Overview of Science Involved with Pharmaceuticals

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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.

Sampling of Organizations Involved with PPCP Activities

- **USGS**: Emerging contaminants national reconnaissance in nation's water resources
- **CDC**: CAFOs, with focus on antibiotics and steroids
- **FDA**: FONSIs or EAs for all new drugs (EIC of 1 ppb is the determining factor)
- **USDA:** CAFOs, with focus on antibiotics and steroids
- **U.S. Grants**: U.S. EPA STAR, USGS/Water Resources Research Institute, AwwaRF, WateReuse Foundation, Sea Grants
- **other GOs**: Health Canada, EMEA (European Medicines Agency), Danish EPA
- **Researchers**: Academic, private (engineering consulting), and public (e.g., water providers) in Europe, Scandinavia, Canada, and U.S.
- **PhRMA**: Pharmaceuticals Research and Manufacturers of America – PIE Task Force
- **Health Care Community**: esp. hospital wastes
- **State and Local Governments**: expanding interest in “take-back” programs; groundwater recharge monitoring

Some Significant Current Projects on Pharmaceuticals

SETAC *Pharmaceuticals Workgroup* (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.

Product Stewardship Institute (PSI), Inc. Project on *Pharmaceutical Wastes* (begun in May 2005) focusing primarily on unwanted or waste pharmaceutical products from households. Scott Cassel, Executive Director, Boston, MA: scott@productstewardship.us

Federal Interagency Task Group on PPCPs. Created in September 2004 by the National Science and Technology Council's subcommittee on Health and the Environment. Chaired by the U.S. FDA and 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. An EPA contact is Christian Daughton: daughton.christian@epa.gov

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., methylbenzylidene camphor); also included are “excipients” (so-called “inert” ingredients used in PPCP manufacturing and formulation).

"Emerging" *Pollutants* vs. Emerging Awareness

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).

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).

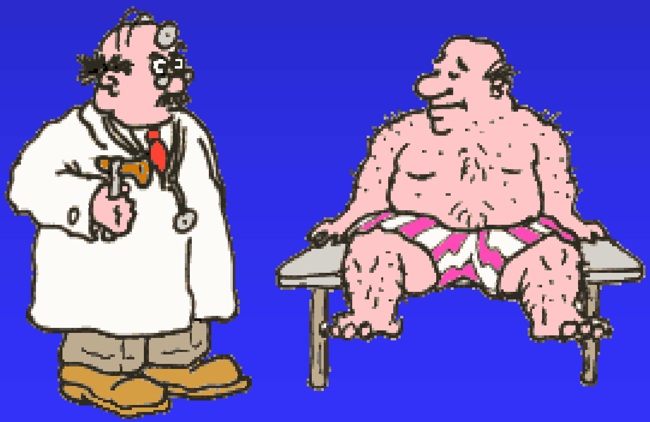
The "dirty dozen" is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

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 August 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 26 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

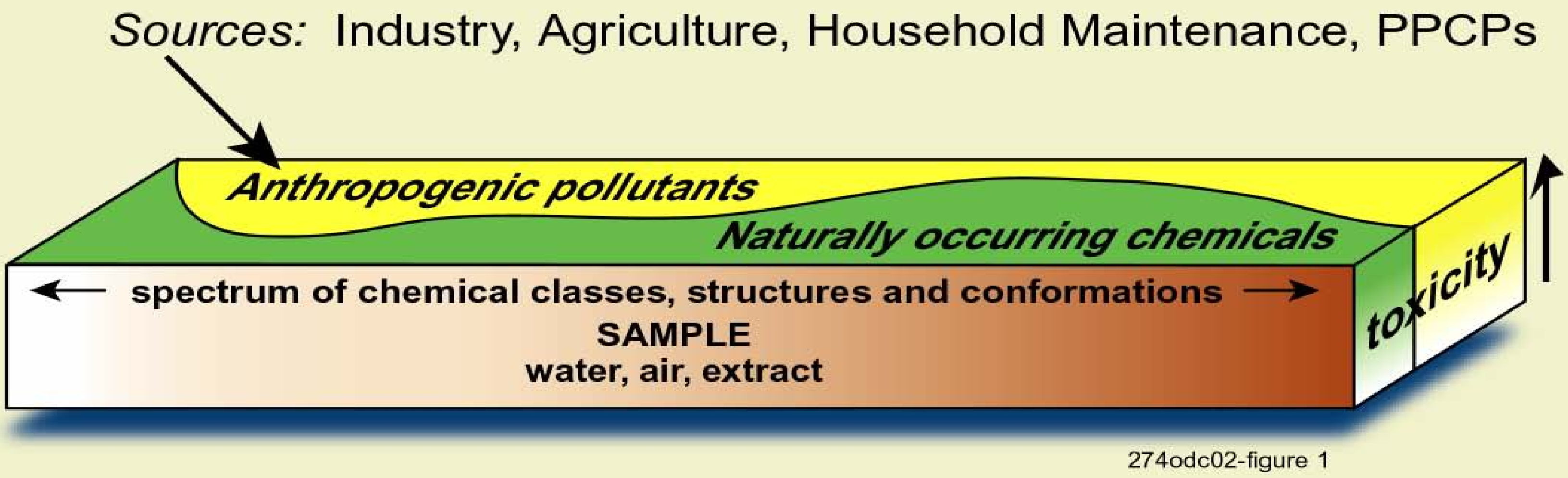
- While the *KNOWN* universe of chemicals might seem large (26 million), the universe of *POTENTIAL* chemicals (those that could possibly be synthesized and those that already exist but which have not yet been identified) is unimaginably large.

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 !**

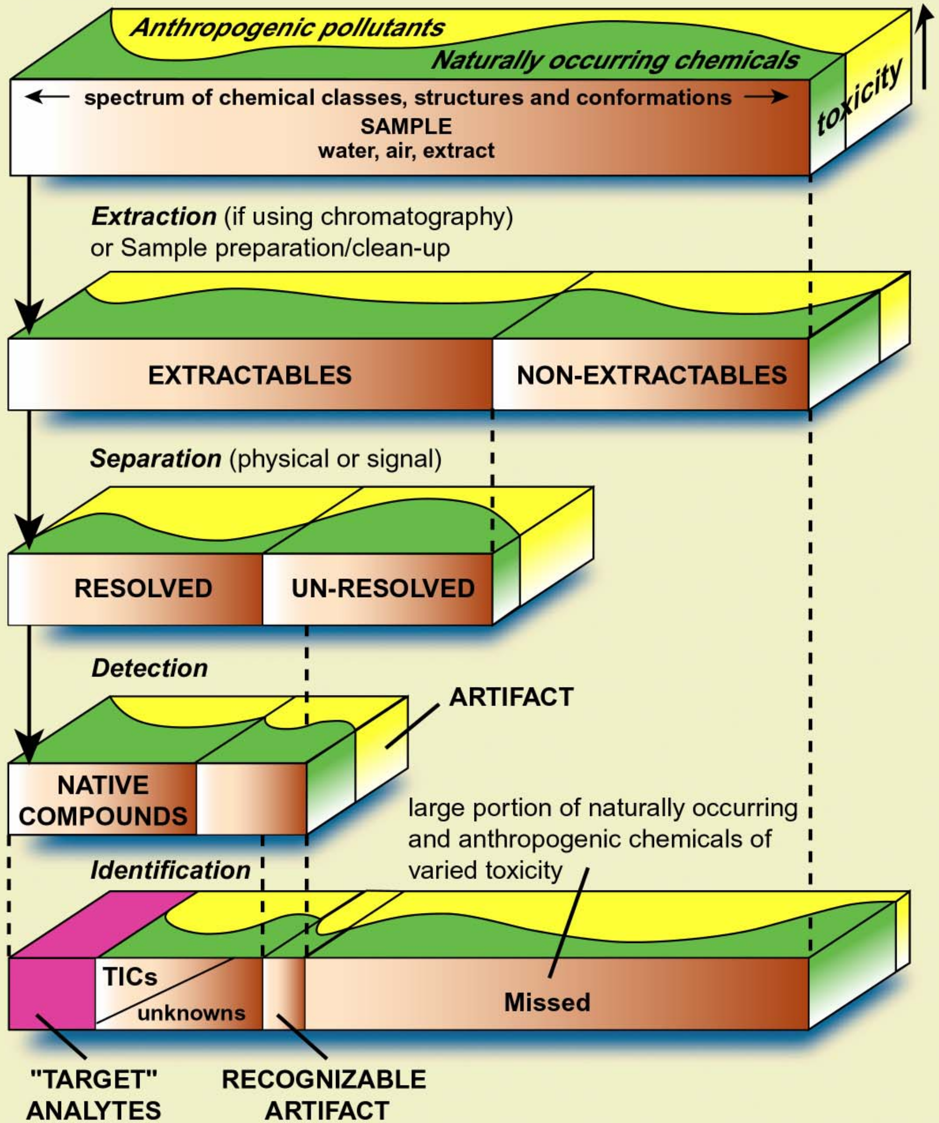
- Expanding the allowable elements to other heteroatoms (e.g., P and halogens), the limits to the numbers of possible structures defies imagination. Also known as “chemical space”.

Universe of Chemicals in the Environment



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

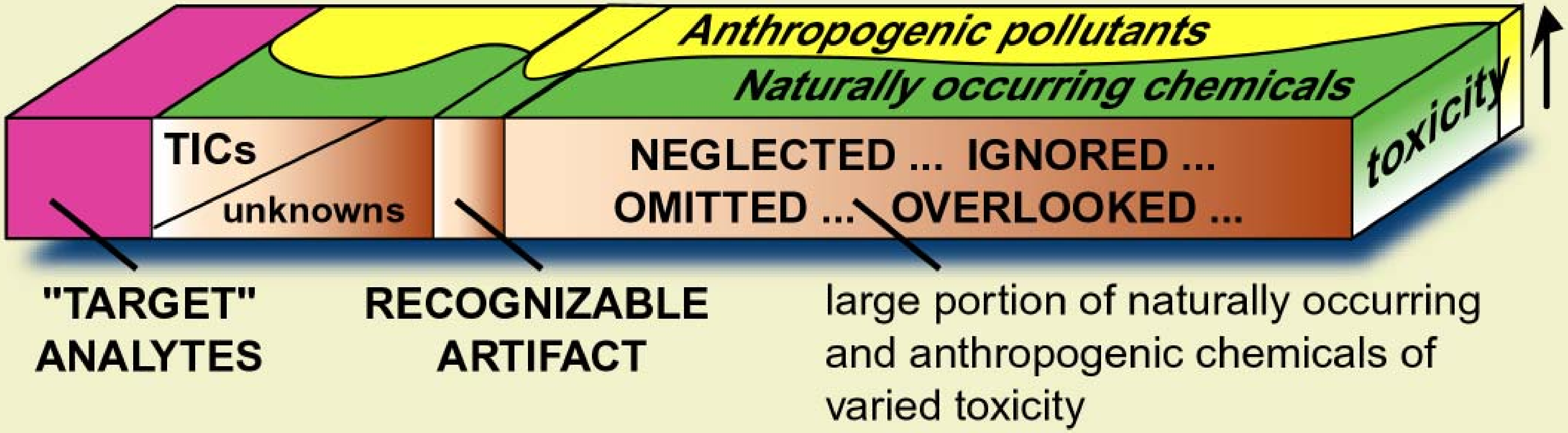
Limitations and Complexity of Environmental Chemical Analysis



TICs = tentatively identified compounds

C.G. Daughton
U.S. EPA July 2002
274odc02-figure 2

Chemical Analysis Output for a Typical Environmental Sample



TICs = tentatively identified compounds

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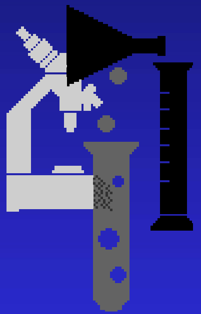
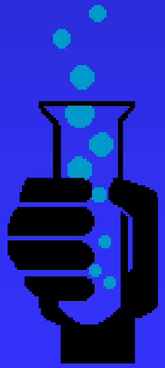
Einstein on:
Environmental Monitoring

"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.



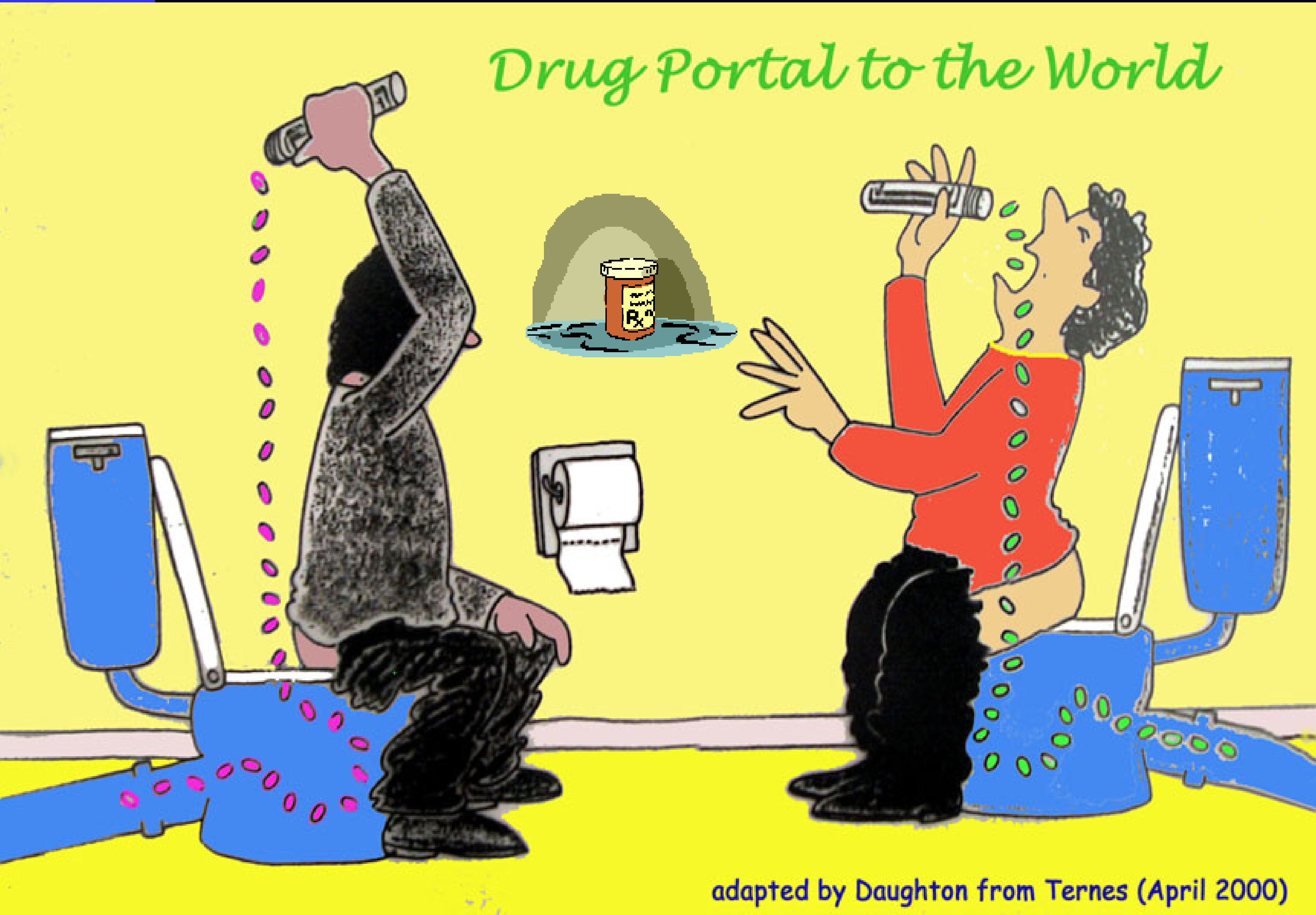
further truisms regarding *Environmental Monitoring*

- 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."


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

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.

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Expanding Uses and Escalating Usage

- Aging population (polypharmacy)
- Growing numbers of drug targets (genomics)
- Individualized therapy (polymorphisms)
- Nutraceuticals
- Lifestyle and cosmetic pharmacy

"The red are for the illness, the blue are for the side effects of the red and the green are for the effects of the blue."

Expanding Uses and Escalating Usage

Geriatric Medicine: Unforeseen routes for increase in medication usage, especially among the elderly

Example:

Distribution of medicines free of charge to elderly patients as disease preventatives.

Proposal to distribute angiotensin-converting enzyme (ACE) inhibitors (the "prils", e.g., captopril, ramipril, and trandolapril) to elderly diabetics to prevent heart attacks, strokes, and kidney failure, yielding very large savings for Medicare.

"Cost-Effectiveness of Full Medicare Coverage of Angiotensin-Converting Enzyme Inhibitors for Beneficiaries with Diabetes," A.B. Rosen, et al, *Annals Internal Medicine*, 2005, 143(2):89-99.

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

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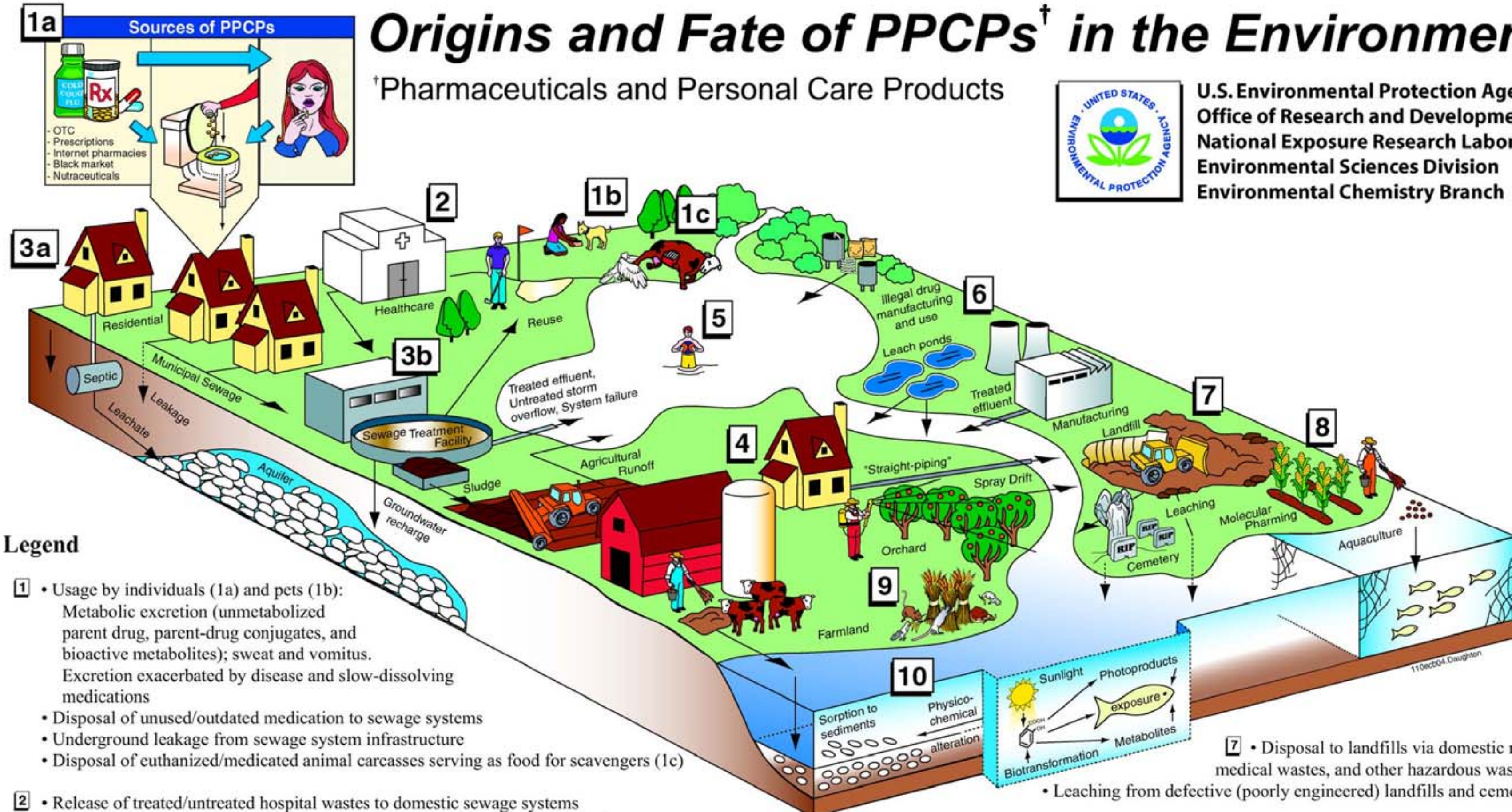

Legend

[1] • 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)

[2] • 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

[3] • Release to private septic/leach fields
• Treated effluent from domestic sewage treatment plants discharged to surface waters or re-injected into aquifers (recharge)
• Overflow of untreated sewage from storm events and system failures directly to surface waters

[4] • 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)

[5] • Direct release to open waters via washing/bathing/swimming

[6] • Discharge of regulated/controlled industrial manufacturing waste streams
• Disposal/release from clandestine drug labs and illicit drug usage

[7] • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
• Leaching from defective (poorly engineered) landfills and cemeteries

[8] • Release to open waters from aquaculture (medicated feed and resulting excreta)
• Future potential for release from molecular pharming (production of therapeutics in crops)

[9] • 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; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → *coqui* frog control

[10] Ultimate environmental transport/fate:
• most PPCPs eventually transported from terrestrial domain to aqueous domain
• phototransformation (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)

Christian G. Daughton, U.S. EPA-Las Vegas

January 2004
(original February 2001)

http://epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf
from: http://epa.gov/nerlesd1/chemistry/pharma/

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

Drug disposal - a MAJOR topic for the public

- Portion of PPCPs in environment originating from disposal versus excretion is not known.
- Public identifies strongly with the topic and is concerned about the possibility for residues in drinking water.
- Inquiries continually received from public, media, healthcare community, and regulators regarding guidance or advice on how the end-user should dispose of drugs.
- No federal agency has ever issued any guidance or advice regarding drug disposal (but FDA has historically assumed that EPA has the lead for public inquiries). This has bred great confusion for local and state governments.
- **Proper disposal is greatly complicated by the inherent conflict between the need to protect public safety and the need to minimize aquatic exposure.**
- The major limitation in implementing drug “take-back” or “returns” programs is the Controlled Substances Act (as administered by the DEA).

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

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.

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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.

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.

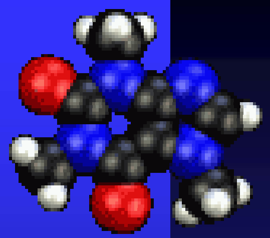
- concluded -

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).

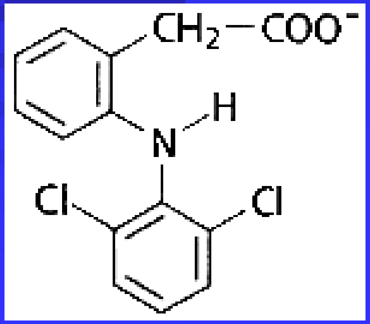
No safe and effective chemical-controls until discovery by USDA that **acetaminophen (80 mg) will effectively kill Brown Tree snakes within 3 days** of even a brief exposure to baited, dead mice.

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 *Gyps*.



- 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

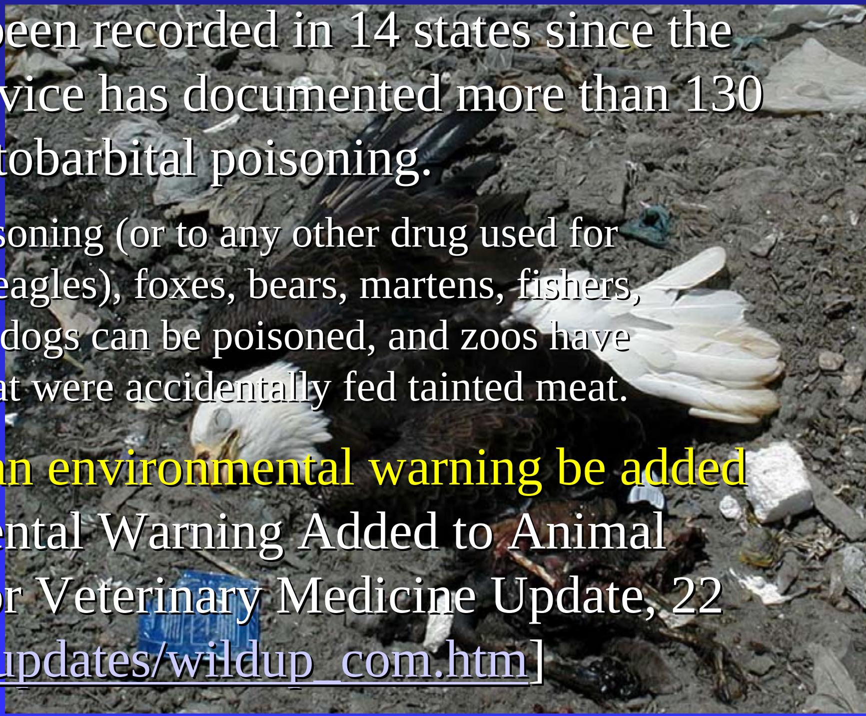
- Various drugs are used to euthanize domestic pets and other animals.

- 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/index/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)
- 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**

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)
fluoxetine (concentrated in muscle, liver, and brain of fish)

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.

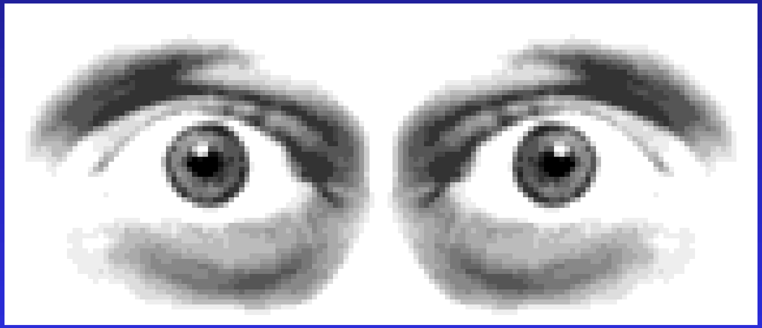
continued >

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



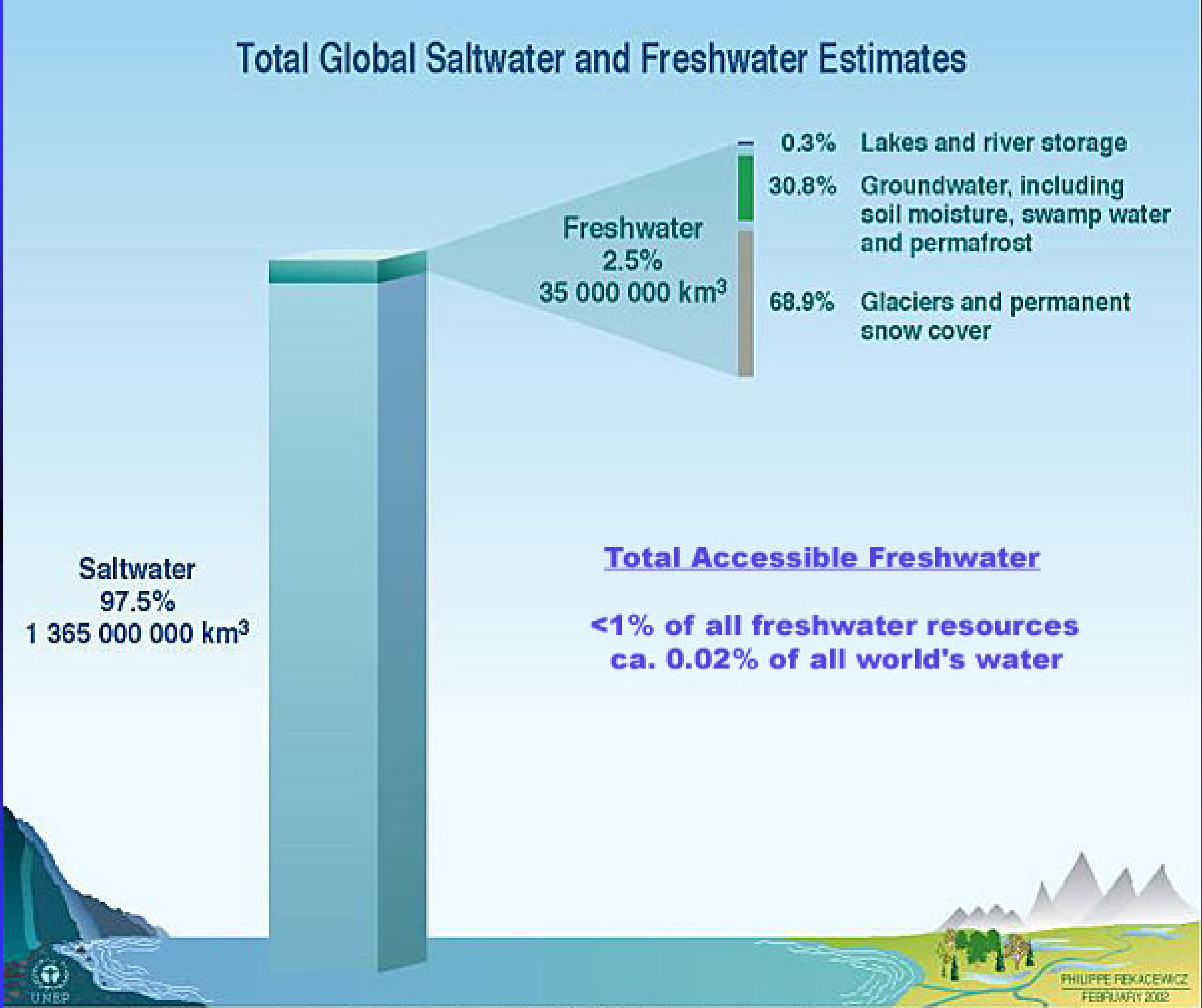
Critical Importance of *Futuring* & *Anticipatory Research*

- Important to design and implement a range of mechanisms for providing insight as to those types of pollutants and sources that could emerge in the future.

- Pollution Prevention and Stewardship programs can be less costly than remediation (Precautionary Principle), pollutant "musical chairs" (pollutant diversion), or "pollution postponement" (storage such as in landfills).

continued >

The World’s Accessible Freshwater Resources

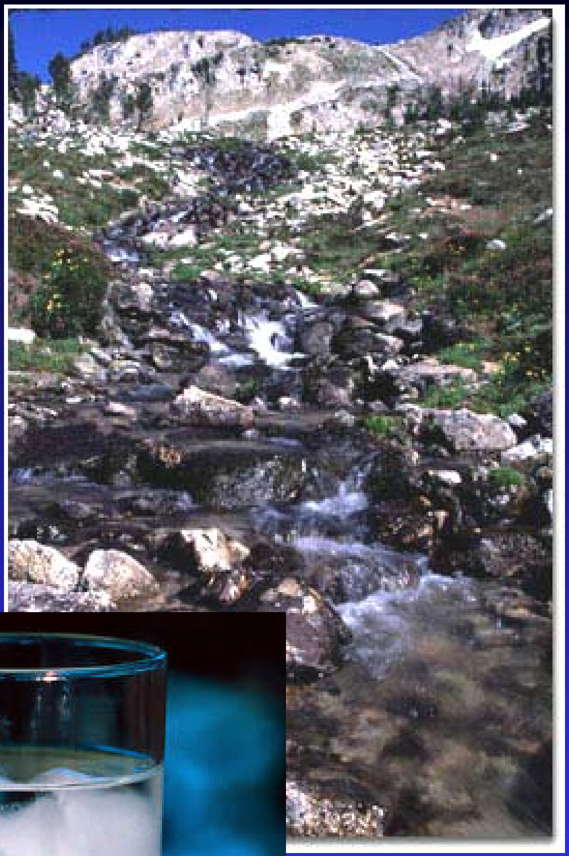


Source: Igor A. Shiklomanov, State Hydrological Institute (SHI, St. Petersburg) and United Nations Educational, Scientific and Cultural Organisation (UNESCO, Paris), 1999.

Critical Importance of Forging Better Linkages between Science and the Public

continued >

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

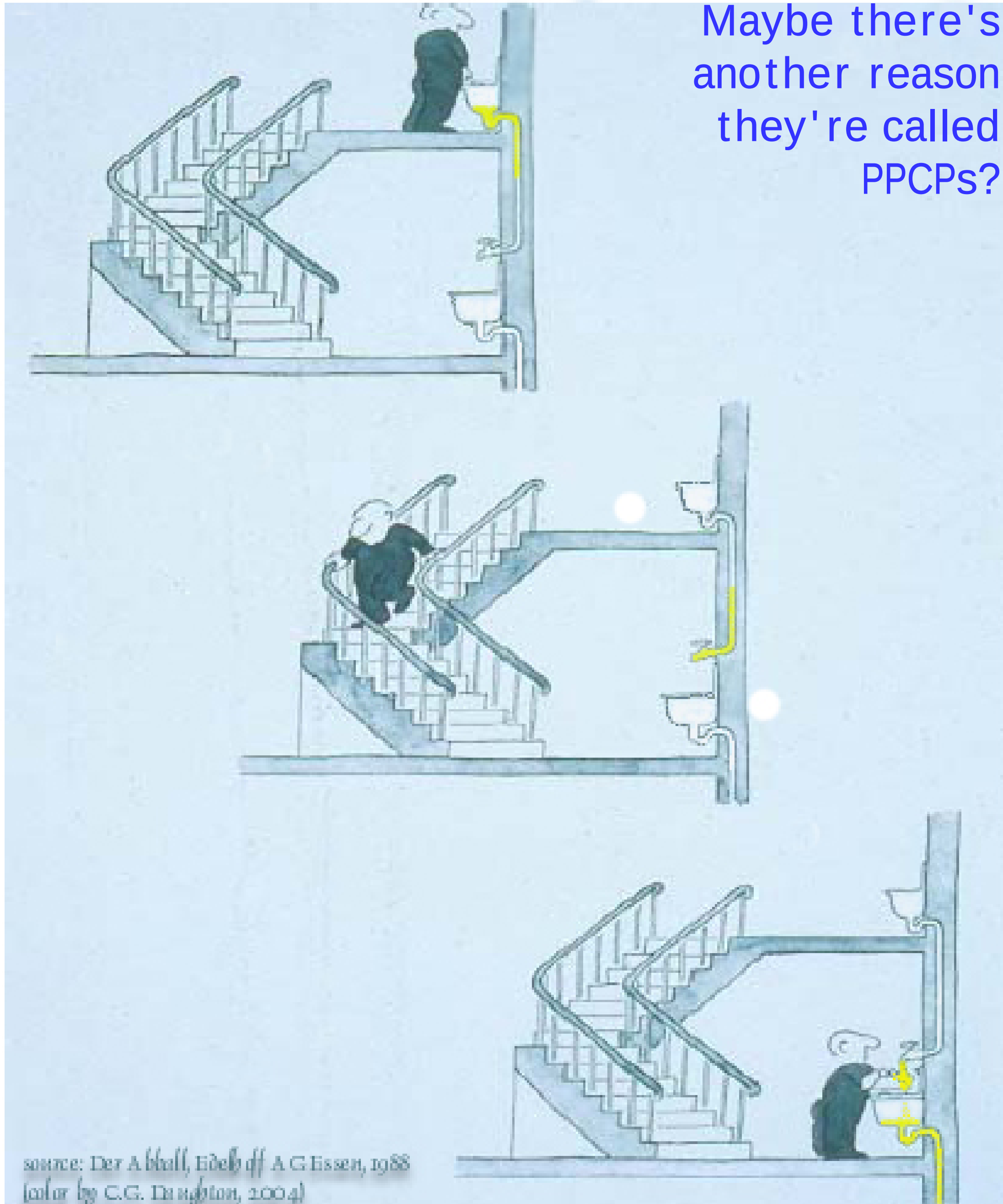
"Increasingly Smaller Recycle Loops": Ever-shortening spatial & temporal hydraulic connectivity between point of wastewater discharge and point of use for drinking will pose serious challenges for ensuring human safety and for framing how risk is perceived by the consumer.

Two Major Issues:

Groundwater Recharge (both indirect and direct)

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

Maybe there's another reason they're called PPCPs?



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 >

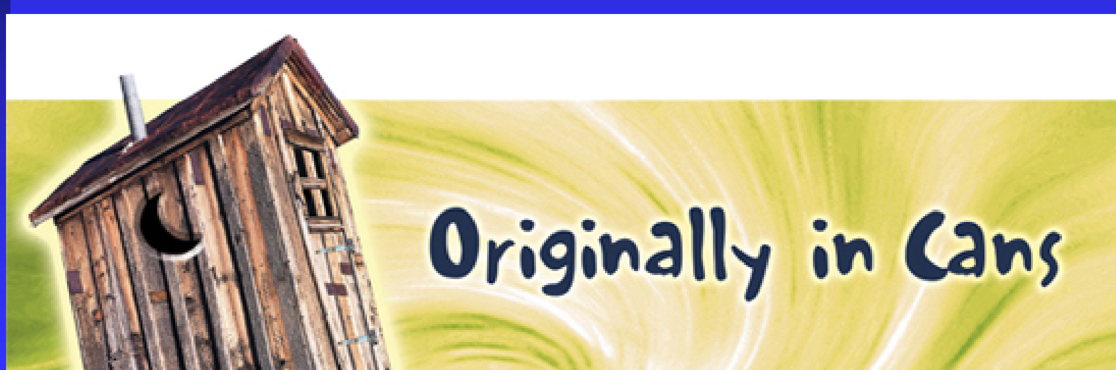
Risk Communication and Water Re-Use

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:

<u>*Outhouse Springs*</u> Bottled Water

Experiment by:
Adams Outdoor Advertising, South Carolina, 2002

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

concluded

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.

Questions

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