Pharmaceuticals in the Environment: Overview of Sources, Concerns, and Solutions

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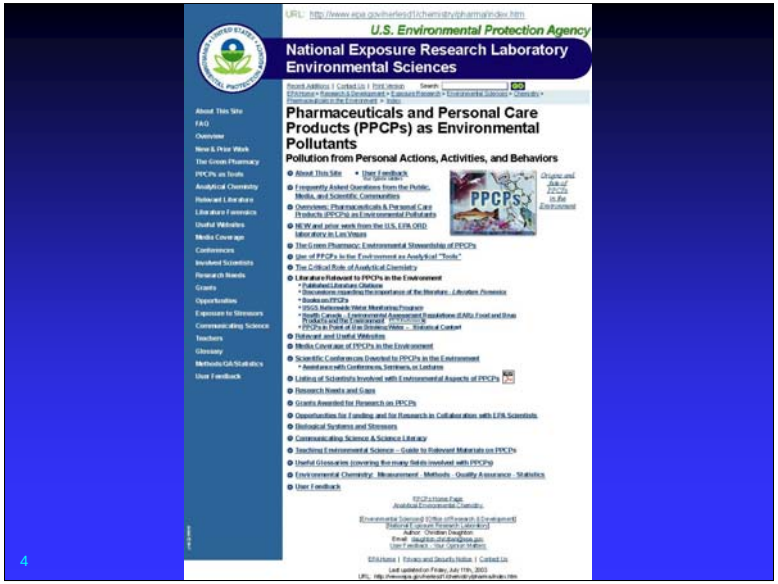
Wealth of other materials and links to most of the ongoing work relevant to this topic are available at the U.S. EPA's ***PPCPs* Web Site:**

http://www.epa.gov/nerlesd1/chemistry/pharma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PPCPs
Origins and Fate of PPCPs in the Environment

Historical Perspective - PPCPs

- PPCPs as environmental pollutants first investigated in Europe - 1980s.
- With the advent of monitoring and research in the U.S., literature has grown exponentially since 2000.
- PPCPs are not truly "emerging" pollutants. It is the understanding of the significance of their occurrence in the environment that is beginning to develop.
- Topic has high public visibility.
- Continues to attract significant media attention - newspapers, magazines (popular, trade, and science), radio, and TV.
- Overall issue comprises numerous facets involving expertise from a broad spectrum of disciplines ranging from human health to ecology - - necessitating communication between the medical/healthcare communities and environmental scientists.

Scope of Issue

- Thousands of distinct chemical entities.
- Numerous (and increasing) therapeutic classes and end uses.
- Large numbers possess very high biological activity.
- Two classes of therapeutics that have received the most attention are the antibiotics (potential for resistance selection among pathogens) and steroidal hormones (overlap with EDCs).
- For the plethora of other classes, however, little is known regarding the potential for effects.
- In general, PPCPs are not regulated water pollutants.
- Regulated pollutants compose but a very small piece of the universe of chemical stressors to which organisms can be exposed on a continual basis.

Landmark Monitoring Studies in U.S.

USGS 2002 (nationwide reconnaissance study)

- During 1999-2000, 142 streams, 55 wells, and 7 effluent samples were analyzed across 36 states.
- 95 contaminants (many of which were PPCPs) identified.
- Multiple co-occurrence common; 1 or more contaminants found in 111 streams.

[Kolpin et al. 2002 "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance," *Environmental Science and Technology*, 36(6): 1202-1211.]

USGS 2004 (comprehensive study of flow streams at a drinking water plant)

- Analyzed for 106 contaminants in 24 samples from multiple process streams
- 40 contaminants detected in 1 or more samples
- 34 detected in more than 10% of samples.

[Stackelberg et al. 2004 "Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant," *Science of the Total Environment*., 329(1-3): 99-113.]

Important to Note: These contaminants were "targeted" for monitoring. Consequently, an unknown number of others remained unidentified because they were not targeted. The data from any monitoring study provides but a narrow glimpse of the overall occurrence of pollutants.

Perspectives on the USGS Monitoring Study

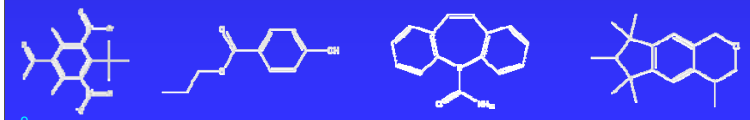
- Numerous unregulated chemicals are ubiquitous trace contaminants in waters. Many emanate from consumer usage for purposes designed and intended by the manufacturer.

- The PPCPs in the ongoing USGS study documented to occur in US surface, ground, and drinking waters probably represent but a fraction of all those that actually occur.

- These occurrence data demonstrate the potential for ANY consumer-use chemical to enter the environment, and thereby **give us the advance opportunity to be watchful regarding the future introduction to commerce of PPCPs with new mechanisms of action and ever-increasing biochemical potencies.**

PPCPs as Environmental Pollutants?

PPCPs are a diverse group of chemicals comprising all human and veterinary drugs (available by prescription or OTC; including biologics" and illicit drugs), diagnostic agents (e.g., X-ray contrast media), "nutraceuticals" (bioactive food supplements such as huperzine A), functional foods ("phoods" and "bepherages"), and other consumer chemicals, such as fragrances (e.g., musks) and sun-screen agents (e.g., 4-methylbenzylidene camphor; octocrylene); also included are "excipients" (so-called "inert" ingredients used in PPCP manufacturing and formulation; e.g., parabens).



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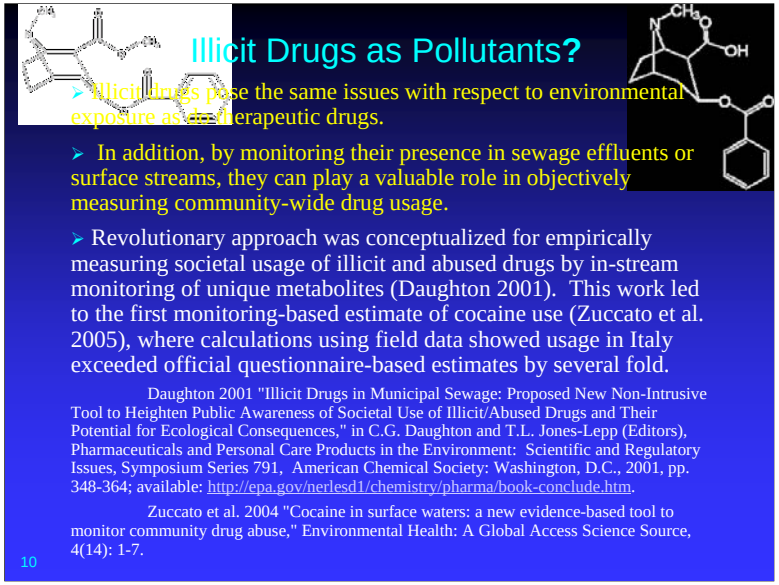
Musk ketone (nitro musk)

Propylparaben

Carbamazepine

Galaxolide (polycyclic musk)



Cocaine

Benzoylecgonine

Groupings of Chemical Pollutants:
Confusion from Their Intersections and Acronyms

Grouping	*Grouped According to:*
EDC (Endocrine Disrupting Chemical) **CMR** (Carcinogenic, Mutagenic, toxic to Reproduction)	toxicological mode of action or endpoint
PBT (Persistent, Bioaccumulative Toxic) **vPvB** (very Persistent, very Bioaccumulative) **POP** (Persistent Organic Pollutant)	environmental properties
micropollutants	frequency or level of occurrence
PPCPs	type of intended usage
priority pollutants and others	legislation
"**emerging" contaminants/pollutants**	novelty, fad, timeliness, or new concern

Origins of PPCPs in the Environment

- Portions of most ingested drugs are excreted in varying unmetabolized amounts (and in undissolved states because of protection by excipients) primarily via the urine and feces.
- Other portions sometimes yield metabolites that are still bioactive. Still other portions are excreted as conjugates.
- Free excreted drugs and derivatives can escape degradation in municipal sewage treatment facilities (removal efficiency is a function of the drug's structure and treatment technology employed); the conjugates can be hydrolyzed back to the free parent drug.
- Un-degraded molecules are then discharged to receiving surface waters or find their way to ground waters, e.g., leaching, recharge.

Origins of PPCPs in the Environment

- Certain pharmaceutically active compounds (e.g., caffeine, aspirin, nicotine) have been known for over 20 years to occur in the environment.
- Environmental occurrence primarily resulting from treated and untreated sewage effluent.
- Only more recently has a larger picture emerged — numerous PPCPs can occur (albeit at very low concentrations).
- Prior discovery delayed primarily by limitations in analytical environmental chemistry (ultra-trace enrichment and detection).
- Domestic sewage is a major source — not just hospital sewage. CAFOs are a major source of antibiotics.

Origins of PPCPs in the Environment

- Other potential routes to the environment include leaching from municipal landfills, runoff from confined animal feeding operations (CAFOs) and medicated pet excreta, loss from aquaculture, spray-drift from agriculture, direct discharge of raw sewage (storm overflow events & residential "straight piping"), sewage discharge from cruise ships (millions of passengers per year), illegal "clan" labs (especially methamphetamine), oral contraceptives used as soil amendment and plant growth tonic (urban legend), and transgenic production of proteinaceous therapeutics by genetically altered plants (aka "molecular farming" — "biopharming").

- Direct discharge to the environment also occurs via dislodgement/washing of externally applied PPCPs.

Expanding Uses and Escalating Usage

- Aging population (polypharmacy)
- Growing numbers of drug targets (genomics)
- Individualized therapy (polymorphisms); off-label prescribing
- Nutraceuticals; functional foods
- Lifestyle and cosmetic pharmacy

PPCPs as “Emerging” Risks?

It is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. It has only become more widely evident in the last decade because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. **There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.**

"Emerging" *Pollutants* vs. Emerging *Knowledge*

The vast majority of all "emerging" pollutants are not new to the environment

- **Two major sources for pollutants that are truly "new" to the environment**:
  - Chemicals newly introduced to commerce (e.g., new drugs or pesticides).
  - New anthropogenic processes (e.g., gallium arsenide quantum dots).
- **Previously unrecognized pollutants can come to our attention as a result of**:
  - New advances in chemical analysis (e.g., "non-target" identification).
  - Ability to detect existing pollutants at ever-lower concentrations (e.g., N-nitrosodimethylamine - NDMA).
  - Exploring environmental "compartments" not previously considered (e.g., foods as a significant source of acrylamide).

“PBTs” - “POPs” - “BCCs”: Only one part of the risk puzzle?

Since the 1970s, the impact of chemical pollution has focused almost exclusively on conventional “priority pollutants”†, especially on those collectively referred to as “persistent, bioaccumulative, toxic” (PBT) pollutants, “persistent organic pollutants” (POPs), or “bioaccumulative chemicals of concern” (BCCs).

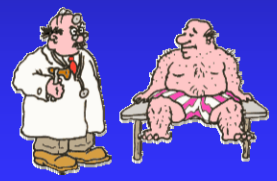
The “dirty dozen” is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

The conventional priority pollutants, however, are only one piece of the larger risk puzzle.

† an historical note: the current “lists” of priority pollutants were originally established in the 1970s in large part based on which chemicals of initial concern could be measured with off-the-shelf chemical analysis technology. Priority pollutants were NOT selected because they posed the sole risks.

What portion of overall risk is contributed by unregulated pollutants?

Can risk be assessed in a truly holistic manner without knowing the actual exposure universe?



The Chemical Universe

The *KNOWN* Universe

- As of April 2006, nearly 28 million organic and inorganic substances had been documented.

(indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry; excluding bio-sequences such as proteins and nucleotides)

- Of these nearly 28 million known chemicals, nearly 10 million were commercially available.
- Representing a 60% increase over the prior 3-year period.
- Of these, fewer than a quarter million (240,000) were inventoried or regulated by numerous government bodies worldwide - - representing less than 2.5% of those that are commercially available or less than 0.9% of the known universe of chemicals.

http://www.epa.gov/nerlesd1/chemistry/pharma/critical.htm

The Chemical Universe

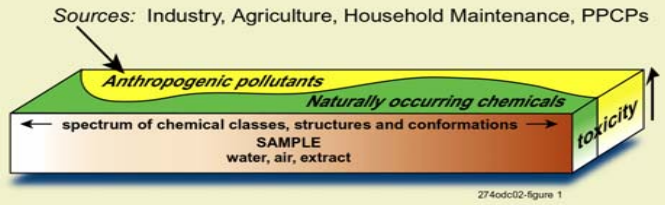
The *POTENTIAL* Universe

- While the *KNOWN* universe of chemicals might seem large (28 million), the universe of *POTENTIAL* chemicals (those that could possibly be synthesized and those that already exist but which have not yet been identified) is unimaginably large.

How many distinct organic chemical entities could hypothetically be synthesized and added to a seemingly limitless, ever-expanding chemical universe?

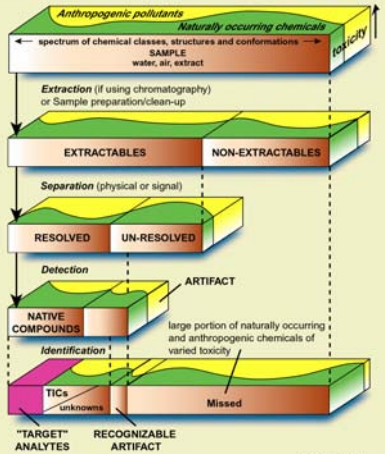
- By limiting synthesis strictly to combinations of 30 atoms of just C, N, O, or S, **more than 10^{60} structures are possible !**
- Expanding the allowable elements to other heteroatoms (e.g., P and halogens), the limits to the numbers of possible structures defies imagination. Also known as “chemical space”.

Universe of Chemicals in the Environment



For more discussion, see:
http://epa.gov/nerlesd1/chemistry/pharma/critical.htm

Limitations and Complexity of Environmental Chemical Analysis



Chemical Analysis Output for a Typical Environmental Sample

"TARGET" ANALYTES

RECOGNIZABLE ARTIFACT

large portion of naturally occurring and anthropogenic chemicals of varied toxicity

TICs = tentatively identified compounds

C.G. Daughton
U.S. EPA July 2002

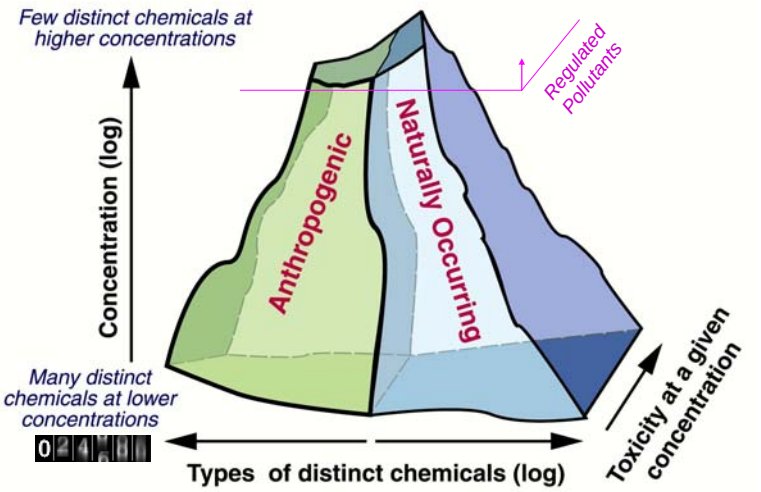
Prevalence of Xenobiotic Occurrence: Some Possible Generalizations Regarding Ubiquity

- The lower the concentration, the higher the probability of larger numbers of distinct chemicals occurring
- **Exponentially more types of chemicals occur at exponentially lower concentrations** (*does the distribution of chemical types versus their concentrations follow a power law, as shown for such a wide array of other phenomenon?* e.g., see: M. Buchanan "Ubiquity", Crown Publishers 2000)
- At the very lowest concentrations (zeptomolar to yoctomolar, zM - yM), the off-the-cuff truism may apply:

"***Everything can be found everywhere***"

- The challenge for environmental monitoring is to "measure only what needs to be measured."

Prevalence/Distribution of Xenobiotic Occurrence



Einstein on:
Environmental Monitoring

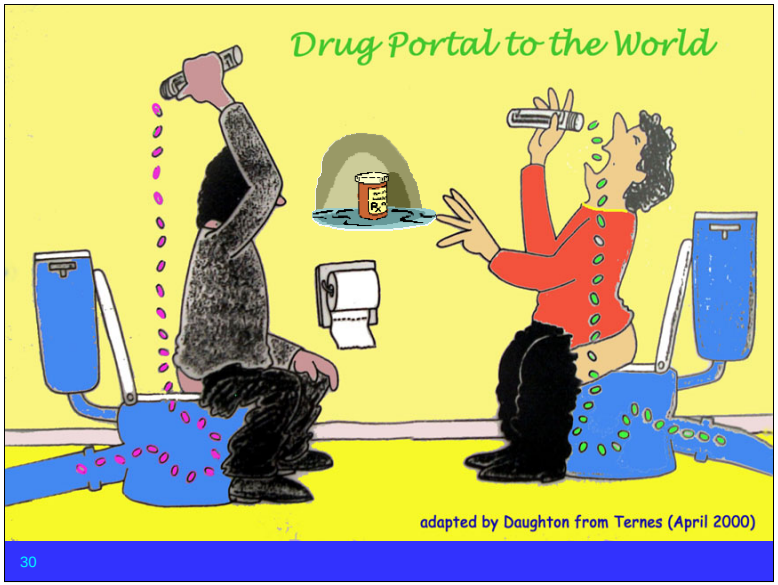
"Not everything that can be counted counts, and not everything that counts can be counted." (oft attributed to Albert Einstein)

corollary for environmental monitoring

Not everything that can be measured is worth measuring, and not everything worth measuring is measurable.

further truisms regarding *Environmental Monitoring*

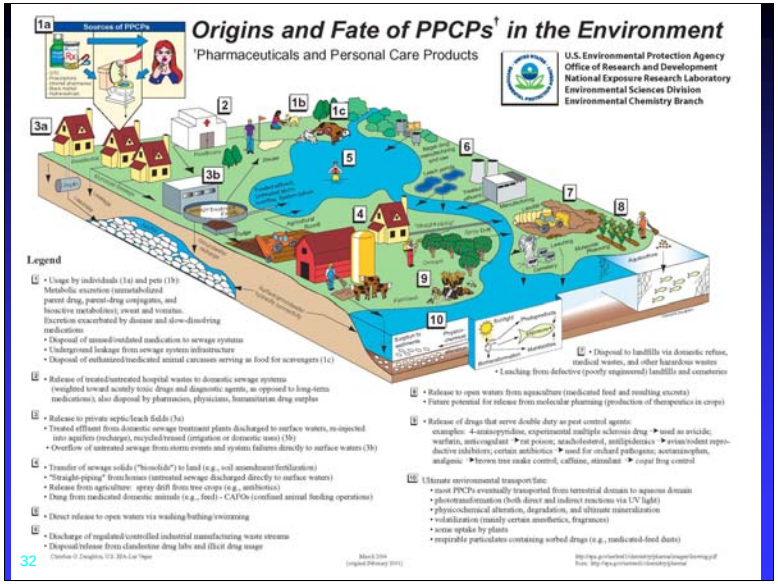
- What one finds usually depends on what one aims to search for.
- Only those compounds targeted for monitoring have the potential for being identified and quantified.
- Those compounds not targeted will elude detection.
- The spectrum of pollutants identified in a sample represent but a portion of those present and they are of unknown overall risk significance.


Drug Portal to the World
adapted by Daughton from Ternes (April 2000)

Environmental Exposure

- Occurs as a result of the combined actions, activities, and behaviors of multitudes of individuals.
- Inadvertent discharge: Excretion to sewage.

  Analogous origins occur from veterinary and agriculture usage (e.g., CAFOs).
- Purposeful discharge: Disposal of expired/unwanted PPCPs to toilets and drains as well as trash.
- Of the eight “grand challenges” identified in the NRC’s 2000 report (*Grand Challenges in Environmental Sciences*), one "encompasses questions about societal-level consumption patterns, since consumption is the primary force driving human perturbations of material cycles.”


Origins and Fate of PPCPs† in the Environment
†Pharmaceuticals and Personal Care Products
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch
Sources of PPCPs
Legend
• Usage by individuals (1a) and pets (1b):
Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus.
Excretion exacerbated by disease and slow-dissolving medications
• Disposal of unused/outdated medication to sewage systems
• Underground leakage from sewage system infrastructure
• Disposal of euthanized/medicated animal carcasses serving as food for scavengers (1c)
• Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus
• Release to private septic/leach fields (3a)
• Treated effluent from domestic sewage treatment plants discharged to surface waters, re-injected into aquifers (recharge), recycled/reused (irrigation or domestic uses) (3b)
• Overflow of untreated sewage from storm events and system failures directly to surface waters (3b)
• Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
• "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
• Release from agriculture: spray drift from tree crops (e.g., antibiotics)
• Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)
• Direct release to open waters via washing/bathing/swimming
• Discharge of regulated/controlled industrial manufacturing waste streams
• Disposal/release from clandestine drug labs and illicit drug usage
• Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
• Leaching from defective (poorly engineered) landfills and cemeteries
• Release to open waters from aquaculture (medicated feed and resulting excreta)
• Future potential for release from molecular pharming (production of therapeutics in crops)
• Release of drugs that serve double duty as pest control agents:
examples: 4-aminopyridine, experimental multiple sclerosis drug ➤used as avicide; warfarin, anticoagulant ➤rat poison; arachidonitol, antiphrenacic ➤avian/rodent reproductive inhibitors; certain antibiotics ➤used for orchard pathogens; acetaminophen, analgesic ➤brown tree snake control; caffeine, stimulant ➤copal frog control
Ultimate environmental transport/fate:
• most PPCPs eventually transported from terrestrial domain to aquatic domain
• photostransformation (both direct and indirect reactions via UV light)
• physicochemical alteration, degradation, and ultimate mineralization
• volatilization (mainly certain anesthetics, fragrances)
• some uptake by plants
• respirable particulates containing sorbed drugs (e.g., medicated-feed dusts)

Inter-Connectedness of Humans and the Environment

- Occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the actions and activities of individuals and their environment.

- PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals.

Ramifications

- Exposure at therapeutic doses is NOT the concern.
- Exposure to non-target organisms could be significant.
- Continual input via treated sewage imparts PPCPs with "pseudo-persistence" even if they have short half-lives.
- Aquatic organisms can suffer continual exposure.
- Potential exists for subtle effects (e.g., neurobehavioral change), even at ppb levels (µg/L).
- Potential exists for inhibition of aquatic defensive mechanisms such as efflux pumps.
- Pose many challenges for the outer envelope of toxicology - especially the many unknowns associated with effects from simultaneous exposure to multiple chemical stressors over long periods of time.
- Potential for additive (cumulative) and interactive (synergistic) effects from multiple exposure.

Toxicity of
Complex Environmental Mixtures:
Poses Major Unanswered Questions

Exposure to Multiple, Trace-Level Xenobiotics below Known Effects Levels

Potential Toxicological Significance as a Result of:

(1) Potential for **additive effects** from multiple agents sharing common mechanisms action (MOAs). Individual concentrations combine to exceed an effects level.

(2) Possible **interactive effects**, especially synergism, where combined action exceeds the sum of individual effects.

(3) **Hormesis** – Effects below purported NOELs. Paradoxical "U-shaped" dose-response curves.

continued >

Potential Toxicological Significance as a Result of:

(4) Dynamic Dose-Response. **Toxicant-Induced Loss of Tolerance (TILT)**: initial exposure sensitizes, and subsequent exposures to levels below those previously tolerated trigger symptoms (e.g., ecological version of MCS or chemical hyperreactivity).

(5) Comparatively little research performed at **extremely low concentrations** (nM-pM and below). Some agents have ability to impart previously unrecognized effects at "ultra-trace" concentrations.

(6) **Non-target species receptor repertoires** not well characterized. Variation in receptor repertoires across species, and unknown overlap with humans leads to countless questions regarding potential effects.

continued >

Potential Toxicological Significance as a Result of:

(7) Susceptible **genetic outliers** within species.

(8) **MOAs not fully understood**. Even most drugs can each have a multitude of effects. Most MOAs for the therapeutic endpoints, however, remain to be discovered, even for humans.

(9) **Dose-dependent transitions in MOAs** (multi-phasic dose-response curves resulting from shifts in the MOA over the dose continuum)

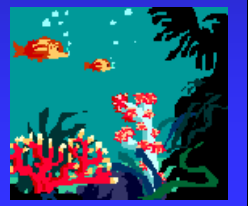
- concluded -

Potency as a Factor in Environmental Risk

- The ADI (accepted daily intake) for APIs (active pharmaceutical ingredients) is a direct function of the therapeutic dose.
- The therapeutic dose, in turn, is a function of potency. With increasing potency, the lower the dose.
- Predicted or measured environmental concentrations (P/MECs) are therefore inversely related to potency.
- Risk can therefore be considered 'self-leveling".
- This contrasts sharply with industrial chemicals, for example, whose potencies have much less connection with potencies.

PPCPs in Receiving Waters: A Global, Ubiquitous Process with Unique Local Expression

- Important to recognize that ALL municipal sewage, regardless of location, will contain PPCPs. Issue is not unique to any particular municipal area.
- Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs.



Aquatic organisms — captive to continual, life-cycle chemical exposures

- Aquatic Exposure is Key: Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.

- Re-evaluation of "Persistence": Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat). These can be referred to as ***pseudo-persistent*** **chemicals** (**P2's**).

Bioconcentration: New Paradigm ?

- Low octanol-water partition coefficients (high polarity) would seem to preclude bioconcentration for most PPCPs.

Examples of those subject to bioconcentration include: synthetic musks, sunscreen filters, parabens, triclosan, triclocarban.

- But certain drugs, despite their low lipid solubilities, are being detected in aquatic tissues in concentrations enriched from those in the ambient water. This is perhaps partly a result of drugs being designed to take advantage of gaining intracellular access via active transport :

Examples:

estrogens (concentrated in fish bile 60,000 X)
gemfibrozil (concentrated in fish tissue, 113 X)
diclofenac (concentrated in fish organs, up to 2,700 X)
fluoxetine (concentrated in muscle, liver, and brain of fish)

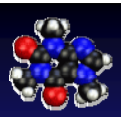
Drugs Having Double Uses: Medicinals and Pest-Control Agents

(alternative sources for introduction to the environment)

Some chemicals serve double duty as both drugs and as pest-control agents. While this shows the broad utility of certain drugs, it also poses the possibility that these alternative uses serve as additional sources for their introduction to the environment.

Examples include:

- **4-aminopyridine**: experimental multiple sclerosis drug and an avicide
- **warfarin**: anticoagulant and a rat poison
- **triclosan**: general biocide and gingivitis agent used in toothpaste
- **azacholesterols**: antilipidemic drugs and avian/rodent reproductive inhibitors [e.g., Ornitrol]
- **antibiotics**: used for orchard pathogens
- **acetaminophen**: an analgesic and useful for control of Brown Tree snake
- **caffeine:** stimulant and approved for control of *coqui* frog in Hawaii; also repels and kills snails and slugs at concentrations exceeding 0.5%
- **NSAIDs**: e.g., veterinary diclofenac; vultures in Asia poisoned by disposed carcasses
- **pentobarbital**: used in animal euthanasia; raptors poisoned by disposed carcasses



Caffeine for control of frog pests

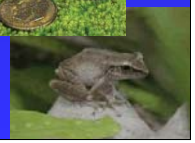
U.S. EPA approved (27 Sept 2001) specific exemption from FIFRA allowing use of caffeine to control *coqui* frogs in Hawaii.

Exemption allows application of 100-200 pounds per acre (max total 1,200 lbs/year).

In absence of natural predators, *coqui* frog can reproduce to high densities (10,000/acre).

Out-compete native birds by massive consumption of insects.

Chirping frequency is extremely piercing and annoying (upwards of 100 db).



Acetaminophen for control of Brown Tree snakes

Brown Tree snakes (*Boiga irregularis*), native to eastern Indonesia, become invasive pests on Guam starting in the 1940's/1950's.

Without natural predators, the Brown Tree snake's population in Guam is estimated at upwards of 15,000 per square mile.

Have decimated certain native bird, bat, and reptile populations, as well as caused extensive economic losses (agriculture, pets, human bites, electric grid outages/repairs).

No safe and effective chemical-controls until discovery by USDA that **acetaminophen (80 mg) will effectively kill Brown Tree snakes within 3 days** of even a brief exposure to baited, dead mice.

Acute effects of larger doses of acetaminophen on local non-target species have not been detected.

[see: J. J. Johnston et al. "Risk Assessment of an Acetaminophen Baiting Program for Chemical Control of Brown Tree Snakes on Guam: Evaluation of Baits, Snake Residues, and Potential Primary and Secondary Hazards," *Environ. Sci. Technol*. 2002, 36(17):3827-3833; also: http://www.aphis.usda.gov/lpa/inside_aphis/features10d.html].

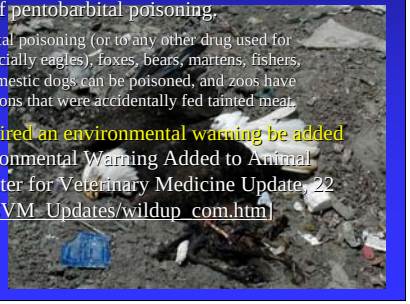
Decline of *Gyps* spp. Vultures in Pakistan & India – Possible Link with Diclofenac

- Beginning in the early 1990s, vultures (especially white-backed vultures such as *Gyps bengalensis*) have experienced dramatic population declines (as great as 95%) in Southern Asia – particularly India and spreading to Pakistan and Nepal.
- Various hypothesized causes have ranged from pathogens to pesticides. The causative agent(s) result in acute renal failure (manifested as visceral gout from accumulation of uric acid), leading to death of the breeding population.
- Prof. J. Lindsay Oaks (Washington State University) et al. present evidence that (at least in Pakistan) the die-offs are strongly linked with diclofenac poisoning ("Diclofenac Residues as the Cause of Vulture Population Decline in Pakistan," *Nature*, 28 January 2004).
- Diclofenac, although primarily a human NSAID, is used in veterinary medicine in certain countries. In India, diclofenac is used for cattle, whose carcasses are a major food source for G*yps*.

- Diclofenac seems to be selectively toxic to *Gyps* spp. versus other carrion-eating raptors.
- Health hazards grow from the accumulation of uneaten cattle carcasses (as well as human), which now serve to attract growing packs of dangerous feral dogs, which can also carry rabies. As of 2005, India will phase-out the veterinary use of diclofenac.

Animal Euthanasia and Secondary Poisoning of Wildlife

- Various drugs are used to euthanize domestic pets and other animals.
- The principle drug is pentobarbital. High doses are used. Most of the body-burden residue escapes excretion and persists indefinitely. The carcass, if not disposed of according to local regulations, can be consumed by scavenger wildlife. But determined wildlife can even uncover well-buried carcasses.
- Wildlife pentobarbital poisonings have been recorded in 14 states since the mid-1980s. The U.S. Fish and Wildlife Service has documented more than 130 bald and golden eagles as casualties of pentobarbital poisoning.
- Wildlife vulnerable to accidental pentobarbital poisoning (or to any other drug used for euthanasia) include a wide range of birds (especially eagles), foxes, bears, martens, fishers, coyotes, lynx, bobcats, cougars, and otters. Domestic dogs can be poisoned, and zoos have documented the deaths of tigers, cougars and lions that were accidentally fed tainted meat.
- In July 2003, the FDA's CVM required an environmental warning be added to animal euthanasia products ["Environmental Warning Added to Animal Euthanasia Products," U.S. FDA, Center for Veterinary Medicine Update, 22 July 2003: http://www.fda.gov/cvm/CVM_Updates/wildup_com.htm]



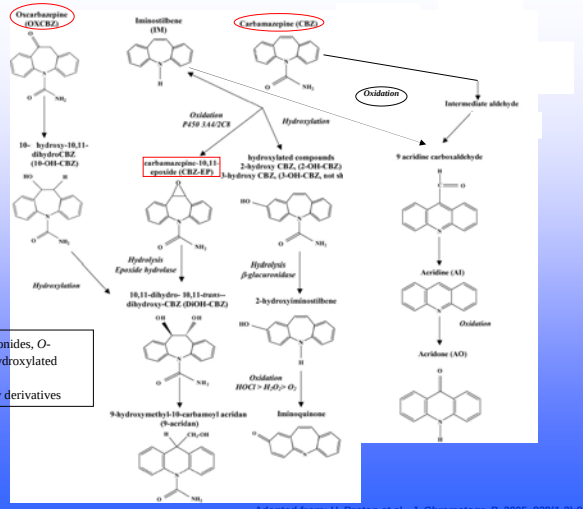
Mercury in Skin Lightening Soaps and Creams

http://www.nyc.gov/html/doh/html/pr/pr008-05.shtml

http://www.mercurypolicy.org/new/documents/SoapHgFactSheet012005.pdf

http://www.mercurypolicy.org/new/documents/UNEPHGSOAPPRESNTATION.pdf

Carbamazepine & Oxcarbazepine: *Complex Metabolism*



Multitude of *N*-glucuronides, *O*-conjugates (of monohydroxylated derivatives), and methylsulfinylhydroxy derivatives

Adapted from: H. Breton et al., *J. Chromatogr. B*, 2005, 828(1-2):80-90.

Pharmacokinetics and Predicting Environmental Fate

Using carbamazepine (CBZ) as but one example, the following generalities emerge:

- Pharmacokinetics essential to understand complexity of metabolites that can be excreted [CBZ has at least 30 different human metabolites].
- Wide spectrum of metabolites can be created from a single active ingredient.
- Many of these metabolites are excreted and can become pollutants themselves.
- Excreted conjugates can serve as hidden reservoirs of the parent chemical if they are subsequently hydrolyzed (e.g., by microbial activity).
- Extensively metabolized drugs such as CBZ (less than 3% is excreted unchanged in the urine) can nonetheless persist in the environment.
- Pharmacokinetics is not necessarily a predictor of waste treatment efficacy. CBZ is an example - - extensively metabolized by humans but relatively refractory to microbial degradation in waste treatment and in the environment.

Potential for Subtle Effects?

continued >

Potential for Subtle (currently unrecognized) Effects?

- Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time? For example, latent damage, only surfacing later in life. The issue of “resiliency”.
- Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause?
- Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological) — e.g., subtle shifts in behavior or intelligence.
- Advances required in developing/implementing new aquatic toxicity tests to better ensure that such effects can be detected.

continued >

Sidebar: Incremental Poisoning Designed to Appear "Natural" – a "Popular" Historical Practice

The use of slow poisoning in homicides (usually administered by food and drink) was practiced widely in Europe from the early to late 1600s – with a resurgence in the 1800s:

"The atrocious system of poisoning, by poisons so slow in their operation, as to make the victim appear, to ordinary observers, as if dying from a gradual decay of nature, has been practised in all ages."

"Those who are curious in the matter may refer to Beckmann on Secret Poisons, in his History of Inventions, in which he has collected several instances of it from the Greek and Roman writers. Early in the sixteenth century the crime seems to have gradually increased, till, in the seventeenth, it spread over Europe like a pestilence. It was often exercised by pretended witches and sorcerers, and finally became a branch of education amongst all who laid any claim to magical and supernatural arts. In the twenty-first year of Henry VIII. an act was passed, rendering it high-treason: those found guilty of it, were to be boiled to death."

The Slow Poisoners in Extraordinary Popular Delusions and the Madness of Crowds, by Charles MacKay, 1841

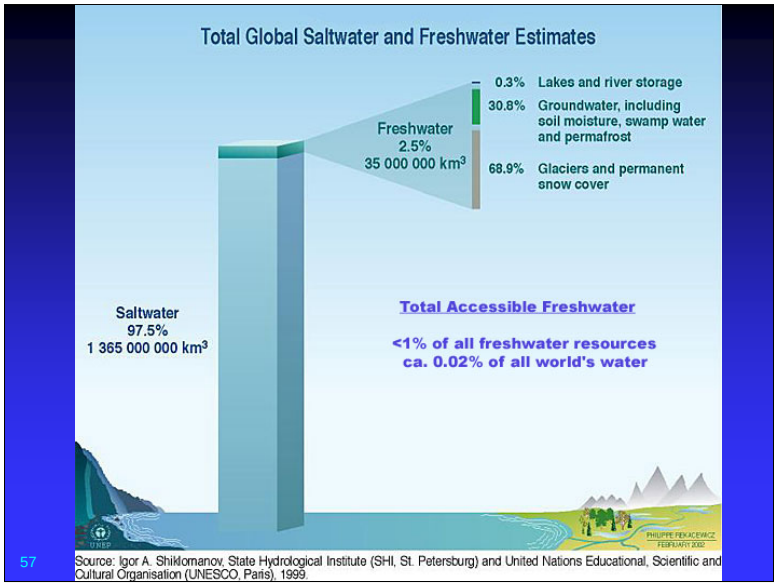
Potential Subtle, Difficult-to-Detect Effects:

some examples

- Profound effects on development, spawning, and wide array of other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants (ppb levels).
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of efflux pump inhibitors in compromising aquatic health?

Peeking at the Future

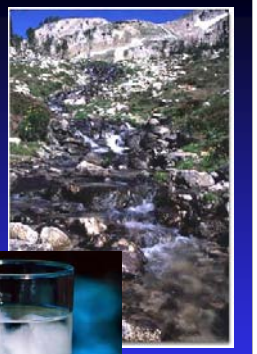
The ratio of the area of the yellow square to the blue background roughly represents the fraction of the world’s total water that is accessible freshwater.



http://www.unep.org/vitalwater/01.htm

Which water would you choose ?

Recycled Sewage or Snow Melt ?



"Clean" water depends on one's perspective ...

San Francisco Exploratorium

A Sip of Conflict -or- *The Conflicted Sip*


Maybe there's another reason they're called PPCPs?
source: Der Abstieg, Edeltraut A G Essen, 1958
color by C.G. Drayton, 2004

Key to Maintaining & Improving the Public's Confidence in Water Supplies

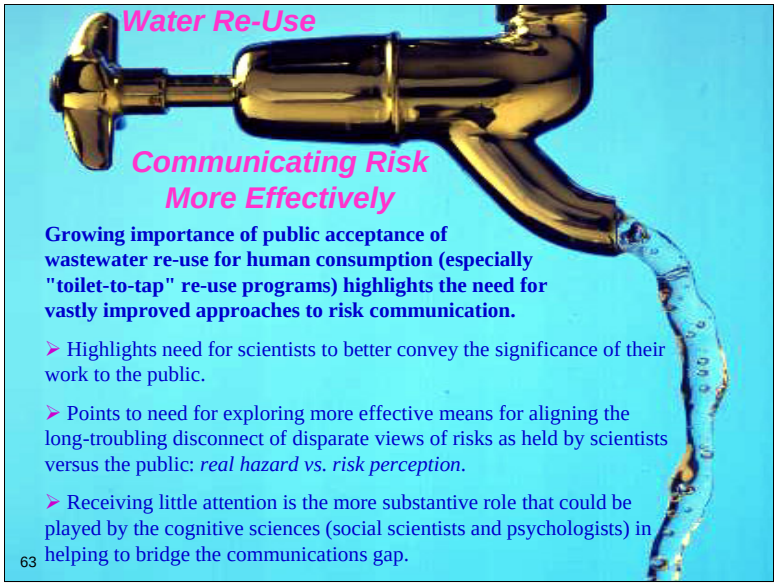
Growing pressures to re-use wastewaters for drinking

"Increasingly Smaller Recycle Loops": Ever-shortening spatial & temporal hydraulic connectivity between point of wastewater discharge and point of use for drinking will pose serious challenges for ensuring human safety and for framing how risk is perceived by the consumer.

Two Major Issues:

Groundwater Recharge (both indirect and direct)

De-Centralized Water Re-Use - - "Toilet-to-tap"



Water Re-Use

Communicating Risk More Effectively

Growing importance of public acceptance of wastewater re-use for human consumption (especially "toilet-to-tap" re-use programs) highlights the need for vastly improved approaches to risk communication.

- Highlights need for scientists to better convey the significance of their work to the public.
- Points to need for exploring more effective means for aligning the long-troubling disconnect of disparate views of risks as held by scientists versus the public: *real hazard vs. risk perception*.
- Receiving little attention is the more substantive role that could be played by the cognitive sciences (social scientists and psychologists) in helping to bridge the communications gap.

Societal Outcomes that Derive from Risk Are a Function of:

- "True" risk (which usually cannot be fully knowable)
- How risk is **communicated** by science and regulators
- How risk is **perceived** by the public

continued >

Communication of Hazard vs. Perception of Risk

Need for an ongoing, society-wide dialog regarding all sources of exposure and the universe of toxicants to which we are continually exposed - - both naturally occurring and anthropogenic.

Recognize our inability to convey the extent and significance of UNCERTAINTY.

Have we inadvertently misled the public into believing that science's knowledge base is sufficiently large that we can assess risk in a holistic manner?

Science's inability to clearly communicate the full reality (extent) of the chemical stressor universe and its proper perspective and context has led to the public's inability to fully understand the significance of exposure to stressors.

This is perhaps one of the single most significant challenges for environmental science because it might be preventing the most cost-effective decisions and implementation of measures leading to the maximal return for both human and ecological health.

Key Role of Beliefs in Public Acceptance of Recycled Water

- The principles of logic upon which certain beliefs are based derive from what are known as the "common laws of magic," one of which is the *Law of Association*, which in turn comprises the sub-laws of *Similarity* and *Contact* or *Contagion*. These "laws" partly originated with the Alchemists, and therefore have a distant relationship with chemistry.
- The Law of Similarity states that like things produce like things (effects resemble their causes).
- The Law of Contagion holds that once contaminated, always contaminated. "Things that have once been in contact with each other continue to act on each other at a distance even after physical contact has been severed." Once objects come into contact with each other they will continue to influence each other, even after separation.

continued >

Key Role of Beliefs in Public Acceptance of Recycled Water

- Historically, some water re-use projects have become "branded" with negative images by consumers.
- Negative images cannot necessarily be erased or corrected by more or even better science. In fact, studies show that additional supportive data often serves to exacerbate already-formed negative images.
- Instead, we must involve social psychologists to bridge the communications gap between science and the public.
- The "yuck factor" associated with so-called "toilet-to-tap" programs, for example, derives from beliefs that have long been imbedded in social belief constructs, and these beliefs are refractory to being influenced by positive findings of science.

continued >

Risk Communication and Water Re-Use

An examination in new light of the problems with communicating risk, especially with regard to groundwater injection and water reuse:

Daughton C.G. "Groundwater Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds," In Fate and Transport of Pharmaceuticals and Endocrine Disrupting Compounds (EDCs) During Ground Water Recharge (special issue), *Ground Water Monitoring & Remediation*, **2004**, 24(2): 127-138.

http://www.epa.gov/nerlesd1/chemistry/ppcp/images/water-reuse.pdf

continued >

Real-world lesson in communicating:

Outhouse Springs
Bottled Water

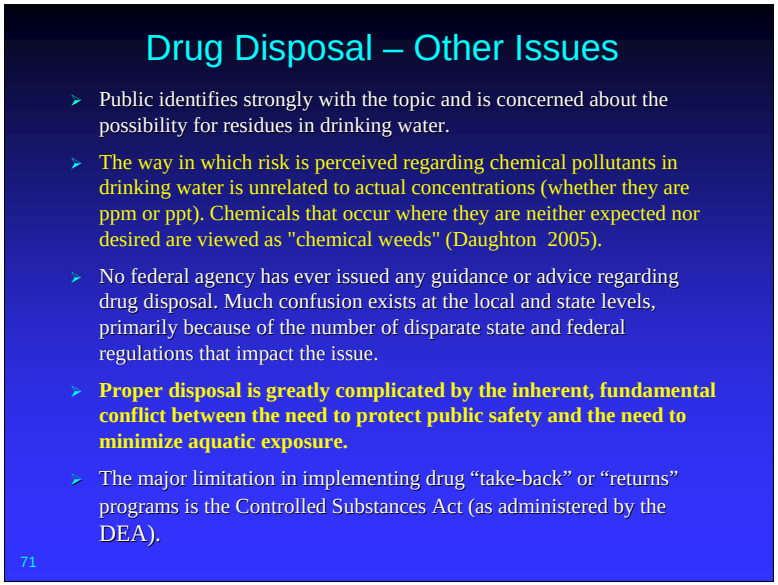
Experiment by: *Adams Outdoor Advertising*, South Carolina, 2002

http://www.outhousesprings.com/index.html

concluded

Drug Disposal: The Key Questions Regarding Its Environmental Significance

- **What portion of environmental drug residues originate from direct disposal versus excretion and bathing?** This ratio is totally unknown.
- Does this fraction vary from drug to drug, or among packaging types (e.g., bulk bottles versus blister packs)?
- It is possible that direct disposal may indeed be a significant source of environmental residues for a limited number of drugs, such as for OTC medicines (especially those that are bulk purchased in such large quantities that they expire before being completely used). In contrast, disposal is probably not a significant source for those drugs provided by unit dispensing and for those that are costly or prescribed in short courses.
- It is quite possible, therefore, that even if environmentally sound drug disposal could be implemented, the resulting reduction in overall environmental loads of PPCPs might be negligible (at least for most drugs).



Drugs in water serve as road signs for the water cycle ... as billboards that say "this water used to be sewage"

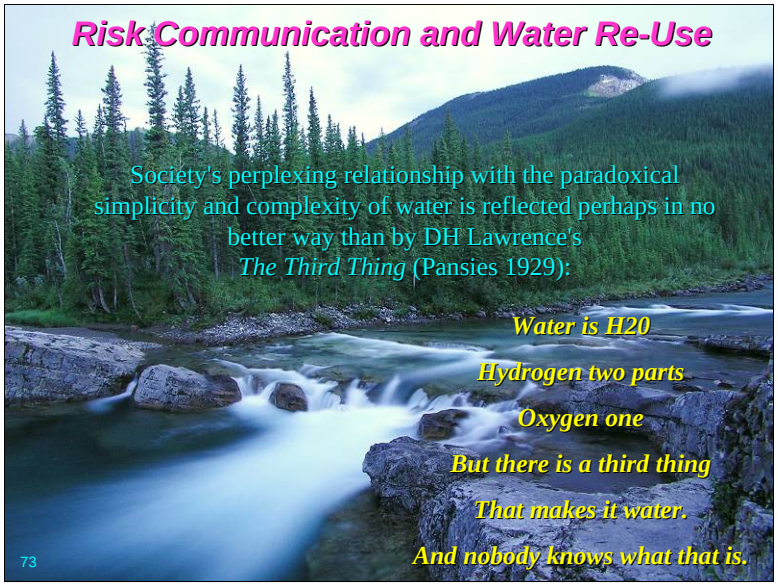
Chemical equivalent of garden weeds - not necessarily harmful but certainly unwelcome or undesired.

PPCPs: *Pollution Reduction*

Numerous suggestions for a comprehensive pollution reduction program centered on environmental stewardship have been compiled in a two-part monograph published in *Environmental Health Perspectives 111*, 2003. This and other materials relevant to this topic are available here:

"How should unwanted/unneeded medications be disposed?"

http://epa.gov/nerlesd1/chemistry/pharma/faq.htm#disposal


Risk Communication and Water Re-Use
Society's perplexing relationship with the paradoxical simplicity and complexity of water is reflected perhaps in no better way than by DH Lawrence's
The Third Thing (Pansies 1929):
Water is H20
Hydrogen two parts
Oxygen one
But there is a third thing
That makes it water.
And nobody knows what that is.
73

Inter-Organization Projects on Pharmaceuticals

Federal Interagency Task Force on Pharmaceuticals. Created in September 2004 by the White House's National Science and Technology Council's subcommittee on Health and the Environment (now Toxics and Risks). Co-chaired by the U.S. FDA and EPA. Comprises representatives from the CDC, NIEHS, USGS, USDA, FDA, NOAA, and EPA. A major objective is to recommend how the various federal agencies having roles related to pharmaceuticals as environmental pollutants can prioritize research, better coordinate their efforts, and collaborate more effectively.

SETAC *Pharmaceutical Advisory Group* (PAG; formed at the Portland meeting in Fall 2004 by Dr. Hans Sanderson, Soap and Detergent Association, Washington, DC: hsanderson@sdahq.org). Comprises subcommittees on: Environmental Effects; Chemical Fate & Predicted Environmental Concentrations; Water Treatment & Management; Environmental Risk Assessment; Future Criteria for Risk Management; Mixtures.

Questions

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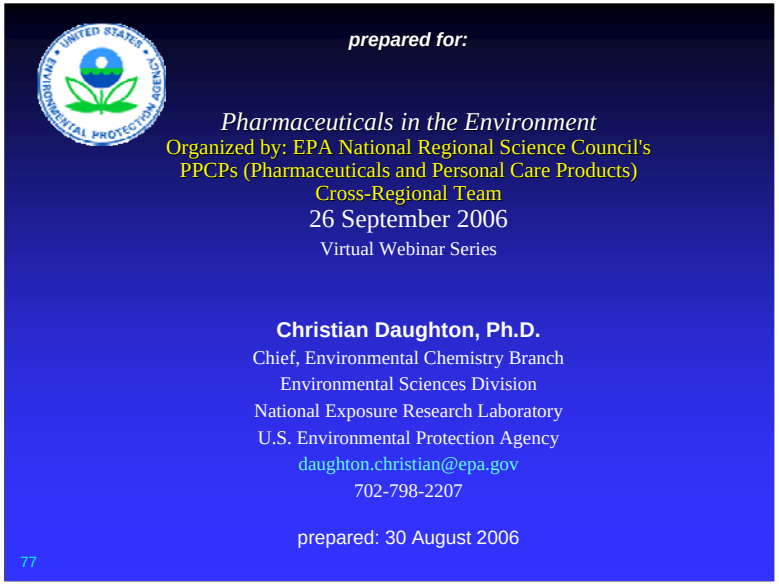
702-798-2207

http://www.epa.gov/nerlesd1/chemistry/pharma/


graphic prepared by:
C.G. Daughton, U.S. EPA
September 2002
Optical Photomicrographs of Crystalline Drugs
acetaminophen
fluoxetine
sildenafil
albuterol
ranitidine
caffeine
diazepam
for more photomicrographs of crystalline drugs, see:
© Molecular Expressions, Michael W. Davidson & The Florida State University Research Foundation
http://micro.magnet.fsu.edu



presentation invited (18 August 2006) by Bobbye Smith, Ph.D. (EPA, Region 9)

"Pharmaceuticals in the Environment: Overview of Sources, Concerns, and Solutions," invited presentation for *Pharmaceuticals in the Environment*, webinar series organized by the EPA National Regional Science Council's PPCPs (Pharmaceuticals and Personal Care Products) Cross-Regional Team, 26 September, 2006.

Pharmaceuticals and Personal Care Products – What's Happening in the Regions

Jan Baxter, R.G.p., P.G.

For the National Regional Science Council PPCPs Team

Pharmaceuticals in the Environment

NRSC PPCPs Seminar Series

September 26, 2006

Presentation Outline

- What Are EPA Regions
- Some of the EPA HQ Activities
- National Regional Science Council's Top 14 Short Term Science Needs
- What's Happening in the Regions
- Summary

EPA Regions

- US EPA is divided into a DC Headquarters, 10 geographically based Regions & 13 Research Labs
- Each Region has a Congressionally approved Administrator
- Regional focus is implementation

EPA Regions


WA
OR
ID
MT
ND
MN
SD
WY
NE
IA
MO
KS
CO
UT
NV
CA
AZ
NM
OK
TX
AR
LA
WI
MI
IL
IN
OH
WV
KY
TN
MS
AL
GA
FL
SC
NC
VA
PA
NY
NH
VT
ME
MA
RI
CT
NJ
DE
MD
DC
HI
Guam
Trust Territories
American Samoa
Northern Mariana Islands
AK
PR
VI

Associated Legislation

- Food Quality Protection Act (FQPA)
- Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA)
- Toxic Substances Control Act (TSCA)
- Clean Water Act (CWA)
  - Ambient Water Quality Criteria & Standards
    - Human Health & Aquatic Life
    - Risk-Based (only)
- Safe Drinking Water Act (SDWA)
  - Drinking Water Standards & Health Advisories
    - Human Health
    - Risk (MCL-G) & Treatment Technology (MCL) - based

PPCPs and SDWA

- May or may not lead to regulatory determination
  - need occurrence & toxicity/risk data
- Known or suspected EDCs or PPCPs causing adverse effects will be considered in the Contaminant Candidate Listing (CCL) process
  - need screening tools & hazard determination
  - www.epa.gov/safewater/ccl/index.html

USEPA/OW PPCP-Related Work

- OW participating on PPCPs Interagency workgroup
- PPCP Literature Database
  - Updating database of peer-reviewed literature
  - Over 400 citations and summaries
  - Searchable by keyword, author, title
- POTW National Study
  - Measuring the occurrence of PPCPs in influent, effluent, and primary sludge to evaluate available methods
  - Analyzing for 78 PPCPs
  - First samples taken September 2005 in Kalamazoo, MI. Six more sites to be sampled in 2006.

USEPA/OW PPCP-Related Work

- Unregulated Contaminants Monitoring Rule (UCMR) - No PPCPs currently listed
  - www.epa.gov/safewater/ccl/index.html
- Nonylphenol Aquatic Life Criteria
  - Decreased Reproduction is basis for chronic criterion
  - Coordinated with OPPT - Final: 2005
- Biosolids
  - PPCPs not included in upcoming biosolids survey - no analytical methods
  - OW providing funds to ORD to develop methods for identification and quantitation of 3 classes of drugs and estrogen-related compounds in biosolids

National Regional Science Council's Short Term Science Needs Project

- In 2005 identified cross-regional & cross-programmatic science needs
- From > 100 science needs, PPCPs in Top 14
- For the Regions - PPCPs include:
  - products from Waste Water Treatment Plants (WWTPs) and septic systems
  - veterinary pharms associated with agriculture & mariculture
  - personal care products including surfactants and fragrances

What's Happening in the New England Region (Region 1)

- Developed HPLC/MS/MS method for steroid hormones and other EDCs in water- part of study of 40 WWTPs in CT, ME, VT
- Grant to Northeast Recycling Center (NERC) evaluating approaches to dispose of used consumer drugs
- Grant to Hospitals for a Healthy Environment (H2E) to address hospital pharm waste
- In August 2007 New England Interstate Water Pollution Control Commission (NEIWPCC) is holding Water Science Forum on PPCPs: State of the Science

What's Happening in the Mid-Atlantic Region (Region 3)

- Intersex male bass found in South Branch of the Potomac River
- Vtg Gene expression assay underway to assess presence of estrogenic EDCs
- Regional Project "Environmental Consequences of the Use of Veterinary Antimicrobials"
- 2 Villanova University studies – 1) ultrasound for treatment of pharms in wastewater & 2) evaluation of tap and bottled water
- Monitoring around animal operations near drinking water intakes in Pennsylvania by EPA/ PA/SRBC

What's Happening in Region 5

- Regional Laboratory developing analytical methods
  - alkyl and nonyl phenols plus AP and NP ethoxylates
- UW Superior & St Cloud MN perform toxicity tests to help develop Water Quality Criteria on nonylphenol
- Liver assay by ORD to correlate chronic toxicity values - Vtg gene expression assays
- Regional Project "Wastewater Treatment Plants Sewage Sludge and PBTs"
- Multiple studies of PPCPs in the Chicago Waterways, both in the past and currently underway
- Hydrophilic Xenoestrogens: Responses & Oxidatve Removal Study ongoing
- R5 Pharmaceutical Outreach Campaign starting in Fall of 2006

What's Happening in the Mountains & Plains Region (Region 8)

- Effluent Study (Year 1):
  - Research by U of CO showed reproductive disruption in native White Suckers
  - Downstream sites showed sex ratio-skewed towards females, intersex fish found
- "Consortium for Research and Education on Emerging Contaminants" formed
- In 2006 U of CO study showed wastewater effluent from Boulder and Denver were associated with intersex features in fish

What's Happening in the Pacific Southwest Region (Region 9)

- The Region helped California build the capacity to do FM fish EDC - Vtg gene expression assay
- Studies from 2000-2004 in Orange County, CA showed EDC effects near a POTW marine outfall
- Summer of 2005 - helped organize the Las Vegas "Pharmaceuticals in the Environment" Workshop
- May 2006 - SF Bay Area Cities & Other Local Agencies Held a Pharmaceutical Take-Back Event
- Summer of 2006 - R9 organized WERF/EPA 2006 "Pacific Southwest Organic Residuals Symposium"
- Disseminating information on PPCPs for > 4 yrs to States, Tribes, local agencies, and industry

What's Happening in the Pacific Northwest (Region 10)

- Characterizing surface and groundwater in the vicinity of CAFOs in OR, ID
- Preliminary assessment of mariculture operations in ID, WA, OR
- Preliminary assessment of Alaskan shipboard wastes
- Regional Lab developing capacity to perform Vtg gene expression assays for EDCs
- Pilot take-back projects are currently being planned for the Seattle area

Unanswered Questions:

- Is there evidence of harm to human health or the environment at the levels that are detectable?
- What are the sources of PPCPs in the environment ?
- Can PPCP sources be controlled or reduced?
- Given the current focus on endocrine-active PPCPs, what types of effects might other classes of PPCPs be having on the environment?

Summary

- EDC exposure effects (e.g., intersex features, bioassay results) possibly from PPCPs, have been found in fish in several Regions
- In at least one Region, wastewater from sewage treatment plants has been associated with fish intersex features
- EPA is continuing to do research on PPCPs, in particular POTW effluents and vet pharms
- Regions are focusing on information gathering and supporting stewardship efforts

PPCPs Cross-Regional Team

Cynthia Greene, Peter Philbrook	Region 1
Marie O'Shea and Roland Hemmett	Region 2
Virginia Thompson, Amy Bergdale	Region 3
Jenny Scifres	Region 4
Robert Pepin, Al Alwan, Peter Howe, Donna Twickler, Jacqueline Fisher Todd Nettesheim	Region 5
Sharon Osowski	Region 6
Brenda Groskinsky	Region 7
Patti Tyler	Region 8
Jan Baxter, Luisa Valiela, Wendi Shafir, Bobbye Smith	Region 9
Michael Watson	Region 10

Thank You

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