Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants: Pollution from Consumption and Use

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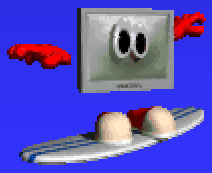
Wealth of other materials and links to most of the ongoing work relevant to this topic are available at the U.S. EPA's ***PPCPs* Web Site**:

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



Historical Perspective - PPCPs

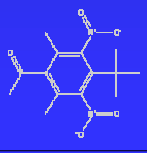
- PPCPs as environmental pollutants first investigated in Europe - 1980s.
- With the advent of monitoring and research in the U.S., literature has grown exponentially since 2000.
- PPCPs are not truly "emerging" pollutants. It is the understanding of the significance of their occurrence in the environment 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.

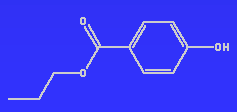
Scope of Issue

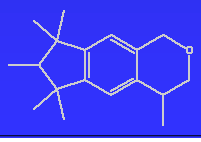
- Thousands of distinct chemical entities.
- Numerous (and increasing) therapeutic classes and end uses.
- Large numbers possess very high biological activity.
- Two classes of therapeutics that have received the most attention are the antibiotics (potential for resistance selection among pathogens) 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.

PPCPs as Environmental Pollutants?

PPCPs are a diverse group of chemicals comprising all human and veterinary drugs (available by prescription or over-the-counter; including the new genre of "biologics"), diagnostic agents (e.g., X-ray contrast media), "nutraceuticals" (bioactive food supplements such as huperzine A), 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).







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
PPCPs	type of intended usage
priority pollutants and others	legislation
"**emerging" contaminants/pollutants**	novelty, fad, timeliness, or new concern

Endocrine Modulators and Homeostasis

Hormones: secreted from endocrine sources and some neurons; transported by blood to remote targets (nuclear receptors). Regulate gene transcription (e.g., sex steroids). Slow-acting.	**continuum** biochemical agents for maintaining cellular, organ, and organism **HOMEOSTASIS** and controlling physiological processes	**Neurotransmitters:** secreted from neurons and act on immediately adjacent target cells for a short time (e.g., acetylcholine).
Pheromones: secreted by exocrine glands; targets outside body; integrate social activities between animals.		**Local signaling molecules:** secreted from cells of many different tissues; act locally; quickly degraded.
Endocrine Physiology	**Neuroendocrinology**	**Neurophysiology**

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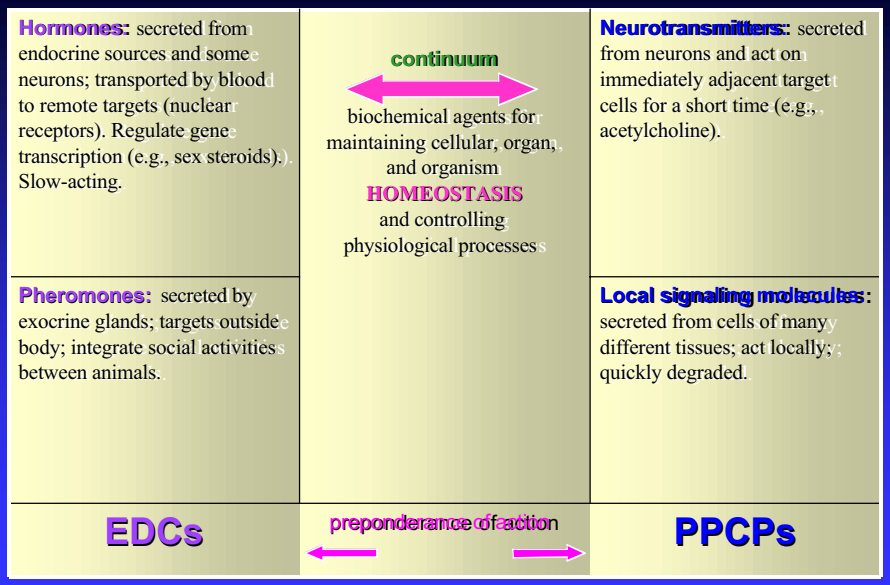
EDCs versus PPCPs



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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), 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)
- Nutraceuticals
- 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.**

"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).

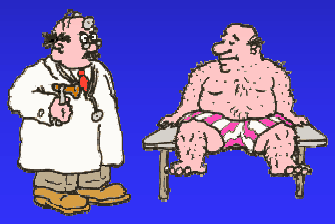
The "dirty dozen" is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

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 October 2005, over 26 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 the nearly 27 million known chemicals, nearly 9 million were commercially available.
- Representing a 12% increase over the prior year.
- Of these, fewer than a quarter million (240,000) were inventoried or regulated by numerous government bodies worldwide - - representing less than 3% of those that are commercially available or less than 1% of the known universe of chemicals.

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

The Chemical Universe

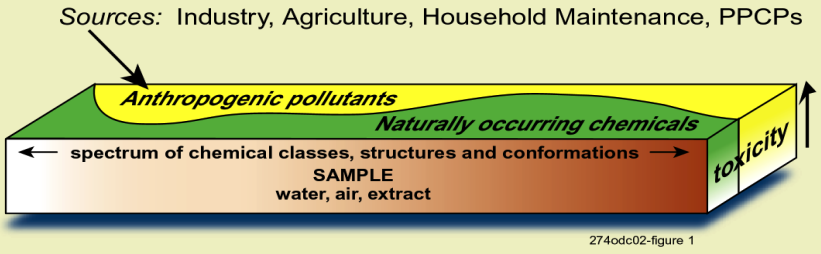
The *POTENTIAL* Universe

- While the *KNOWN* universe of chemicals might seem large (26 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?

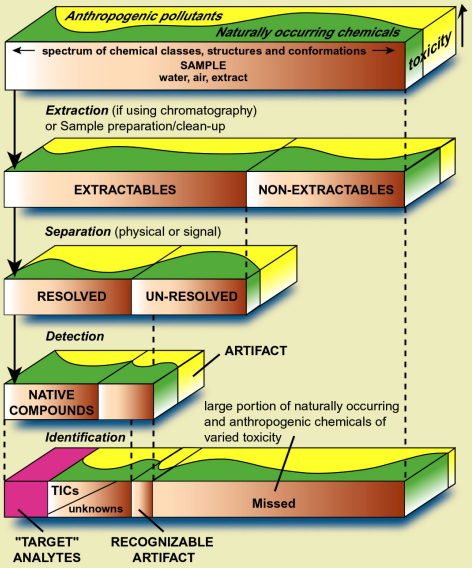
- By limiting synthesis strictly to combinations of 30 atoms of just C, N, O, or S, **more than 10^{60} structures are possible !**
- Expanding the allowable elements to other heteroatoms (e.g., P and halogens), the limits to the numbers of possible structures defies imagination. Also known as "chemical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



TICs = tentatively identified compounds

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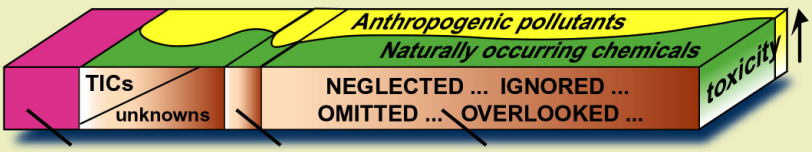
Chemical Analysis Output for a Typical Environmental Sample



"TARGET" ANALYTES

RECOGNIZABLE ARTIFACT

large portion of naturally occurring and anthropogenic chemicals of varied toxicity

TICs = tentatively identified compounds

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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***"

Einstein on: *Environmental Monitoring*

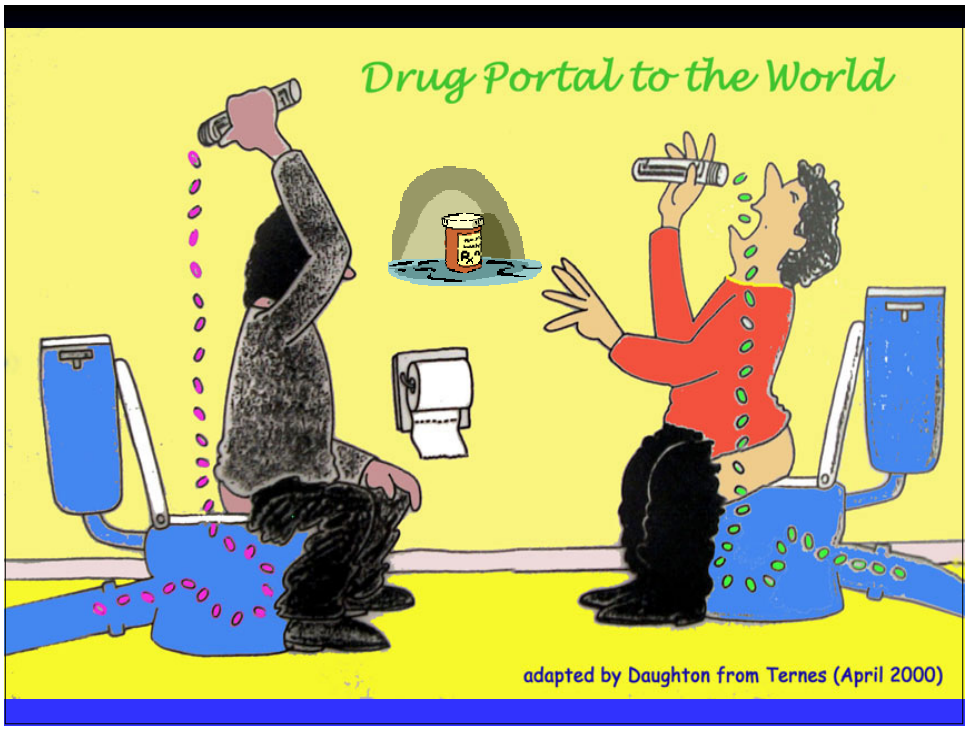
"Not everything that can be counted counts, and not everything that counts can be counted." (oft attributed to Albert Einstein)

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*

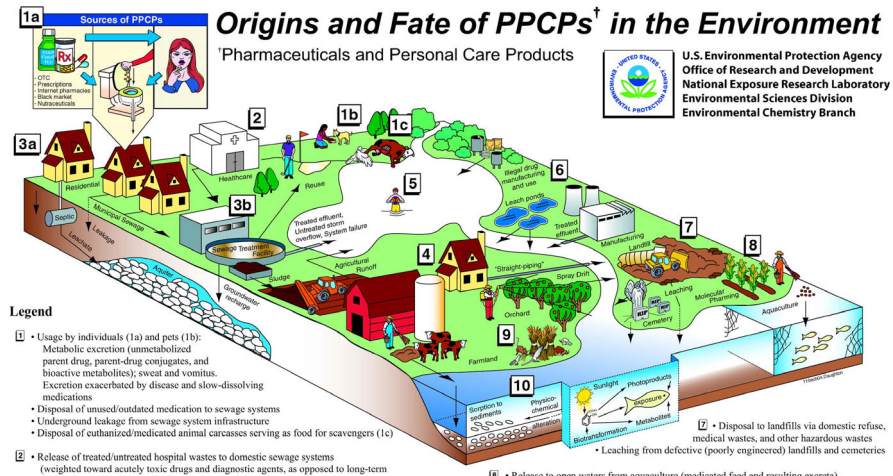
- What one finds usually depends on what one aims to search for.
- Only those compounds targeted for monitoring have the potential for being identified and quantified.
- Those compounds not targeted will elude detection.
- The spectrum of pollutants identified in a sample represent but a portion of those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



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."



Available: http://www.epa.gov/nerlesd1/chemistry/pharma/image/drawing.pdf

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 (_g/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.

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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).

(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.

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Potential Toxicological Significance as a Result of:

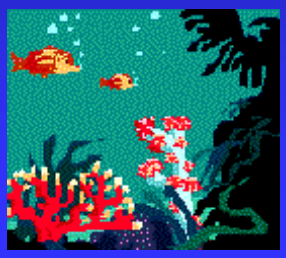
(7) Susceptible **genetic outliers** within species.

(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.

- concluded -

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)**.

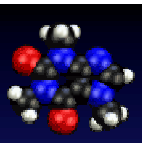
Drugs Having Double Uses: Medicinals and Pest-Control Agents

(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. The potential significance of these alternative uses as sources for environmental release has never been explored.

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).

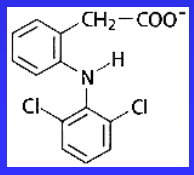
No safe and effective chemical-controls until discovery by USDA that **acetaminophen (80 mg) will effectively kill Brown Tree snakes within 3 days** of even a brief exposure to baited, dead mice.

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

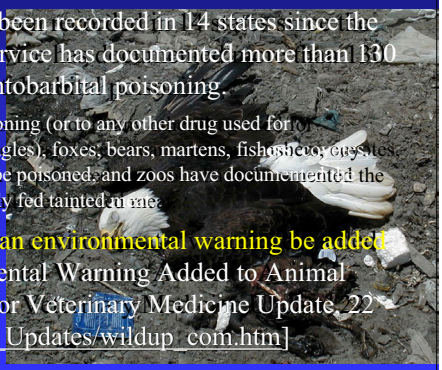
- Beginning in the early 1990s, vultures (especially white-backed vultures such as *Gyps bengalensis*) have experienced dramatic population declines (as great as 95%) in Southern Asia – particularly India and spreading to Pakistan and Nepal.
- Various hypothesized causes have ranged from pathogens to 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, fishes, 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]



Personal Care Products as Exposure Sources for Conventional Pollutants

- Ayurveda and folk remedies (e.g., litargirio, or litharge): **lead (Pb)** and other metals (upwards of 80% by weight)
- Skin lightening creams and disinfectant soaps (imported): upwards of 3% **mercuric iodine** (wt/wt) in soaps and 10% **ammoniated mercury** in skin lightening creams
- Dermal products: **phthalates** (esp. diethyl and dibutyl), **solvents**, **dyes**, **parabens** (4-hydroxybenzoic acid alkyl esters)
- Lice and tick control shampoos: **lindane** and **permethrins**
- Shampoos and soaps: **alkylphenolic surfactants**

Potential for Subtle Effects?

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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.

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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

Which water would you choose ?
Recycled Sewage or Snow Melt ?

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"

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.

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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

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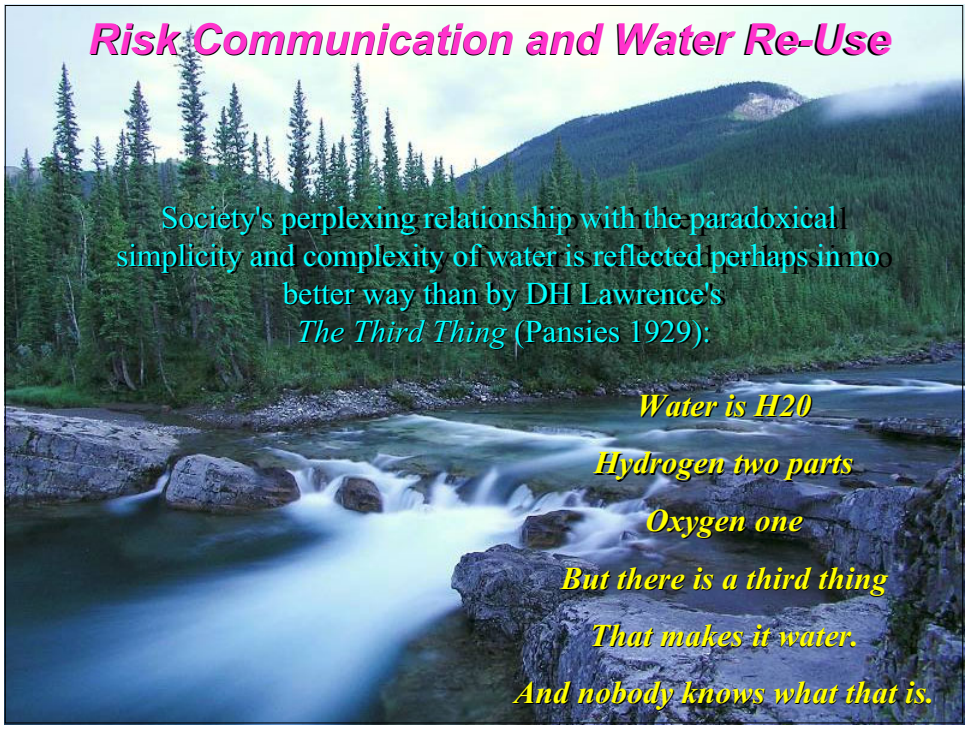

Future topics where PPCPs could play major roles

- Water recycling: With water reuse, especially "toilet-to-tap" programs, the occurrence of even ultra-trace levels of human-use drugs in water serves to highlight to the public what the origin of the water was. This risk-communication/perception problem will pose major problems with regard to public acceptance.
- Biosolids: The occurrence and fate of PPCPs in biosolids was unknown (NRC July 2002 report: *Biosolids Applied to Land: Advancing Standards and Practices*).
- Biopharming: Environmental ramifications of molecular farming or "biopharming" (plant-made pharmaceuticals) are unknown.
- Nanomaterials: The environmental fate and ramifications of nanomaterials (which will play ever-growing roles in nanomedicine) are unknown.
- Homeland Security: Certain PPCPs hold the potential for being used in water sabotage (e.g., psychoactive agents; teratogens).

Questions

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