Significance and Treatment of Drugs in Wastewater

NEWMOA Conference on Drugs In Water
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The Pharmaceutical Marketplace

- US Prescription Drug Sales
  - Up 8.3% to $235.4 billion in 2004
  - Compared to $217.3 billion in 2003
  - Volume of US dispensed prescriptions grew 3.2%
- New molecular entities approved
  - 31 in 2004
  - 21 in 2003
- Steady growth in sales of 7.5% to 8.5% annually
- Comparable to global compounded annual growth rate projected at 7 to 10% through 2008

IMS Data, 2004

Relative Antibiotic Use for Animals & Humans

United States

4800 tonnes used for humans (1997)

7,234 tonnes used for farm animals

USA human population is 270 million people

Cattle - 36 million

Swine – 114 million

Sheep – 7.8 million

Poultry – 1.8 billion

Canada (estimated)

500 tonnes used for humans

800 tonnes used for farm animals

Canada's human population is 30 million people

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Environmental Concentrations of Pharmaceuticals

Drinking Water	**Up to 0.3 ug/L**
Surface Water	**Up to 2 ug/L**
Groundwater	**Up to 1 ug/L**
Municipal sewage (treated)	**Up to 10 ug/L**
Biosolids (treated)	**Up to 10,000 ug/kg d.w.**
Agricultural soils	**Up to 10 ug/kg d.w.**

Metcalfe et al., 2004, 2003a,b; Golet et al., 2003; Christian et al., 2003; Campognolo et al., 2002; Kolpin et al, 2002; Heberer, 2002; Sacher et al., 2001; Ternes et al. 2001; Halling-Sorensen et al, 2000; Meyer et al, 2000; Rimkus, 1999; Holm et al, 1995

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Regulatory Responses

- **EU:** 10 ng/L cut-off value (surface water) for Tier II ERA. Rigorous procedures for ERA of pharmaceuticals under development and review

- **USA:** 1 ug/L cut-off value for Tier II ERA precludes most pharmaceuticals from assessment

- **Canada:** ERA procedures under review. Health Canada has responsibility for development of ERA

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Are We in Trouble…..Or Not???

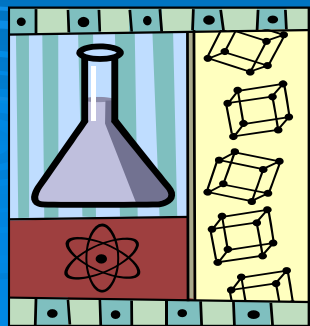
- In the absence of definitive data, the argument has been made that the presence of EDCs, (including but not limited to drugs), and other drugs, many of which are not EDCs but include antibiotics, anti-cholesterol products, psychoactives, etc. is not an issue.
- In the absence of definitive data, others promote the Precautionary Principle

Precautionary Principle

- "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically." Wingspread Conference, Racine, WI 1998

Below the Dose/Response Curve: Endocrine Disruptors

- Endocrine Disruptors: chemicals that interfere with the normal function of the endocrine system (glands including thyroid, adrenals, ovaries, testicles)
- Mimic hormone, trigger identical response, block a hormone
  - Interaction with the hormone receptor
  - Alter enzymes involved with the hormone function
  - Damage the tissues that create the hormone
- Do not follow the normal dose/response curve
- Active at much lower doses, especially in the fetus and newborn
- Estradiols, progesterone, testosterone
- Lindane



Playing in an Ecosystem Near You

- Low sperm counts(50% reduction since 1939)
- Infertility
- Genital deformities
- Hormonally triggered human cancers
- Neurological disorders in children
  - Hyperactivity, attention deficit
  - Lowered IQ, rage reaction
- Developmental & reproductive problems in wildlife
- www.ourstolenfuture.org

Research Efforts

- Thousands of compounds still need to be tested to determine if they are EDCs
- Lack of knowledge regarding how quickly known/suspected EDCs are broken down in the environment or wastewater treatment plants and into what form
- Validated chemical and bioassay test methods are being evolved
- Continued identification and evaluation of the effects of EDCs on aquatic organisms, other wildlife, humans needs to occur
- Evaluation of effects of complex mixture of EDCs

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005.

Examples of Pharmaceutically Related EDCs

Chemical Class: Steroids/Sterols	Examples of Compounds within Class	Potential Sources to Surface Water
Naturally occurring mammalian Hormones	17-B-estradiol, estrone, testosterone, estriol	Human excretion, animal excretion, healthcare and consumer disposal of unwanted/exp meds
Synthetic hormones	Diethylstilbestrol (DES), ethinyl estradiol	Human use and excretion, animal use and excretion, healthcare and consumer disposal of unwanted/exp meds
Phytoestrogens	Genistein, coumestrol	Human excretion, natural plant decay, food processing plant effluent, agriculture, pulp mill effluent

Excerpted and modified from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005.

Baseline Contributions through Excretion of Endogenous Hormones, Phytoestrogens*

- Excretion rates for estradiol, estrone, estriol
  - 7 micrograms/day (µg/d) for a male
  - 6,900 µg/d for a pregnant woman
- Excretion rates for phytoestrogens in urine
  - 600 µg/d
- Impact on sewage treatment plant/million population served
  - 10 pounds of 17-β-estradiol and estrone
  - 500 pounds of phytoestrogens

*WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005.

Contributions of Excretion and Discarded EDCs

- Contraception and Hormone Replacement Therapy
  - Ethinyl estradiol – synthetic estrogen used for birth control
    - 6 µg/d of ethinyl estradiol for woman on contraceptives
    - Measured at approximately 2% of total endogenous estrogen
  - HRT usage undistinguishable from excreted endogenous estrogens
- Anabolic steroid usage: legal and illegal
- Sewering of unused/expired medications
  - IV disposal by healthcare facilities
  - Flushing by consumers

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

The Fate of EDCs

- Water solubility
  - More highly soluble compounds tend to remain in water or waste water
  - More fat soluble compounds tend to adsorb to solids in a wastewater treatment facility
  - Water solubility of EDCs is highly variable
    - Steroids/sterols e.g. Ethinyl estradiol 11.3 mg/L
    - Organohalides e.g. DDT 0.0031 mg/L

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

The Fate of EDCs

- Degradation
  - Chemical reactions
    - Hydrolysis
    - Photolysis
  - Microbial action
    - Biodegradation
  - Halogenated compounds e.g. DDT, PCB most persistent
  - “Pseudo-persistence”* based on continuous influx of chemicals normally degraded

Daughton, Christian, Origins and Ramifications of Pharmaceuticals & Personal Care Products as Environmental Contaminants

The Fate of EDCs

- Bioaccumulation
  - Estrogen mimics such as DDT may bioaccumulate at the top of the food chain due to persistence and fat solubility
  - Steroid/sterols EDCs (estradiol, estrone, phytoestrogen) water soluble, do not appear to bioaccumulate in aquatic organisms

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

Wastewater Treatment Methods

- Primary
  - Sedimentation
  - Disinfection: chlorination, ozonation, UV light
- Seconday
  - Biological process followed by sedimentation, disinfection
- Tertiary
  - Additioinal biological treatment
  - Additional chemical treatments to remove nutrients
- Advanced Treatment
  - Processes targeted at a single pollutant or class of compounds
    - Activated carbon, membrane separation, microfiltration, ultrafiltration, reverse osmosis, ion exchange

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

Effects of Treatment on EDCs

- Biological transformation
  - May transform an EDC rendered inert by the body back to its active form by removing the chemical attached by the liver or other organ
  - May degrade an EDC rendering it inactive
- Temperature effects
- Normal seasonal variation in water temperature may reduce removal efficiency of EDCs from 90% to 60% in winter

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

Comparison of Steroid/Sterol Removal

Class of EDC	Activated Carbon	Membrane separation	Reverse Osmosis
Naturally occuring steroids	>90%	40 -80%	90->99%
Synthetic steroids	>90		95->99
Phytoestrogens	Effective in analagous situation		Effective in analagous situation

Excerpted from WERF Technical Brief: Endocrine Disrupting Compounds and Implications for Wastewater Treatment, 2005

Today's Kaleidescope

- Impact of pharmaceuticals on aquatic organisms
- Presence of PPCPs in wastewater irrigation run-off
- Treatment challenges of drugs in drinking water
- Plant eating drugs???
- Using PPCPs as biomarkers

Effects of Pharmaceuticals on Daphnia Survival, Growth and Reproduction

- Single species lab toxicity tests with Daphnia magna, a freshwater zooplanton
  - Rapid reproduction
  - Sensitive to chemical environment
  - Critical role in freshwater ecosystems
- Two types of bioassays
  - Acute exposure to simulate an environmental pulse
  - Chronic exposure

Colleen M. Flaherty, Stanley I Dodson. Effects of pharmaceuticals on Daphnia survival, growth, and reproduction. Chemosphere, In press, 2005.

Drugs Studied

- Clofibric acid: cholesterol-lowering metabolite (Atromid-S, clofibrate); chemical relative of herbicide 2,4-D
- Erythromycin: human and veterinary antibiotic
- Fluoxetine: Selective serotonin reuptake inhibitor (SSRI), antidepressant (>40 million people globally)
- Lincomycin: Human and vet antibiotic
- Sulfamethoxazole: Human and vet antimicrobial (sulfa drug)
- Triclosan: Antibacterial/antimicrobial in consumer products
- Trimethoprim: Human and vet antimicrobial

Clofibric Acid

- Acute exposure (1, 10 and 100 µg/l) doubled the proportion of male offspring and was statistically significant at the 10 µg/l level and above
- Control ratio of males was 29.5% compared to 50.3% of 10 µg/l level
- Increases in male sex ratios in Daphnia have been linked to exposure to other chemicals, such as pesticides
- Chronic exposure did not significantly affect growth or development, possibly due to Daphnia's induction of P-450, a detoxification enzyme

Fluoxetine

- Known to stimulate invertebrate reproduction (zebra mussels)
- Probably through increased bioavailability of serotonin, which is responsible for regulating egg development and molting
- Acute exposure produced no changes
- Chronic exposure to 36 µg/l elicited a significant increase in offspring: 74 over 6 broods as compared to 28 of control group
- Based on other studies, the trade-off is a higher minimum food intake requirement

Clofibric Acid and Fluoxetine

- Acute exposure to 36 µg/l fluoxetine and 100 µg/l clofibric acid, caused significant mortality
- On average, 62.5% died by day 6, compared to a 10% control mortality rate
- A 36 µg/l /10 µg/l mixture led to morphological abnormalities in an average of 19% resulting in mobility problems and premature death

Erythromycin, Triclosan, & Trimethoprim

- Total antibiotic concentration of 30 µg/l (10 µg/l each) elicited a significant decrease in sex ratio
- On average 20% fewer male offspring than controls
- Antibiotic effects on sex determination are complex
- Effects of mixtures are not predictable from results of single pharmaceutical bioassays
- May be related to presence of sex-regulating microbes in some invertebrates; not known in Daphnia

Conclusions of Daphnia Study

- Fewer numbers of Daphnia could reduce water clarity
- Lead to a decline in the health of fish and other plankton-eating predators
- Future risk assessments should include reproductive and/or developmental effects at lower doses than the lethal dose
- Effects of a mixture of chemicals cannot be predicted by studies of single chemicals
- Both acute and chronic exposure studies should be conducted

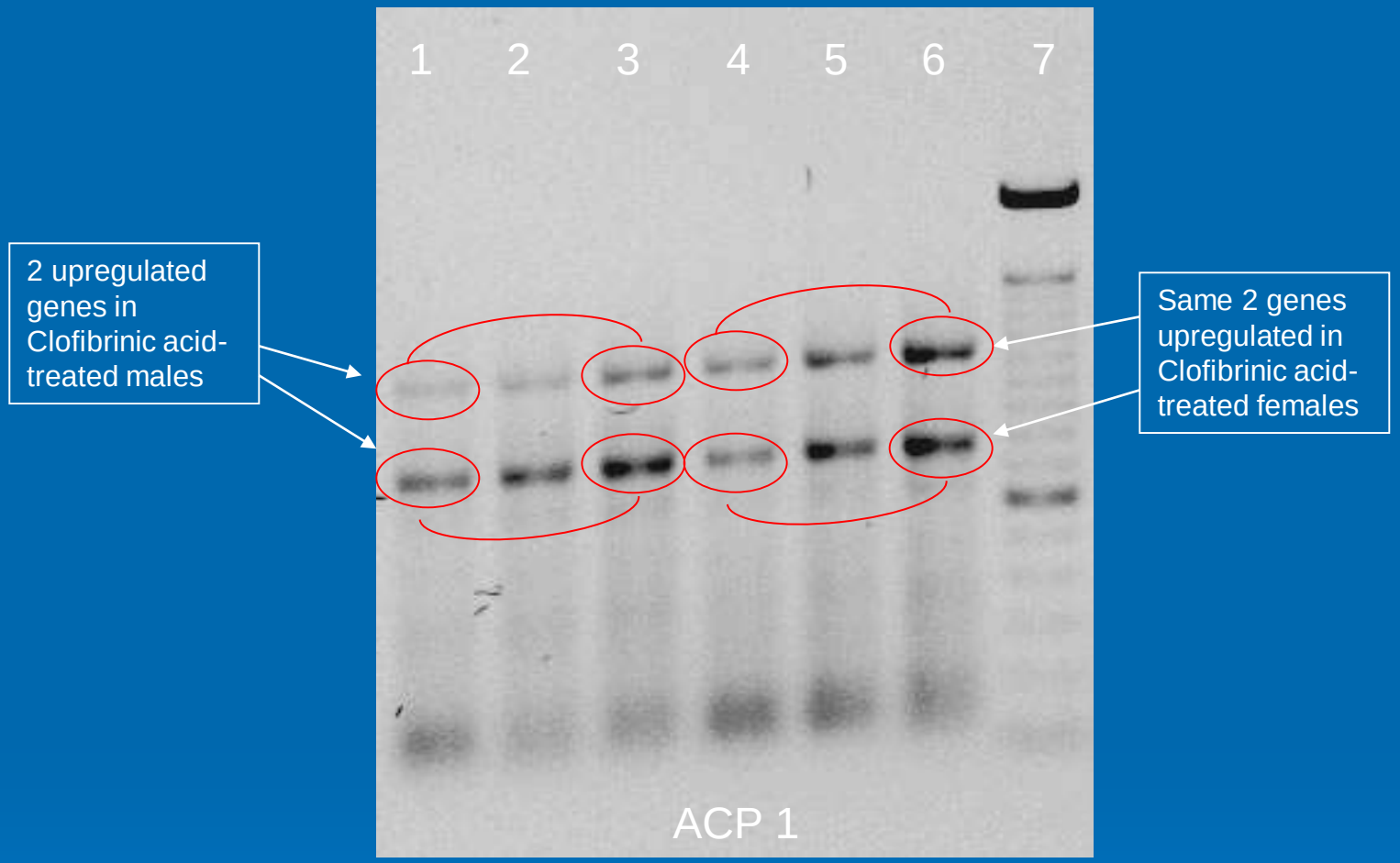
Genomic and Physiological Indicators of Effects of Pharmacueticals on Aquatic Organisms

Rebecca Klaper, Great Lakes WATER Institute

- Fathead minnow, *Pimephales promelas*
- Common baitfish in Wisconsin, native
- EPA aquatic toxicology model species

Parameters of the Experiment

- Drugs tested
  - Clofibric acid and naproxen sodium at 1000 nanograms/l (1 ppb) and 100 nanograms/l
- Test was to have been run for one week
- Had to terminate after 24 hours
- Clofibric acid induced milky, mucous response, difficulty with respiration, severe motility inhibition
- Naproxen effected behavior (slower), not as dramatic
- Also examined gene expression



Courtesy of Rebecca Klaper, Great Lakes WATER Institute

PPCPs in Runoff from Fields Irrigated with Treated Wastewater

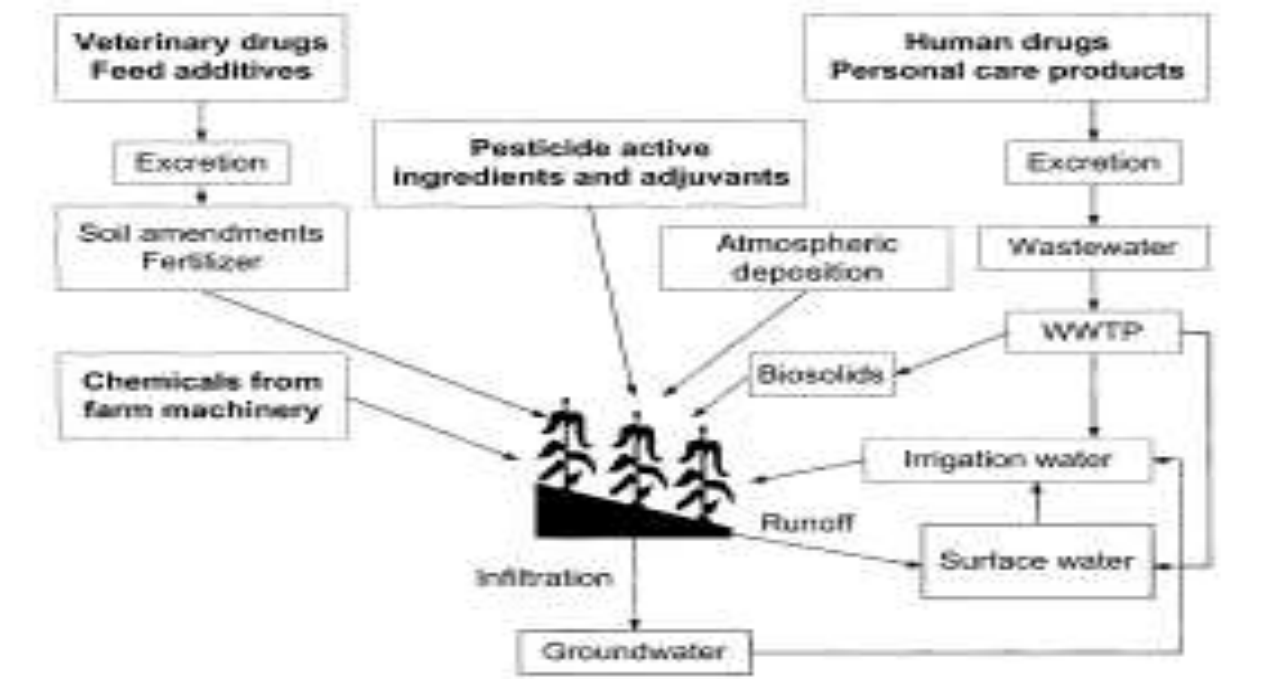


Figure 1. Routes of xenobiotic organic chemical (bold) introduction into agricultural systems. WWTP, wastewater treatment plant.

Joel A. Pedersen, et. al. Xenobiotic Organic Comopunds in Runoff from Fields Irrigated with Treated Wastewater, Journal of Agricultural and Food Chemistry, 2003, 51, 1360-1372.

PPCPs Found in Tertiary Treated Wastewater Runoff

- Carisoprodol – muscle relaxant, analgesic
- P-toluenesulfonamide- oral hypoglycemic metabolite
- Caffeine – detected in irrigation water only, not runoff
- Synthetic polycyclic musk fragrances
- Additional fragrances and fixatives
- DEET (N,N-diethyltoluamide) insect repellent

Management Implications

- Full suite of potentially toxic compounds entering surface waters be considered
- Current ecotoxicity tests insufficiently comprehensive
- Treated wastewater irrigation and sewage sludge-derived soil amendments and animal manures should be further investigted
- Food crops may take up wastewater-derived contaminants in irrigation water and biosolids

Drug Eating Plants???!!!

- Soil heavily polluted with chloroquine, quinacrine, or metronidazole (all antimicrobials) killed soy bean plants at different doses
- Soils treated with animal manure, sludge, and/or wastewater irrigation all contain levels of antibiotics which are apparently taken up to some degree by the plants
- Implications
  - Crop yields may be effected, especially over time
  - Food crops may actually contain traces of antibiotics

Jjemba, P.K. The effect of chloroquine, quinacrine, and metronidazole on both soybean plants and soil microbiota. *Chemosphere* 2002, *46*, 1019-1025.

PPCPs in Drinking Water

- Comparison of naproxen levels pre- and post-treament at drinking water plants
  - Intake of Mississippi River water at Louisiana plant = 63 to 65 ng/l of naproxen
  - Samples collected at the precipitator = 63 to 68 ng/l
    - Conventional treatment processes and 2 mg/l PAC (powdered activated carbon) did not remove naproxen
  - Samples collected after chlorination exhibited non-detectable concentrations of naproxen
- Oxidation (chlorination and ozonation) and sorption (dual media) processes may be effective treatments for reduction of some PPCPs,,,,HOWEVER…..

Glen R. Boyd, et al. PPCPs in surface and treated wasters of Louisiana, USA and Ontario, Canada. The Science of the Total Environment 311 (2003) 135-149

Negative Effects of Naproxen Chlorination Products on Biofilm

- Introduction of chlorine-naproxen solution demonstrated adverse effect on biofilm reactor
- The amount of biomass in the bioreactor decreased for 20 days following the addition of the chlorine-naproxen solution
- Subsequent research demonstrated the likely cause was the intermediate and/or end products in the chlorine-naproxen solution
- More research needed to be sure one solution doesn't create another problem

Glen R. Boyd, et al. Naproxen removal from water by chlorination and biofilm processes, Water Research 39 (2005) 668-676

Using PPCPs and EDCs to Detect Non-point Source Sewage Contamination

- Stormwater canals and Bayou St. John in New Orleans, LA
- During a 6 monthperiod, samples from two stormwater canals and an urban recerational waterway were analyzed for 9 PPCP and EDC compounds
- Five compounds attributed to non-point source sewage contamination were found in the canals
- Two compounds (naproxen and bisphenol A) were deted from all 3 sies
- Concentrations increaesd with rainfall events, further demonstating sewage contamination

Glen R. Boyd, et al. PPCPs and EDCs in stormwater canals and Bayou St. John in New Orleans, LA, USA. Science of the Total Environment 333 (2004) 137-148

So Where Does All This Information Leave Us?

- The Unkown is much bigger than the Known
- The ecosystem, of which we are an integral and highly influential part, is subtle and complex
- We cannot product data and knowledge at a rate fast enough to inform policy
- We must start managing to the highest safety level possible

Reduce Source Pollution

- Encourage alternatives to drain disposal of unused pharmaceuticals in healthcare facilities
- Enforce existing RCRA hazardous waste regulations in healthcare facilities, which include 5% of drugs
  - Tools for compliance available
- Encourage a higher level of management for other drugs of concern that should be in RCRA
  - Over 100 chemotherapy agents are not regulated federally as hazardous waste
- Develop consumer take-back programs
  - NERC, Lynn Rubenstein, Exec Director
  - Maine Legislation, Steve Gressi, M.D.
- Lobby for a change in the Controlled Substances Act
  - Enable reverse distributors & pharmacies to take back controlled substances that have been already dispensed

Encourage Product Stewardship

- Develop a dialog with pharmaceutical manufacturers
- Continue to enable reverse distribution of outdated pharmaceuticals
- Promote recycling of drugs retained within the healthcare system at long term facilities

Modernize Wastewater and Drinking Water Infrastructure

- How do you make sludge sexy?
- Where does the political will come from?
- How can you take advantage of the public's growing concern to allocate funding to this much needed effort?

Discussion

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