Treatment of Pharmaceutical Wastewaters to Reduce API Risks

 

Ed Helmig & Dave Riedel

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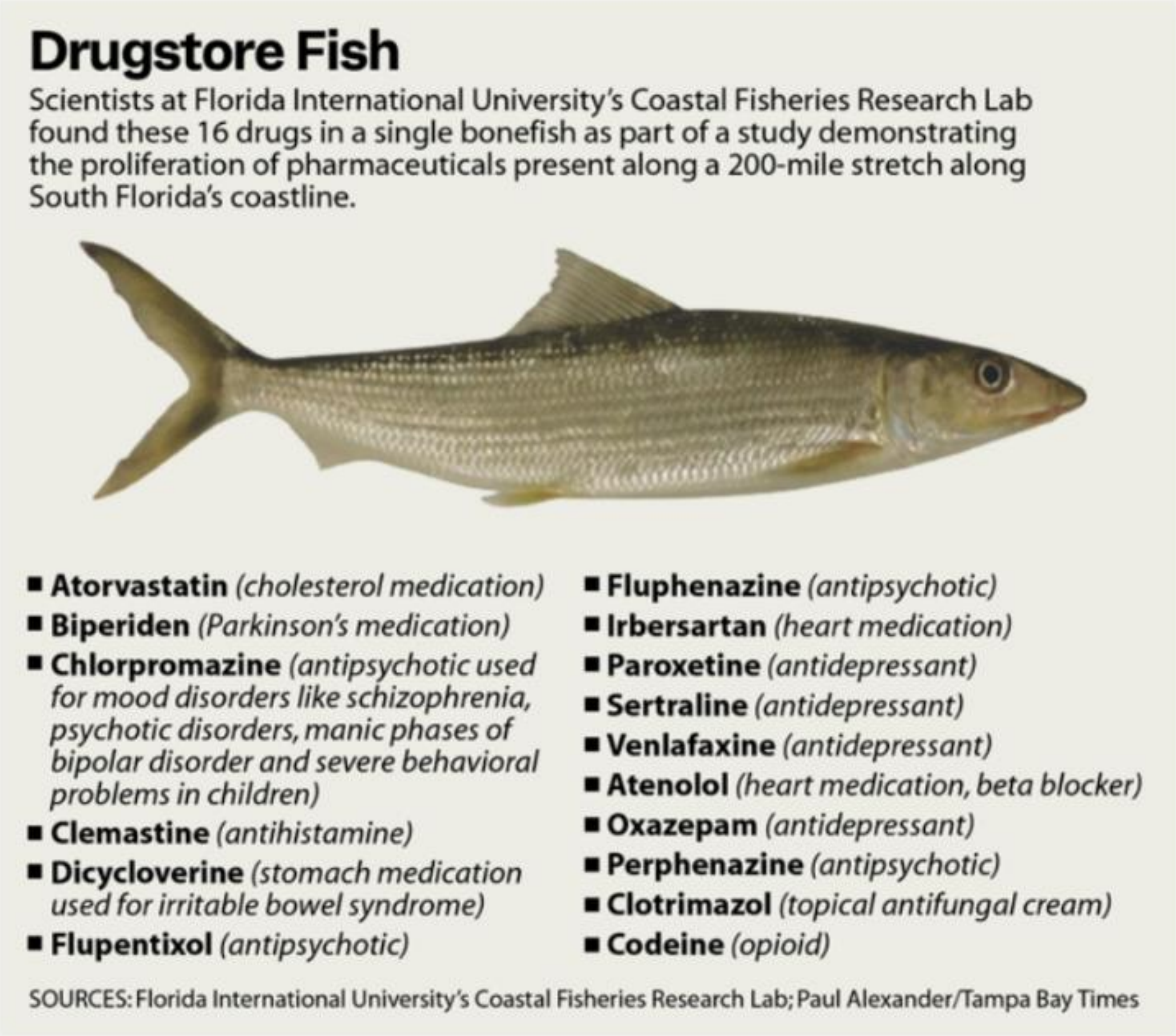
Image by Ed Helmig

Why is this topic important?

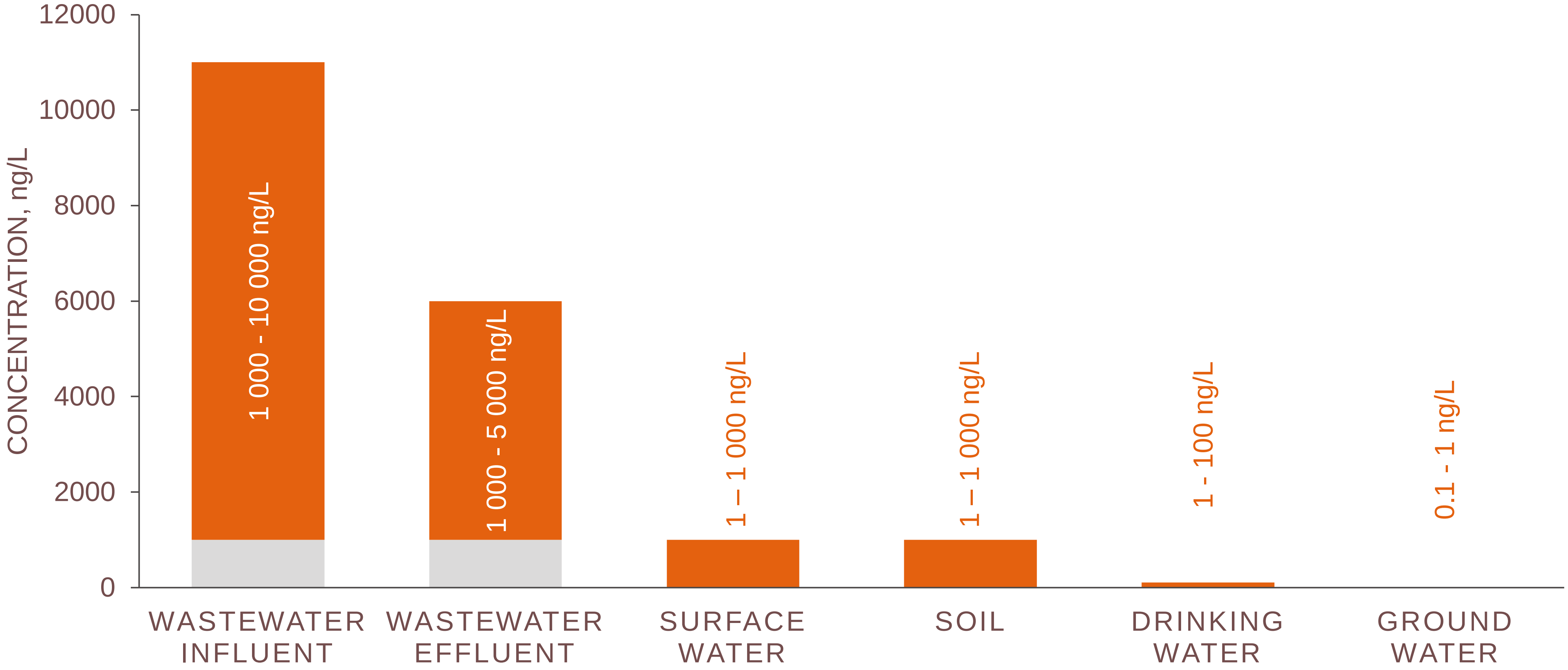
From first-hand experience:

- Ionophore antibiotics in sludge killed dogs-company reputation damaged
- Venlafaxine found in drinking water-company reputation damaged
- Hormone found in pig feed and soft drinks-criminal investigation, fine and damage to company reputation
- Very potent chemotherapy drug being discharged at 10,000 time the predicted no effect level (PNEC)-company built WWTP to address risk
- Multiple large-scale pharmaceutical facilities (US and Switzerland) discharging inadequately treated wastewater to rivers



Inside Climate News

Typical Concentrations in the Water Cycle



Thread

1. **Define the scope and magnitude of the problem**

- Understand the APIs and risks

2. **Spend time understanding manufacturing**

- Insight into waste stream characteristics and volumes
- Learn where waste streams are generated and how they might be segregated or treated at source
- Develop sampling strategy

3. **Understand what you need to treat (APIs and matrix)**

- This dictates unit processes
- Informs us about unit sizing, treatment process complexity and cost

4. **Treatability**

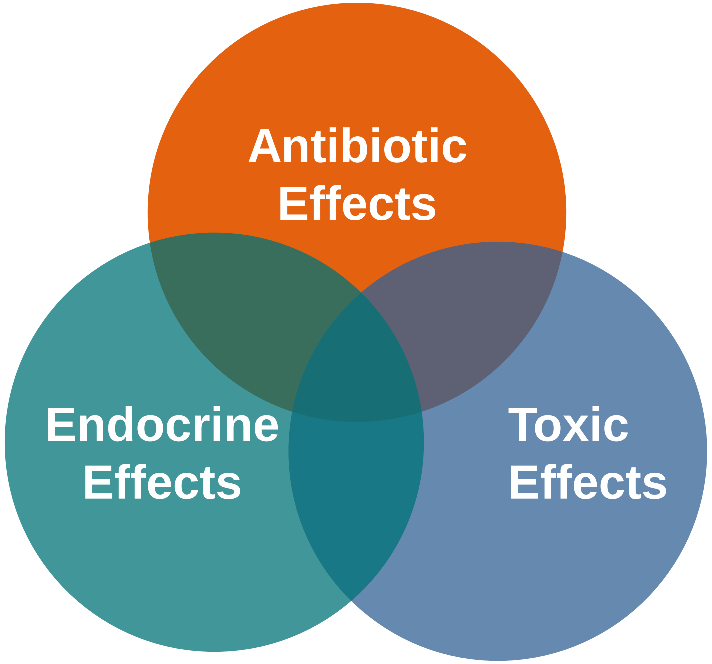
- Theory vs reality
- Pretreatment (bulk organics and solids removal) required to get to molecules of concern
- Final scale up decisions can be made after treatability (stoichiometry and kinetics get defined here)
- Energy
- Process safety

API Categories and Effects

API Categories

- Endocrine Disrupting Compounds (EDCs)
- Toxic Compounds
- Antibiotic/Antimicrobial Agents

API Effects



Measuring effects is just as important as measuring APIs and both can be very difficult and time consuming!

Antibiotic Focus

Types of antibiotics and basis for concern

Real World Perspective

Antibiotics are among the most important drugs we make and consume, and they have saved millions of lives. However, there are three properties that we must never forget:

1. *They are designed to kill certain kinds of cells and therefore have a toxicity threshold*
2. *The dose makes the poison*
3. *Bacteria are clever and evolve quickly and can develop resistance to antibiotics rendering them ineffective.*

Different classes of antibiotics

B-Lactams
Inhibit bacteria cell wall biosynthesis

Examples
- Amoxicillin
- Flucloxacillin
- Cefalexin

Aminoglycosides
Inhibit the synthesis of proteins by bacteria

Examples
- Streptomycin
- Neomycin
- Kanamycin
- Paromomycin

Glycopeptides
Inhibit bacteria cell wall biosynthesis

Examples
- Vancomycin
- Teicoplanin

Ansamycins
Inhibit the synthesis of RNA by bacteria

Examples
- Geldanamycin
- Rifamycin
- Naphthomycin

Quinolones
Interfere with bacteria DNA replication and transcription

Examples
- Ciprofloxacin
- Levofloxacin
- Trovafloxacin

Streptogramins
Inhibit the synthesis of proteins by bacteria

Examples
- Pristinamycin IIA
- Pristinamycin IA

Lipopeptides
Disrupt multiple cell membrane functions

Examples
- Daptomycin
- Surfactin

Sulfonamides
Prevent bacteria growth and multiplication

Examples
- Prontosil
- Sulfanilamide
- Sulfadiazine
- Sulfisoxazole

Chloramphenicol
Inhibits synthesis of proteins

No longer a first line drug in any developed country

Tetracyclines
Inhibits synthesis of proteins by bacteria

Examples
- Tetracycline
- Doxycycline
- Lymecycline
- Oxytetracycline

Macrolides
Inhibits protein synthesis by bacteria

Examples
- Erythromycin
- Clarithromycin
- Azithromycin

Oxazolidinones
Inhibits synthesis of proteins by bacteria

Examples
- Linezolid
- Posizolid
- Tedizolid
- Cycloserine

Commonly act as bactericidal agents, causing bacterial cell death

Commonly act as bacteriostatic agents, restrict growth & multiplication

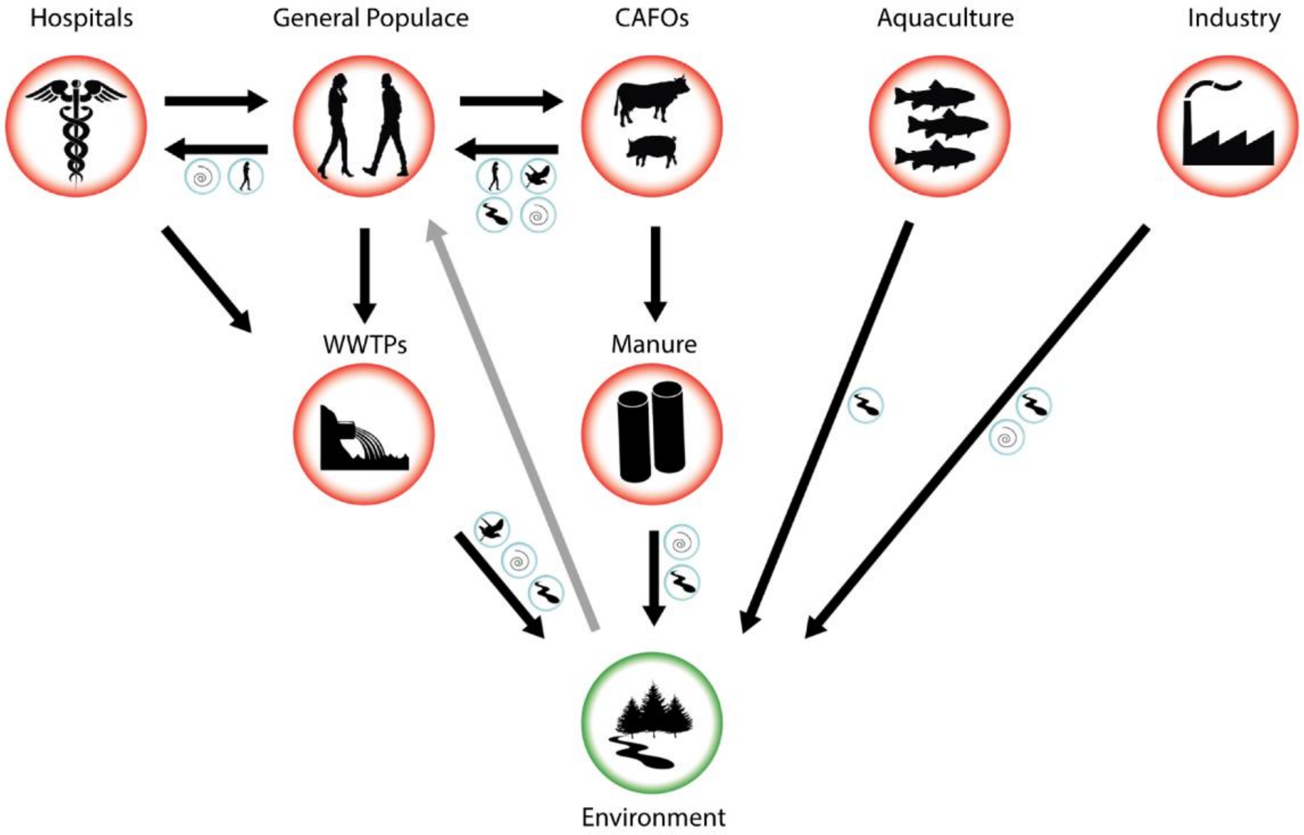
Source: https://www.reactgroup.org/toolbox/understand

Pathways to the Environment

Schematic flow of antibiotic resistance-carrying bacteria (ARBs) and antibiotic resistance genes (ARGs) from hotspots of evolution and transmission (red circles) to the environment (green circle).

Blue circles indicate possible vectors that may aid transmission between specific environments including air, surface waters, humans, and other animal vectors.

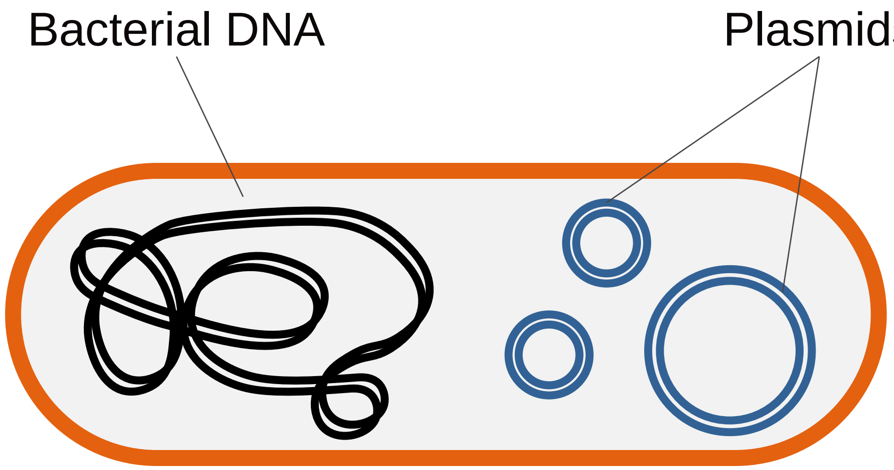
Black arrows indicate known flows of ARBs and ARGs, grey arrow indicates a possible transmission route from a contaminated environment back to the general populace.



Source: https://www.mdpi.com/2076-2607/7/6/180

The mechanics of gene transfer and acquired antimicrobial resistance

A plasmid is a small, circular, double-stranded DNA molecule that is distinct from a cell's chromosomal DNA. Plasmids naturally exist in bacterial cells, and they also occur in some eukaryotes. Often, the genes carried in plasmids provide bacteria with genetic advantages, such as antibiotic resistance.



Estimates and Measurements

Arriving at a Predicted Environmental Concentration (PEC)

How do we know how much we are releasing to the environment?

Real World Perspective

This is tedious and high precision work that can be very time consuming. Estimates and measurements can span the range from kilograms (10^3 grams) to less than 0.1 nanograms (10^{-9} grams) meaning that the range spans 12 orders of magnitude or 1,000,000,000,000.

Focus on Manufacturing

Many unique manufacturing processes!

To estimate the PEC, we need:

- Process understanding/map
- Mass balances & losses
- Attenuation (dilution/treatment/stream flows)

To measure actual environmental concentrations, we need:

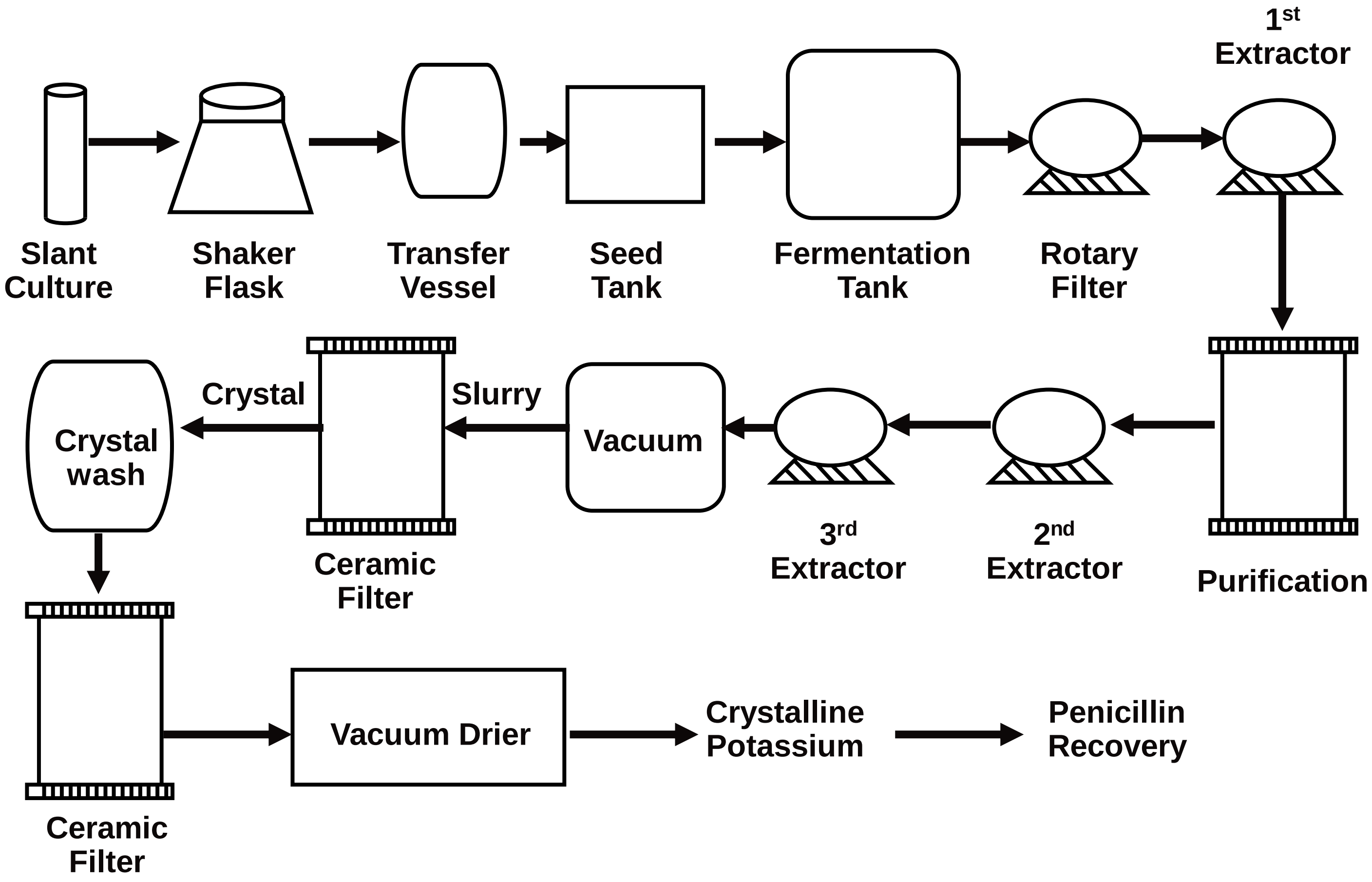
- Production schedules & sampling plan
- Transit times in sewers and treatment systems
- Highly sophisticated analytical methods that can detect APIs as low as 0.1 parts per trillion (ppt or nanograms per liter)

Good estimates start with a process map and mass balance

It is important to identify where in the process the API is created

API loss estimates for fermentation are among the most complex. Most losses occur in the downstream crystallization, washing/purification and conversion to solid dosage form steps… not the fermenters.

Centrifuges and filter presses tend to be the largest source of losses



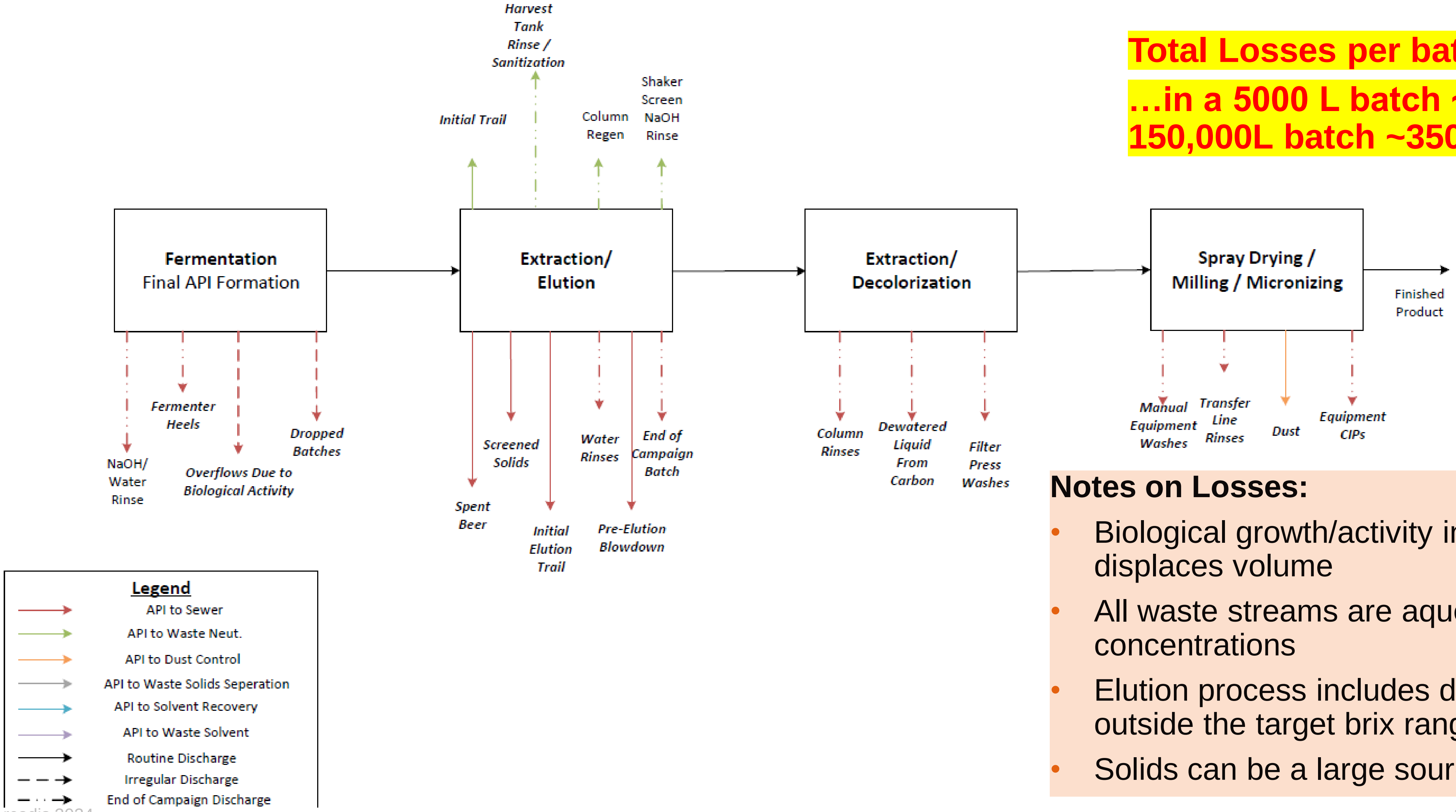
PRODUCTION PROCESS OF PENICILLIN

Mass Balances

Real World Perspective

API manufacturing processes are very complex with dozens of steps. Missing a step, failure to account for heels, losses to solvent recovery systems, losses to dust collectors during charging and discharging, and missed rinse steps all contribute to errors in mass balances.

Process Mass Balance Example 1



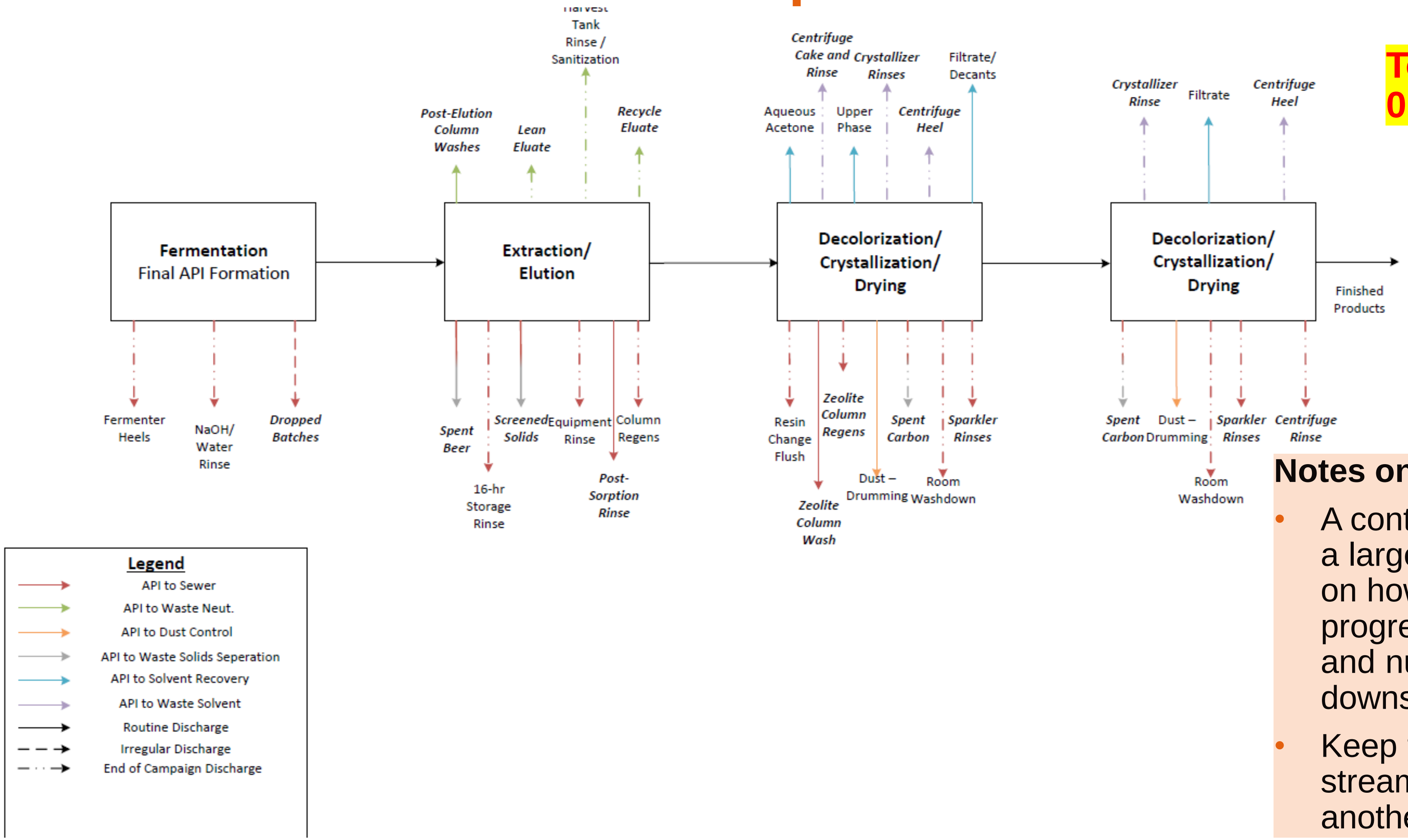
Total Losses per batch: 0.2 – 0.3%

…in a 5000 L batch ~15 kg vs. a 150,000L batch ~350kg of losses!

Notes on Losses:

- Biological growth/activity in fermenter displaces volume
- All waste streams are aqueous – low solvent concentrations
- Elution process includes discharge of trails outside the target brix range
- Solids can be a large source of API

Process Mass Balance Example 2

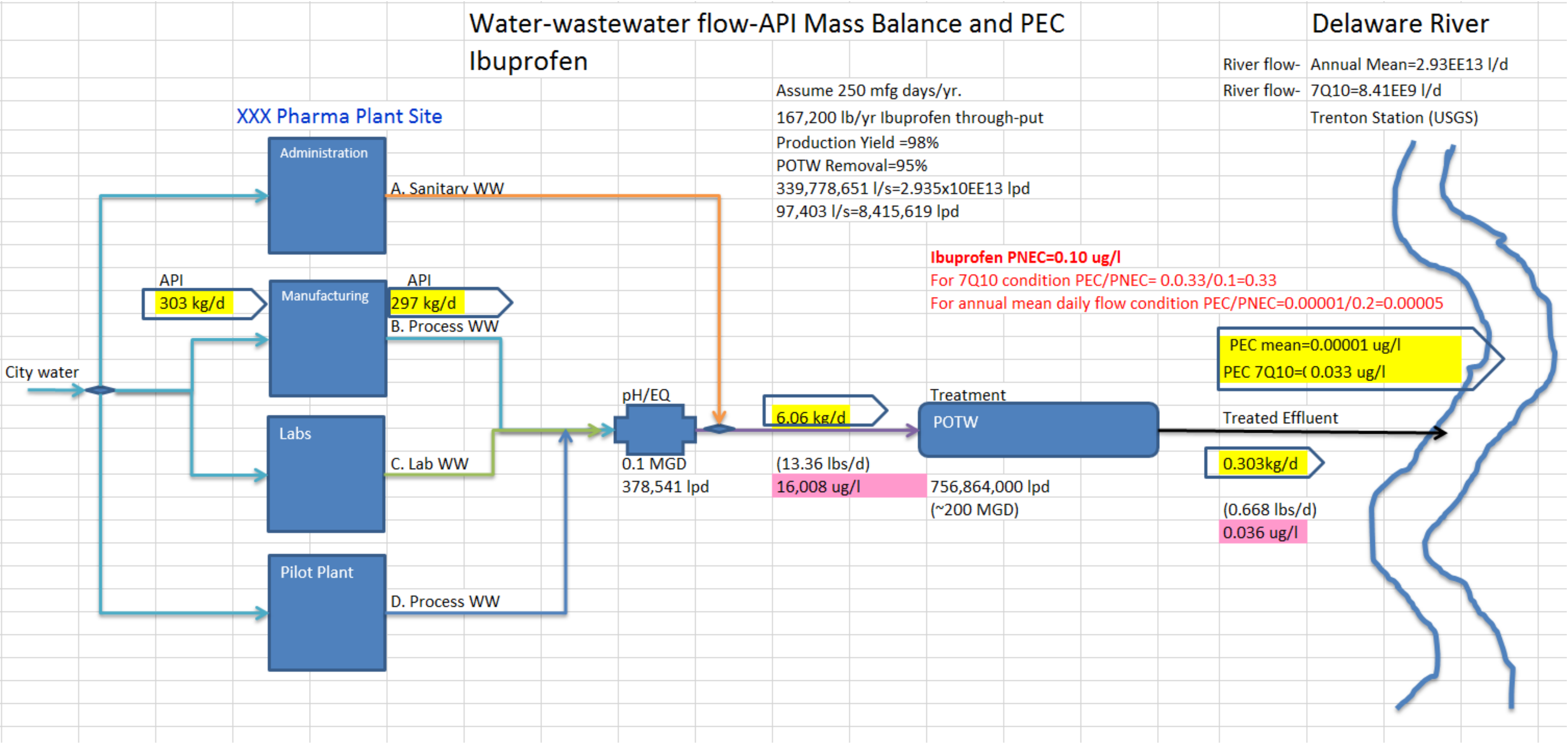


Total Losses per batch: 0.15 – 0.2%

Notes on Losses:

- A contaminated fermenter can be a large source of API, depending on how far into the process it has progressed. Also, a large organic and nutrient load on a downstream biological WRRF.
- Keep track of solvent waste streams – if treated onsite, will be another vector of API to WW.

Complete Mass Balance: Source to Sink



Doing the Math

API Mass Balance

Excel Spreadsheet & Sensitivity Analysis

Predicted Environmental Concentration and Sensitivity Analysis

Ibuprofen

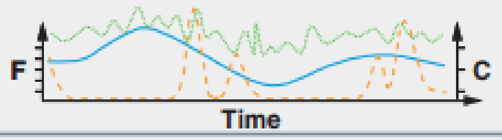
XXX Pharma, WAWA, PA.

						Dilution		Removal					
#	Scenario	API	Input	1-Yield	Discharge	POTW	River	Site	POTW	Mass to River	PEC	PNEC	PEC/PNEC
			kg/d		kg/d	lpd	lpd	1-removal	1-removal	kg/d	ppb	ppb	
1	Mean daily river flow	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0	0.05	0.303	0.00001045	0.1	0.000104480
2	River 7Q10 low flow	Ibuprofen	303	0.02	6.06	7.57E+08	8.42E+09	0	0.05	0.303	0.03303353	0.1	0.330335262
3	90% yield-production	Ibuprofen	303	0.1	30.3	7.57E+08	2.90E+13	0	0.05	1.515	0.00005224	0.1	0.000522400
4	95% yield-production	Ibuprofen	303	0.05	15.15	7.57E+08	2.90E+13	0	0.05	0.7575	0.00002612	0.1	0.000261200
5	99% yield-production	Ibuprofen	303	0.01	3.03	7.57E+08	2.90E+13	0	0.05	0.1515	0.00000522	0.1	0.000052240
6	On site WWT- 85% Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0.15	0.05	0.04545	0.00000157	0.1	0.000015672
7	On site WWT- 95% Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0.05	0.05	0.01515	0.00000052	0.1	0.000005224
8	On site WWT 99% Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0.01	0.05	0.00303	0.00000010	0.1	0.000001045
9	No POTW Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0	1	6.06	0.00020896	0.1	0.002089601
10	50% POTW Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0	0.5	3.03	0.00010448	0.1	0.001044800
11	75% POTW Removal	Ibuprofen	303	0.02	6.06	7.57E+08	2.90E+13	0	0.25	1.515	0.00005224	0.1	0.000522400
12	2X production	Ibuprofen	606	0.02	12.12	7.57E+08	2.90E+13	0	0.05	0.606	0.00002090	0.1	0.000208960
13	4X production	Ibuprofen	1,212	0.02	24.24	7.57E+08	2.90E+13	0	0.05	1.212	0.00004179	0.1	0.000417920
14	Q710+50% POTW flow	Ibuprofen	303	0.02	6.06	3.78E+08	8.42E+09	0	0.05	0.303	0.03445505	0.1	0.344550463

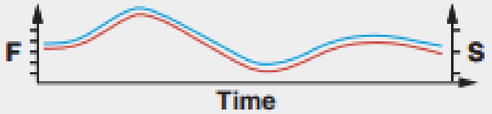
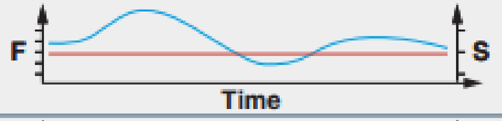
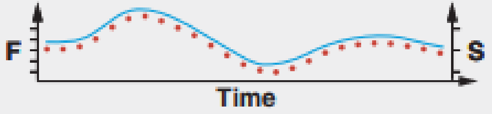
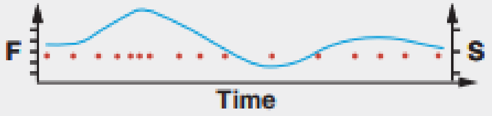
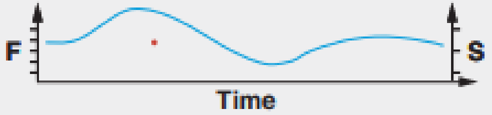
Sampling Methods

Reference: ebo.13.476 (futuremedicine.com)

Conceptual example



Flow (e.g., diurnal variation)
Concentration of a frequently discharged substance
Concentration of a rarely discharged substance

	Sampling mode	Short description		Specific equipment[†]	Flow meter[‡]
Continuous	Flow proportional	Divert a side stream, proportional to the flow in the sewer		Pump with speed control (proportional to external flow signal)[§]	Yes
Continuous	Constant	Divert a constant side stream from the sewer		Pump	No
Discrete	Time proportional	Take a constant sample volume at constant time intervals		Standard auto-sampler	No
Discrete	Flow proportional	Make sample volume proportional to the flow in the sewer taking them at constant time intervals		Auto-sampler with adjustable sampling volume[¶] (proportional to external flow signal)	Yes
Discrete	Volume proportional	Take a constant sample volume at variable time intervals, after a certain volume of wastewater has passed the sampling point		Auto-sampler totaling an external flow signal up to a predefined volume and then triggering a sample[#]	Yes
Discrete	Grab sample	Take one (or a number of) grab sample		Scoop, no power supply	No

Analytical Methods (USEPA)

- **Method 1694:** *Pharmaceuticals and Personal Care Products in Water, Sediment, and Biosolids by HPLC/MS/MS* that covers **seventy-three** pharmaceuticals and personal care products. https://www.epa.gov/sites/default/files/2015-10/documents/method_1694_2007.pdf
- **Method 1698:** *Steroids and Hormones in Water, Soil, Sediment and Biosolids by High Resolution Gas Chromatography/High Resolution Mass Spectroscopy (HRCG/HRMS)* that covers **twenty-seven** steroids and hormones by isotope dilution and internal standard calibration. https://www.epa.gov/sites/default/files/2015-10/documents/method_1698_2007.pdf
- **Method 542:** *Determination of Pharmaceuticals and Personal Care Products in Drinking Water by Solid Phase Extraction and Liquid Chromatography Electrospray Ionization (ESI) Tandem Mass Spectrometry (LC/ESI-MS/MS)* that covers **twelve** analytes. https://www.epa.gov/sites/default/files/2016-09/documents/method-542-determination-pharmaceuticals-personal-care-products-drinking-water.pdf

There are >20,000 APIs in the marketplace and analytical methods that cover <120 APIs.

It is also important to understand that we need analytical methods that have detection limits (in a wastewater matrix) below the PNEC for the API of concern.

Treatment

One of the single most important approaches to reducing risks and protecting our environment!

Real World Perspective

A well designed and operated industrial wastewater treatment plant can be a strategic asset that enables a site to take on products and processes that others can not handle without incurring huge environmental risks and potential liabilities for damage.

Pharmaceutical Discharge Reduction Process

Design API Manufacturing Processes to Minimize Losses

PEC/PNEC to ID Key Risks

Collection & Segregation
- Reduce discharge mass
- Isolate near-source
- Capture pharmaceutical waste streams
- Repair infrastructure

Pre-Treatment Requirements
- Equalization
- pH Control
- Solids Removal
- Oil & Grease Removal
- Dissolved Air Flotation

API Treatment Technology
- Ozone Oxidation
- GAC
- Biological Treatment
- Membrane Filtration
- Evaporation
- Incineration

Post-Treatment
- pH Neutralization
- Cooling
- RO for Reuse
- WW Blending
- Monitoring

Always attempt to minimize API discharge to wastewater as close to the source as possible.

In some cases, combination of technology is required to treat different compounds or arrive at most efficient operating strategy.

Primary Treatment

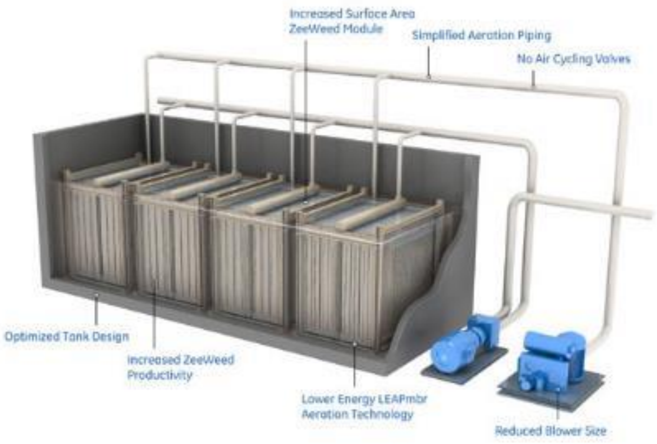
Fractionate your COD! You may be surprised to find that a major portion is particulate (including insoluble API's) and can be removed with simple and inexpensive technologies including primary clarifiers, sand filters and dissolved air flotation (DAF) systems.

CWT GEM® DAF System

https://cwt-global.com/gem-system/

Secondary Treatment

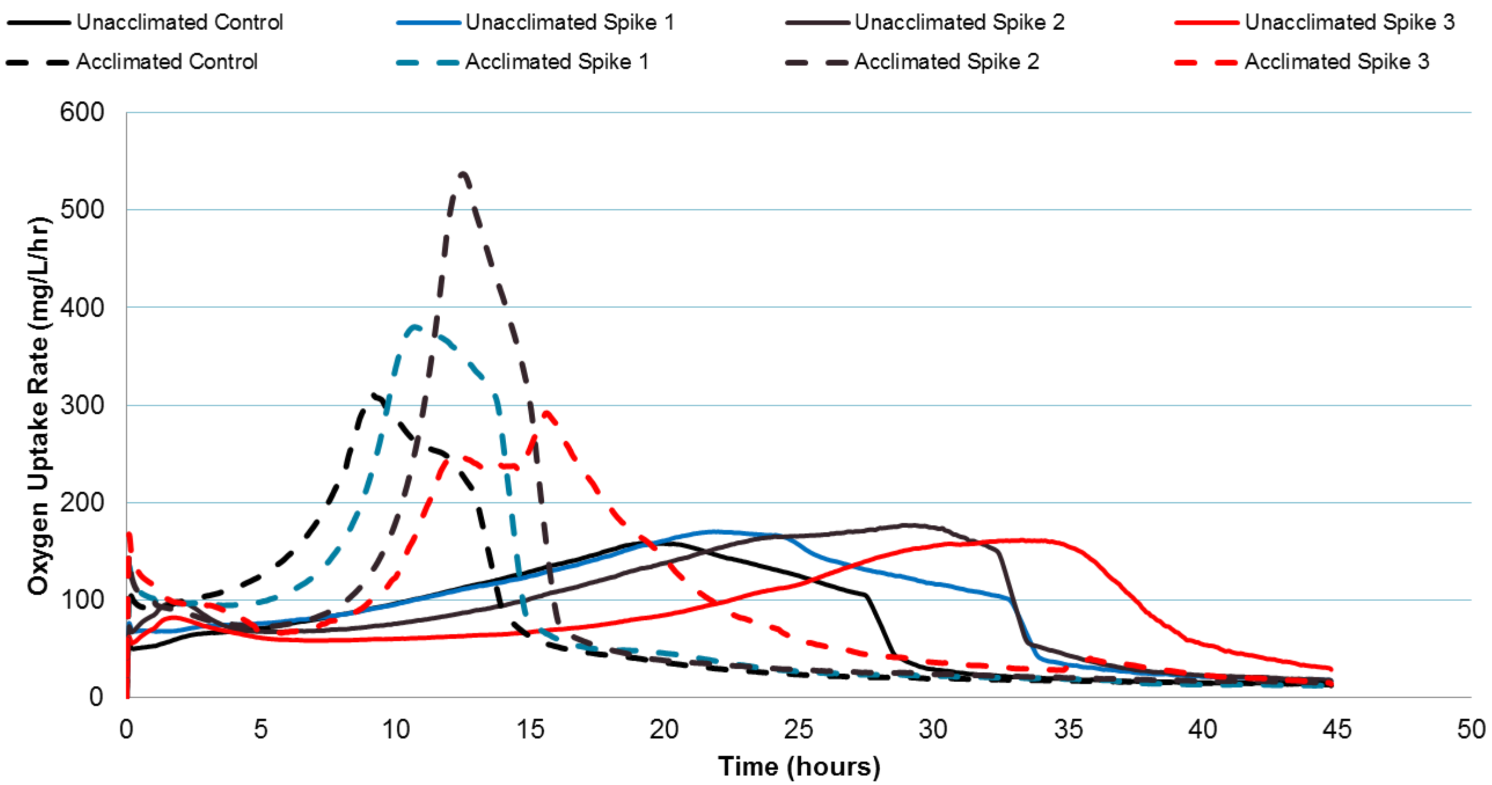
- Typically, biological-based
- Removal pathways include biological oxidation/reduction and sorption to biological solids of contaminants



Images are hyperlinked to source

Relies on a symbiotic culture of microorganisms (biofilms, aerobes, anaerobes, anoxic organisms)

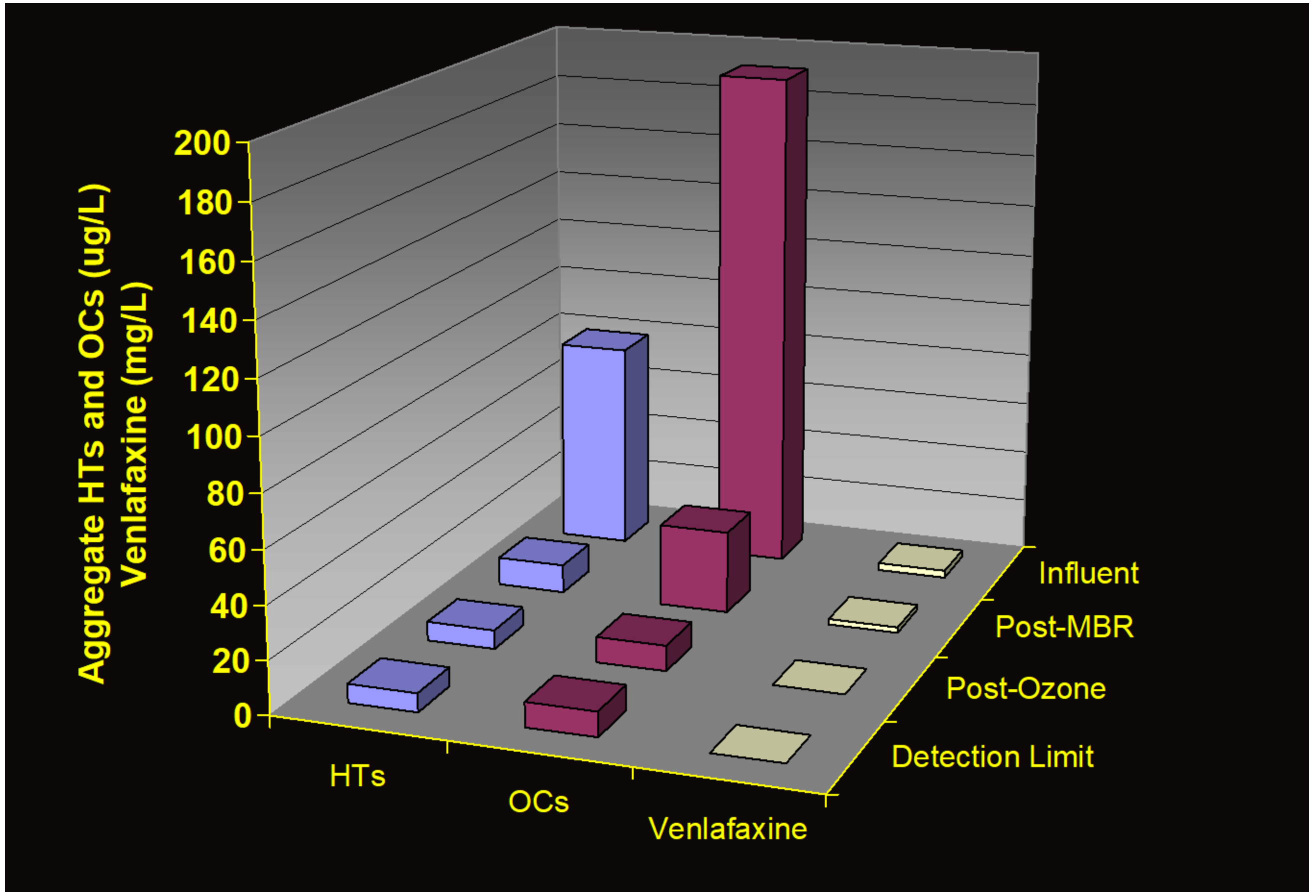
Testing of ionophore antibiotics using respirometry to identify toxicity & inhibition



This highlights the importance of acclimation – remember production may not run continuously

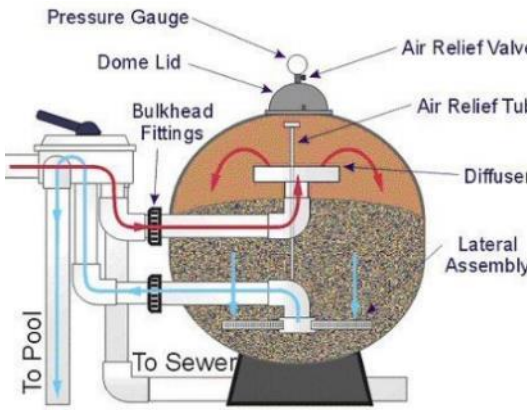
Focus on Membrane Bioreactor (MBR) for Pharmaceutical Production Facilities

- Micro- or ultra-filtration membrane for solids/liquid separation
- Operates at high biomass concentrations
- Longer sludge age
- Improved operability
- Amenable for water reuse applications

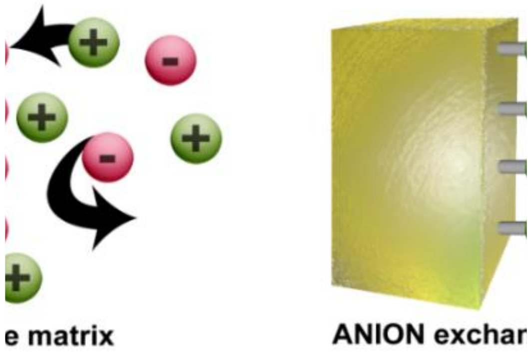


HT-Hormone Therapy : OC-Oral Contraceptives : Venlafaxine-SSRI

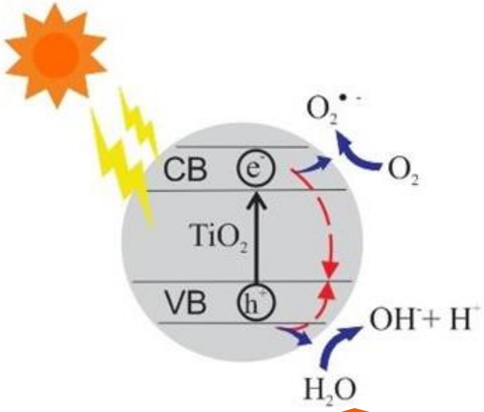
Tertiary Treatment Categories



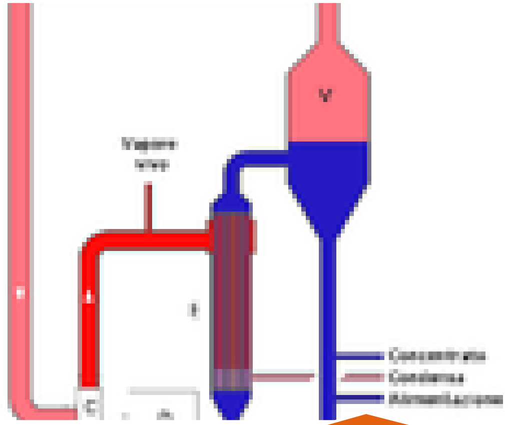
Filtration



Mass Transfer



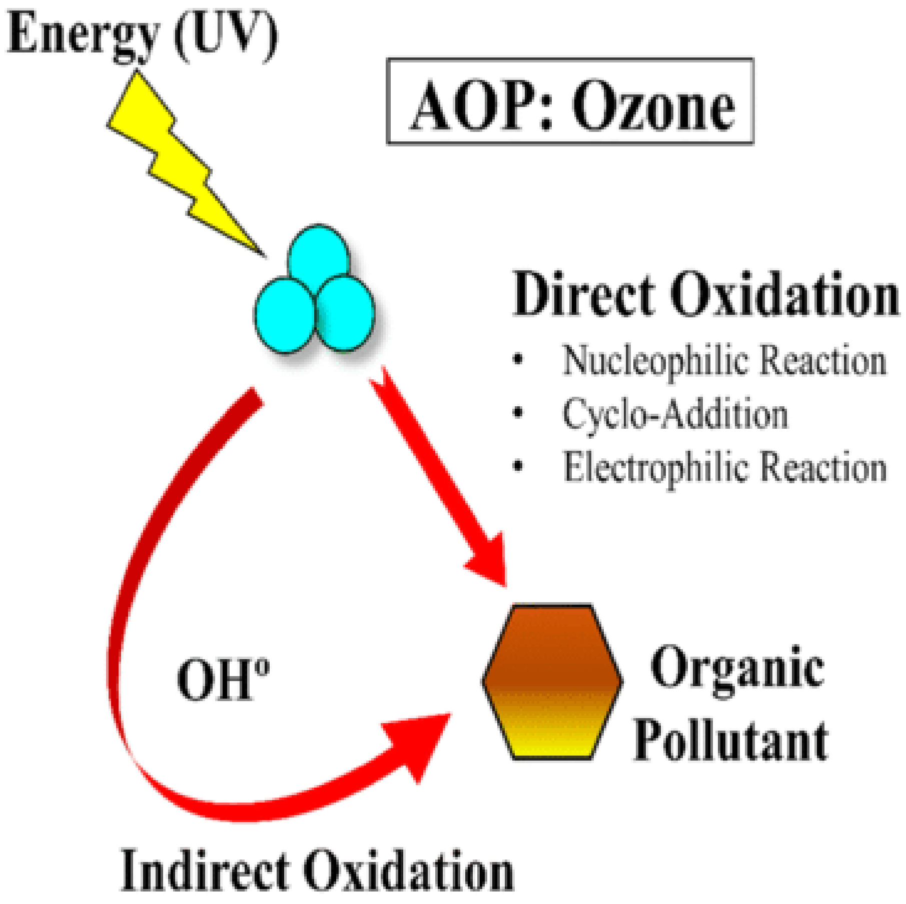
Advanced Oxidation Processes

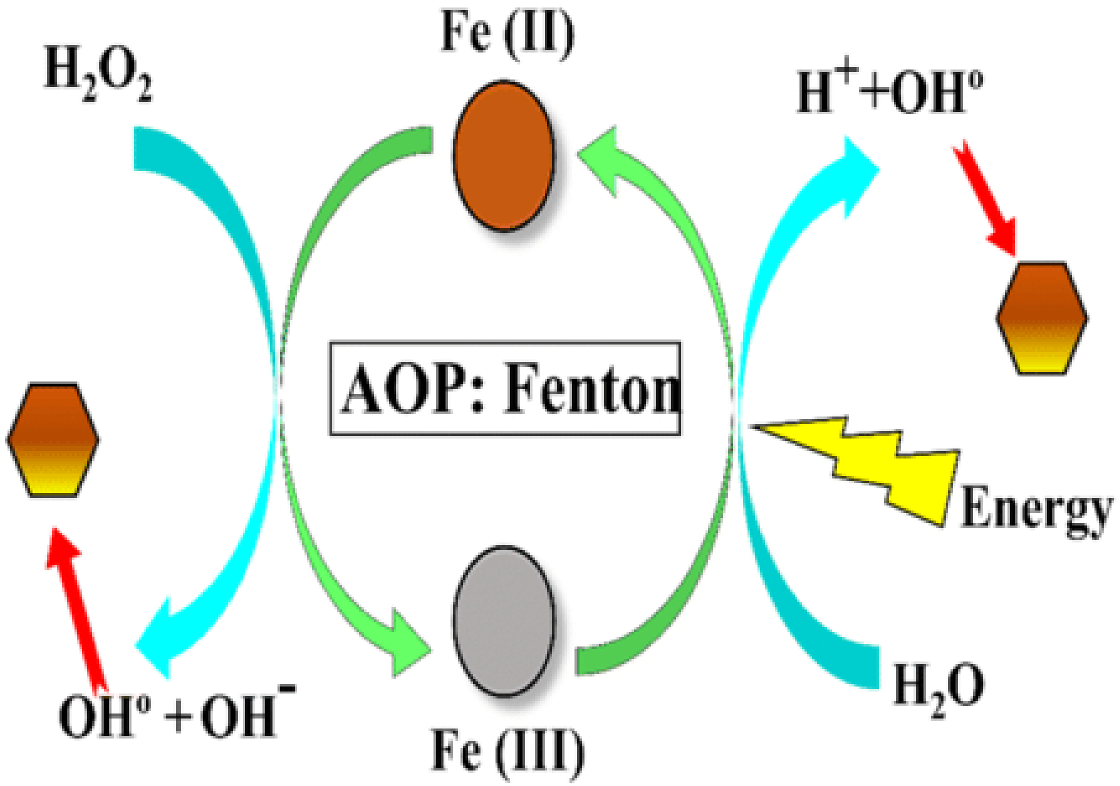


Thermal

Some are suited for general effluent quality improvement, while others specifically remove APIs.

Advanced Oxidation Processes – "The Sledgehammer"





https://www.researchgate.net/journal/Clean-Technologies-and-Environmental-Policy-1618-9558

Tertiary Treatment Comparison

Criteria	Filtration	Mass Transfer	AOP	Thermal
API Fate	Sorbed to solids, RO rejection	Sorbed to media	Mineralization, possible daughter products	Destroyed or Concentrated
CAPEX Range	Low – Medium	Low – Medium	Low – High	Medium – High
OPEX Requirements	Backwash / Reject disposal, CIPs	Backwash / Media disposal	Chemicals, Power, Chemical sludge disposal (process dependent)	Slurry/Brine/ Ash disposal, transportation, heat energy

Treatment? This is what works!

Benchmark Industrial Treatment System Removes Active Pharmaceutical Ingredients from Wastewater

INTRODUCTION

Wyeth owned and operated an advanced Industrial Wastewater Treatment Plant (WWTP) in Ireland. The facility is among the first full-scale pharmaceutical manufacturing sites to build and operate a wastewater treatment system specifically designed to remove Active Pharmaceutical Ingredients (APIs) from wastewater.

The overall project involved a six-step sequence of work as follows:

1. Analytical method development
2. Technology screening, bench and pilot scale treatability testing
3. Engineering design and equipment procurement
4. Construction
5. Commissioning, start-up and operator training
6. Full-scale performance verification.

PROJECT DRIVERS

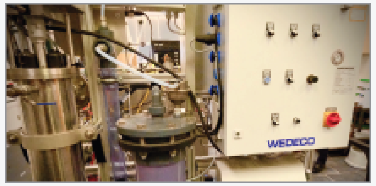
The project was initiated in response to the risk for potential contamination of a salmon fishing stream, downstream public water supplies and the intake to a major brewery. Many of the compounds of concern (emerging contaminants or EC's) have the potential to result in development of hermaphroditic characteristics in aquatic species and humans The EC's of concern were also unique, being active ingredients of patented pharmaceutical products. Finally, Predicted No Effects Concentrations (PNECs) as low as 0.1 parts per trillion (ppt) in an organically rich, complex wastewater matrix created analytical methods and treatment technology hurdles that were very high for this project.

TREATMENT CONCEPTS AND OPTIONS

During 2002 and 2003, Wyeth (Ed Helmig-Technology Leader) initiated a test program (analytical methods development plus bench followed by pilot studies) for a wastewater treatment system that would remove APIs from pharmaceutical manufacturing wastewater. Based on the results of numerous technology-screening evaluations, a Membrane Bioreactor (MBR) treatment system was chosen followed by an ultra-high-performance ozone oxidation system as the best combination of technologies for large-scale, end-of-pipe API removal.

Treatment technologies screened:

- Ozonation
- UV-peroxide and other advanced oxidation processes
- Adsorption
- Ultrasound
- Acid, alkaline, and thermal hydrolysis
- Biological reactors (including Membrane Bioreactor)

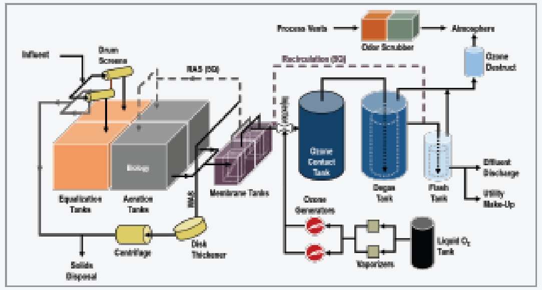


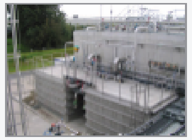
Ozone Bench Study System

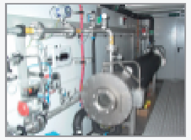
ENGINEERING DESIGN

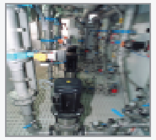
The project design presented several challenges:

- Developing the pretreatment steps so that the core unit operations would work optimally
- Developing an ultra-high-performance ozone system capable of extreme dosages as high as 300 mg/l and doing this safely in a pressurized reactor
- Removing ozone to ensure that ozone would not escape or create a toxicity problem on the back end of the treatment system
- Developing a robust design that had a high turnup/turndown capacity
- Proving it works as advertised: it worked better than we dreamed possible. We drank the effluent and it looked and tasted better than DASANI®!




Membrane Bioreactor

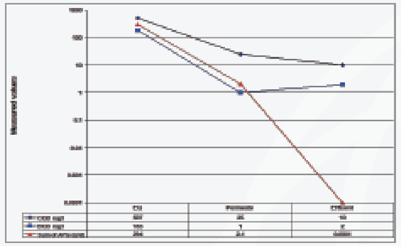

Ozone Generator

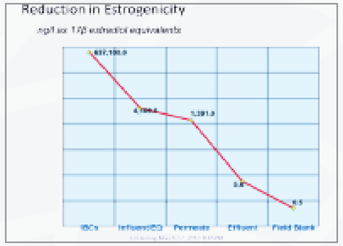

Ozone Injection Skid

OZONE INJECTION SKID

What's so special about this wastewater treatment system?

We pioneered the successful coupling of MBR+Ozone technologies for complete removal of APIs. The ozone system is an ultra-high-performance design that transfers more gas (by a factor of 10 to 100) into liquid than typical designs used in wastewater disinfection and chemical oxidation and has a >97% mass transfer efficiency. This is achieved using a pressurized ozone system with a recirculating loop and venturi eductors that drive large amounts of ozone gas into the recirculating steam and gas/liquid contactor. Once in the contactor the wastewater has a residence time of 20-40 minutes under pressure, followed by degassing in a two-stage system. Unreacted ozone is vented to a thermal catalytic destruct unit. Anything not completely degraded and/or filtered (to 0.04 micron) is completely oxidized. At the time of construction, this was a new and unique combination of technologies among the first of its kind that became an industry best practice and technology benchmark.





RESULTS

- 99.94% Aggregate or Total API/EC reduction
- >1000-fold reduction in estrogenicity from 637,100 ng/l to 5.6 ng/l 17β-estradiol equivalents
- 98% COD Removal
- 99.9% BOD Removal
- 99% Total Suspended Solids Removal
- Non-toxic, reusable effluent

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Putting it all together

Wastewater treatment is a strategic asset and one of the most important blocks in the overall manufacturing process.

Thread Revisited

1. **Define the scope and magnitude of the problem**
- Understand the APIs and risks
2. **Spend time understanding manufacturing**
- Insight into waste stream characteristics and volumes
- Learn where waste streams are generated and how they might be segregated or treated at source
- Develop sampling strategy
3. **Understand what you need to treat (APIs and matrix)**
- This dictates unit processes
- Informs us about unit sizing, treatment process complexity and cost
4. **Treatability**
- Theory vs reality
- Pretreatment (bulk organics and solids removal) required to get to molecules of concern
- Final scale up decisions can be made after treatability (stoichiometry and kinetics get defined here)
- Energy
- Process safety

Thank you for your attention!

Contacts:

Ed Helmig

Principal Engineer – Industrial Water Treatment & Optimization

Cell: 267-230-9544

Edward.Helmig@arcadis-us.com

Dave Riedel

Principal Engineer – Industrial Water Treatment & Optimization

Cell: 703-853-8920

David.Riedel@arcadis.com