

Organizations Involved with PPCP Activities

- **USGS:** Emerging contaminants national reconnaissance in nation's water resources
- **CDC:** CAFOs, with focus on antibiotics and steroids
- **FDA:** FONSI 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, waRF, 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 "takeback" programs; groundwater recharge monitoring

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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.

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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).

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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.**

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"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"¹, 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.

¹An 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.

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What portion of overall risk is contributed by unregulated water pollutants?



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



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The Chemical Universe The *KNOWN* Universe

As of September 2003, over 22 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)

Represented a 6% increase over the prior 9-month period.

Of the 22 million known chemicals, nearly 6 million were commercially available.

Of these, only about a 0.25 million (227,000) were inventoried or regulated by numerous government bodies worldwide -- representing less than 4% of those that are commercially available or 1% of the known universe of chemicals.

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

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The Chemical Universe The *POTENTIAL* Universe

While the *KNOWN* universe of chemicals might seem large (22 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?

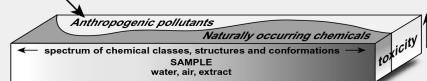
By limiting synthesis strictly to combinations of 30 atoms of just C, N, O, or S, **more than 10⁶⁰ structures are possible!**

Expanding the allowable elements to other heteroatoms (e.g., P and halogens), the limits to the numbers of possible structures defies imagination.

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Universe of Chemicals in the Environment

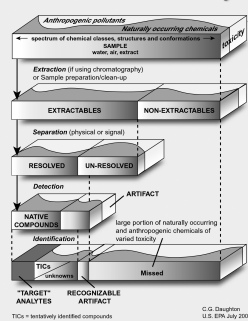
Sources: Industry, Agriculture, Household Maintenance, PPCPs



2746cc02, Figure 1

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

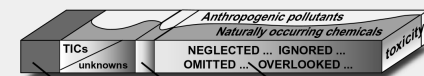
Limitations and Complexity of Environmental Chemical Analysis



C.G. Daughton
U.S. EPA, July 2002
mwhs/nerlesd1

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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


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

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.



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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.

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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”

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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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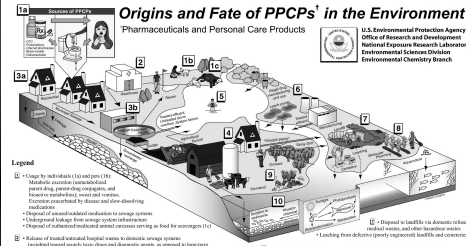
Expanding Uses and Escalating Usage

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



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Origins and Fate of PPCPs¹ in the Environment
Pharmaceuticals and Personal Care Products



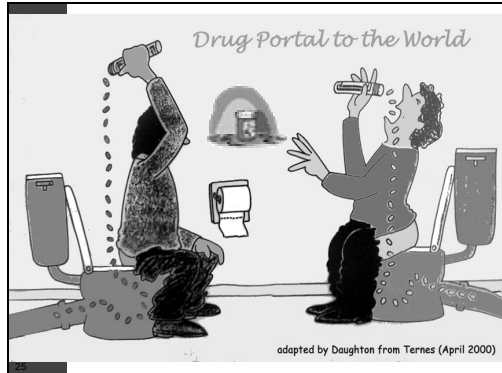
U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch

Legend

- 1. Origin: Manufacture (1) and distribution (2) of pharmaceuticals and personal care products. Includes manufacturing, packaging, and distribution to retailers, wholesalers, and consumers. Includes distribution to drug stores, hospitals, and clinics.
- 2. Disposal of expired/unwanted pharmaceuticals in sewage systems.
- 3. Disposal of expired/unwanted personal care products in landfills or incinerators.
- 4. Release of expired/unwanted pharmaceuticals to sewage systems.
- 5. Excretion of pharmaceuticals from sewage systems into surface waters.
- 6. Release of pharmaceuticals from landfills into surface waters.
- 7. Release of pharmaceuticals from incinerators into surface waters.
- 8. Release of pharmaceuticals from landfills into surface waters.
- 9. Release of pharmaceuticals from landfills into surface waters.
- 10. Release of pharmaceuticals from landfills into surface waters.

Available: <http://www.epa.gov/nerle/rdl/chemistry/pharmausage/origins.pdf>

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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.
- Receive continual inquiries 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).

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PPCPs: Pollution Prevention

Numerous suggestions for a comprehensive pollution prevention 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>

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continued >

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 ($\mu\text{g/L}$).
- 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.

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Toxicity of Complex Environmental Mixtures: Poses Major Unanswered Questions



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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 NOEL. 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.

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- concluded -

Drugs Having Double Uses: Medicinals and Pest-Control Agents (alternative sources for introduction to the environment)

Some chemicals serve double duty as both existing/experimental 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
- statins**: antilipidemic drugs and avian/rodent reproductive inhibitors [e.g., Ornitrol]
- certain **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%.

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Caffeine for control of frog pests

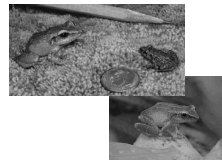
U.S. EPA approved (27 Sept 2001) specific exemption from FIFRA allowing use of caffeine to control *coqui* frogs in Hawaii.

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).



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Acetaminophen for control of Brown Tree snakes

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

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

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

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/foia/inside_aphis/foiafiles/1011.html]



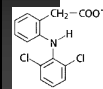
Decline of Gyps spp. Vultures in Pakistan & India – Possible Link with Diclofenac

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.

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. over other carrion-eating raptors.


Health hazards grow from the accumulation of un-eaten 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.



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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 birds (since the mid-1980s). The U.S. Fish and Wildlife Service has documented deaths of bald and golden eagles as casualties of pentobarbital poisonings.
- Wildlife vulnerable to accidental pentobarbital poisonings (euthanasia) include a wide range of birds (especially raptors, waterfowl, and geese), coyotes, lynx, bobcats, cougars, and otters. Domestic animals (including dogs and cats) have also been documented the deaths of tigers, cougars and lions that were fed tainted meat.
- In July 2003, the FDA's CVM required drug manufacturers to register for animal euthanasia products ["Environmental Veterinary Medicine: Euthanasia Products," U.S. FDA, Center for Veterinary Medicine, July 2003; <http://www.fda.gov/cvm/index/medvet.htm>].



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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**

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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 unique to any particular municipal area.
- Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs.




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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)**.




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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)

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Potential for Subtle Effects?



42 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, late nt 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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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?

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Peeking at the Future

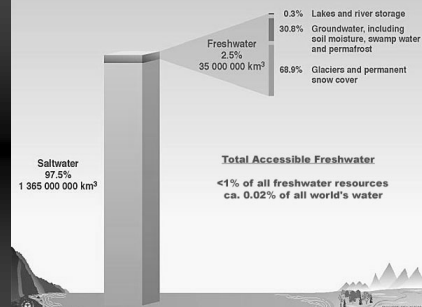


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The World's Accessible Freshwater Resources

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Total Global Saltwater and Freshwater Estimates



47


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

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



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

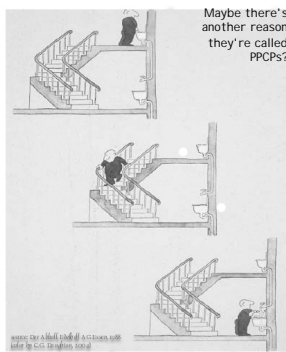


Growing pressures to re-use wastewaters for drinking

"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?

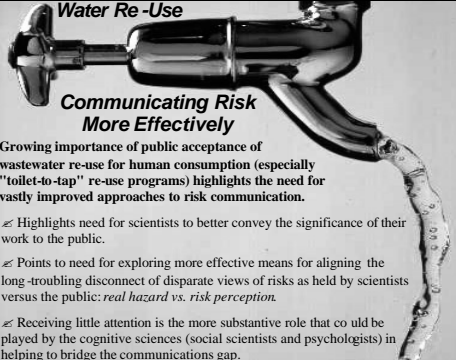
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Water Re-Use

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

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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.



53 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.

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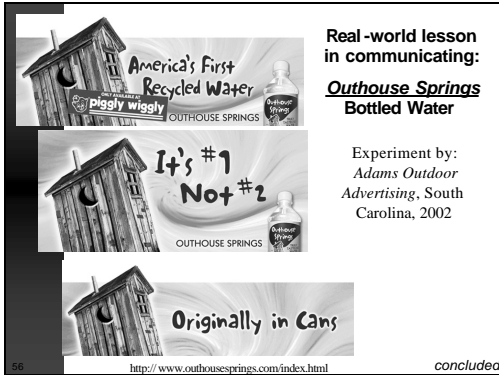
Risk Communication and Water Re-Use

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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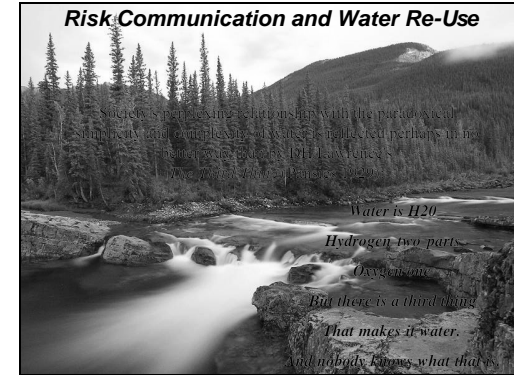


Real-world lesson in communicating:
Outhouse Springs Bottled Water

Experiment by:
Adams Outdoor Advertising, South Carolina, 2002

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

56 *concluded*



Risk Communication and Water Re-Use

Water is H₂O
Hydrogen two part
Oxygen one
But there is a third thing
That makes it water.
and nobody knows what that is




Questions

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

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Environmental and Public Health Officials**
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14 June 2005

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