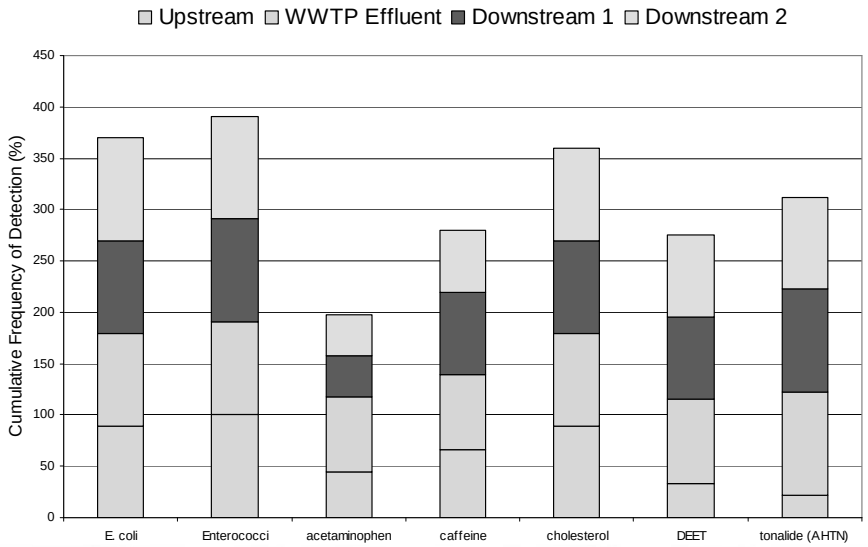
Fecal Sterols Pharmaceuticals Misc. Wastewater Detergents and Fragrances

cotinine	**sitosterol**	**4-nonylphenol monoethoxylate**	**5-methyl-1H-benzotriazle**
cholesterol	**sulfamethoxazole**	**triclosan**	**phenol**
carbamazepine	**caffeine**	**coprostanol**	**triphenylphosphate**
tonalide (AHTN)	**ethanol,2-butoxy-phosphate**	**trimethoprim**	**1,7-dimethylxanthine**
tri(dichlorisopropyl) phosphate	**N,N-diethyltoluamide (DEET)**	**dehydronifedipine**	**pentachlorophenol**
tri(2-chloroethyl) phosphate	**tributylphosphate**	**galaxolide (HHCB)**	**4-octylphenol diethoxylate**
3,4-dichlorophenyl isocyanate	**benzophenone**	**diphenhydramine**	**bisphenol-A**
codeine	**diltiazem**	**acetaminophen**	**1,4-dichlorobenzene**
ethyl citrate	**4-nonylphenol diethoxylate**	**diazinon**	

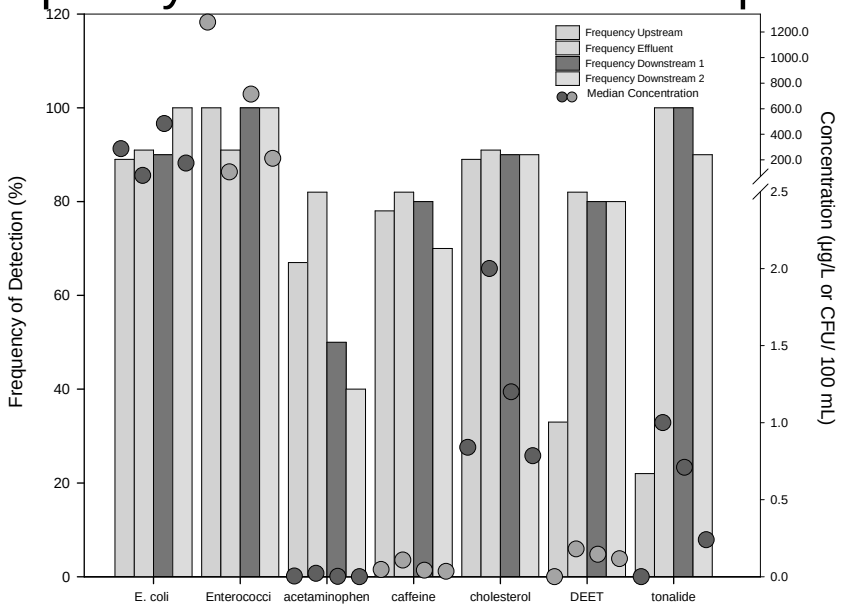
Frequency of Detection by Sample Site



Frequency of Detection by Sample Site
Selected Examples



Frequency and Concentration Comparison



Significant Differences in Concentration Between Sample Sites

None UP-WWTP only UP-WWTP and WWTP-DS2
WWTP-DS2 only UP-WWTP, WWTP-DS1 and WWTP-DS2

1,7-dimethylxanthine	1,4-dichlorobenzene	3,4-dichlorophenyl isocyanate	diltiazem	4-octylphenol diethoxylate
acetaminophen	carbamazepine	4-nonylphenol diethoxylate	diphenhydramine	diazinon
caffeine	codeine	4-nonylphenol monoethoxylate	tri(2-chloroethyl) phosphate	pentachloro-phenol
cotinine	dehydronifedipine	5-methyl-1H-benzotriazle	tri(dichlorisopropyl) phosphate	sitosterol
ethanol,2-butoxy-phosphate	N,N-diethyltoluamide (DEET)	benzophenone	triclosan	**ethyl citrate**
phenol	sulfamethoxazole	bisphenol-A	triphenylphosphate	**galaxolide (HHCB)**
	tributylphosphate	cholesterol		**tonalide (AHTN)**
	trimethoprim	coprostanol		

Lessons Learned

- Pharmaceuticals and other chemicals survive wastewater treatment.
- Upstream “background” levels of many of the pharmaceuticals and wastewater compounds are low (especially when compared to the indicator bacteria), and indicate that they are not too ubiquitous.
- The downstream samples decrease at different rates for the chemicals.
- Pharmaceuticals and other wastewater compounds may be able to be utilized as chemical indicators of human fecal contamination. Factors such as environmental persistence must be considered when preparing compound list.

So, what if we combine the results from both projects?

- 9 compounds were analytes in both studies
- Is there a difference in the frequency of detection and median concentration between those that were unaffected by chlorination and those that were oxidized?

Compounds Common to Both Studies

		All effluents			
		frequency of detection	median concentration		
No Change	caffeine	73 %	0.05 µg/L		
	cotinine	91	0.03		
	1,7-dimethylxanthine	36	<RL[1]		
+Cl	acetaminophen	73	0.006		
	gemfibrozil	0	ND		
Oxidized	cimetidine	27	<RL		
	diltiazem	91	0.05		
	trimethoprim	73	0.04		
	warfarin	0	ND		

[1]Reporting Limit

Compounds Common to Both Studies

		All effluents		Locations that only use chlorine	
		frequency of detection	median concentration	frequency of detection	median concentration
No Change	caffeine	73 %	0.05 µg/L	86 %	0.17 µg/L
	cotinine	91	0.03	100	0.26
	1,7-dimethylxanthine	36	<RL	57	0.39
+Cl	acetaminophen	73	0.006	86	0.02
	gemfibrozil	0	ND	0	ND
Oxidized	cimetidine	27	<RL	14	<RL
	diltiazem	91	0.05	100	0.05
	trimethoprim	73	0.04	71	0.03
	warfarin	0	ND	0	ND

Segregation by Treatment

		Chlorine		UV	
		frequency of detection	median concentration	frequency of detection	median concentration
No Change	caffeine	86 %	0.17 µg/L	50 %	0.03
	cotinine	100	0.26	75	0.02
	1,7-dimethylxanthine	57	0.39	0	<RL
+Cl	acetaminophen	86	0.02	50	0.001
	gemfibrozil	0	ND	0	ND
Oxidized	cimetidine	14	<RL	50	0.06
	diltiazem	100	0.05	75	0.04
	trimethoprim	71	0.03	75	0.04
	warfarin	0	ND	0	ND

35 Most Frequently Detected Compounds

Fecal Sterols Pharmaceuticals Misc. Wastewater Detergents and Fragrances

cotinine	**sitosterol**	**4-nonylphenol monoethoxylate**	**5-methyl-1H-benzotriazle**
cholesterol	**sulfamethoxazole**	**triclosan**	**phenol**
carbamazepine	**caffeine**	**coprostanol**	**triphenylphosphate**
tonalide (AHTN)	**ethanol,2-butoxy-phosphate**	**trimethoprim**	**1,7-dimethylxanthine**
tri(dichlorisopropyl) phosphate	**N,N-diethyltoluamide (DEET)**	**dehydronifedipine**	**pentachlorophenol**
tri(2-chloroethyl) phosphate	**tributylphosphate**	**galaxolide (HHCB)**	**4-octylphenol diethoxylate**
3,4-dichlorophenyl isocyanate	**benzophenone**	**diphenhydramine**	**bisphenol-A**
codeine	**diltiazem**	**acetaminophen**	**1,4-dichlorobenzene**
ethyl citrate	**4-nonylphenol diethoxylate**	**diazinon**	

35 Most Frequently Detected Compounds

Higher in Cl Effluents		Higher in UV Effluents	No Trend
cotinine	sitosterol	4-nonylphenol monoethoxylate	5-methyl-1H-benzotriazle
cholesterol	sulfamethoxazole	triclosan	phenol
carbamazepine	caffeine	coprostanol	triphenylphosphate
tonalide (AHTN)	ethanol,2-butoxy-phosphate	trimethoprim	1,7-dimethylxanthine
tri(dichlorisopropyl) phosphate	N,N-diethyltoluamide (DEET)	dehydronifedipine	pentachlorophenol
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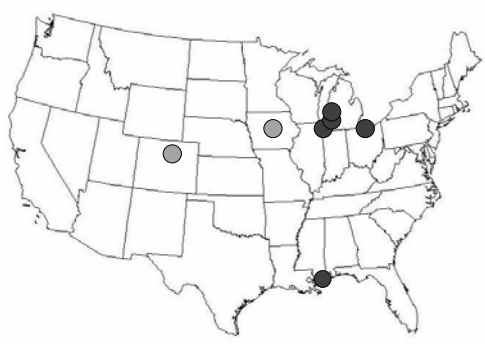
3,4-dichlorophenyl isocyanate	benzophenone	diphenhydramine	bisphenol-A
codeine	diltiazem	acetaminophen	1,4-dichlorobenzene
ethyl citrate	4-nonylphenol diethoxylate	diazinon	enterococci

Lessons Learned

- Chemical removal in WWTPs is dependant on the technologies employed in the plant.
- Lower removal efficiency increases the potential for a chemical to be present in the environment.
- Must still consider secondary treatments used (activated sludge and trickling filter) before finalizing conclusions for this inter-project comparison.

Ongoing and Future Work

- Lagrangian Studies
- Epidemiology Studies
- Drinking Water



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Contact Information

Susan T. Glassmeyer, Ph.D.
US Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
26 W. Martin Luther King Dr
MS 564
Cincinnati, OH 45268

glassmeyer.susan@epa.gov
513-569-7526

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