Washington State and King County's Perspective on Pharmaceutical Stewardship

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Abstract

Local governments across the country are faced with having to address the nascent and complex issue of proper management of waste pharmaceuticals—the latest "waste du jour"—as part of their continued but unhappy role at the end of the consumer product life cycle. We are just now learning about pharmaceutical chemicals turning up in our waters, potentially affecting our fish...and us, too? We are aware that they are showing up in wastewater treatment systems, effluent discharges, and biosolids. Also, we are discovering that there is a hard-to-quantify but potentially huge amount of medications that go unused, and thus become a significant waste management issue, one we want to keep out of wastewater and the environment while we separately figure out how to deal with the substances that get there through regular use. Many pharmaceuticals designate as hazardous waste under the Resource Conservation and Recovery Act (RCRA); others designate under more stringent state regulations, such as those in Washington. Even those pharmaceuticals that do not designate as official hazardous wastes represent problematic chemicals in wastewater systems and the environment.

The vast majority of people in the Seattle area, as well as in Washington State and throughout the country, want a safe, environmentally acceptable way to dispose of old/unwanted/unused pharmaceutical products. Neither flushing nor solid waste disposal are acceptable long-term solutions. Dependence on local household hazardous waste collection services is not the answer. Now is the time to develop a forward-looking, national system via a product stewardship model.

At the moment, only one local government program in Washington State is actively collecting waste pharmaceuticals. The Clark County (Vancouver, WA, area) household hazardous waste program accepts waste pharmaceuticals and has arranged with local retail pharmacies for in-store take-back. Controlled substances are handled via the local sheriff. Because budgets and staffing are low, publicity is restrained and participation to date has been very low. (http://www.co.clark.wa.us/recycle/documents/Medical%20Waste/Medications.pdf)

Two large pilot projects are in development at this time in the Seattle area. Both will test a pharmacy take-back model: one in a private, regional retail chain (Bartell Drugs) and the other at internal pharmacies of a large regional HMO (Group Health Cooperative). In both cases, we are working with representatives to develop collection containers and protocols. As is true across the country, one of the challenges we face is to address Drug Enforcement Administration (DEA) requirements for handling controlled substances. Other concerns include: who can and should take possession of waste medications from consumers (pharmacists? sheriffs? reverse distributors? wholesale service providers that collect from a secure bin? mail-back to a secure entity?) How would these entities sort the wastes for designation (RCRA hazardous, state-only hazardous, non-hazardous, controlled) and transport the material to final disposal?

A national listserv has been set up by state and local waste management personnel to answer questions and share information; it is hosted by the State of Florida (http://lists.dep.state.fl.us/cgi-bin/mailman/listinfo/pharmwaste). Also, work with the Product Stewardship Institute is underway to develop a national dialogue of all major stakeholders (http://www.productstewardship.us).

The United States needs to address this issue in a comprehensive and systematic way. It should not be left to local governments to figure out how to handle these complex wastes. A product stewardship approach is essential. Retail take-back, with handling by the retail entities, reverse distributors, manufacturers, or others, is the preferred model, so that it is convenient to the consumer, comprehensive, safe, professionally managed, and legal. It should be paid for by those marketing the products, not by local ratepayers. Look at the example

across the border to the north: British Columbia has a simple, comprehensive medications take-back program via pharmacies that has been operating for almost 10 years and is privately managed with little governmental involvement save oversight (http://wlapwww.gov.bc.ca/epd/epdpa/ips/meds/meds2003.html). The U.S. Environmental Protection Agency must support a comprehensive approach to pharmaceutical waste management. DEA must provide flexibility regarding its controlled substance regulations to allow for simple, safe solutions to this significant national problem.

Poster Abstracts

Using Genomic Indicators in Aquatic Organisms To Assess Stream Populations Exposed to Emerging Contaminants

Adam Biales[1], Erich Emery[2], Brent Johnson[1], Karen Blocksom[1], Marc Mills[3], Lou Reynolds[4], Amy Bergdale[4], Frank Borsuk[4], Eric Kleiner[3], and James Lazorchak[1]
[1]National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH; [2]Ohio River Valley Water Sanitation Commission; [3]National Risk Management Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH; [4]Region 3, U.S. Environmental Protection Agency, Wheeling, WV

Poster Abstract

Existing ecological monitoring and assessment have been at a population- to landscape-level. At these spatial scales, indicators that are used and monitored do not necessarily have the resolution to detect the subtle effects of endocrine-disrupting chemicals (EDCs) or non-EDC pharmaceuticals. There are monthly reports on the discovery of intersex in male fish, masculinization of female fish, abnormalities in amphibians, as well as declines and loss of such species. From a scientific perspective, this leads to the question: "Are we measuring the right things at the right scale?" The U.S. Environmental Protection Agency has been focused on developing community and population metrics and indices for use in biocriteria development. These criteria eventually will be used to measure performance of restoration and remediation. If existing approaches, however, are not detecting single species loss or detecting the subtle effects of EDCs and non-EDC pharmaceuticals, then other indicators may need to be developed. The Office of Research and Development (ORD) has been working for the past several years to integrate genomic endpoints into risk evaluation and assessments to help protect human and ecological health. Tools such as gene expression, microarrays, proteomics, and metabonomics are being developed and used to assess exposure of aquatic organisms to emerging chemicals. Additionally, ORD is working with the states and intergovernmental agencies such as the Ohio River Valley Water Sanitation Commission to develop monitoring approaches and metrics that will use genomic endpoints to develop more sensitive ways to detect functional effects on fish populations (i.e., feminization of males, masculinization of females, and changes in sex ratios). This poster will present these new tools to show how they can be used to develop a new generation of population health indicators.

PPCP Collaborations at the Federal Level: An Interagency Workshop

Rebecca Daniels
Association of Schools of Public, Health Public Health Fellow, U.S. Environmental Protection Agency

Poster Abstract

In July 2005, seven federal agencies came together to discuss their interest in the topic of pharmaceuticals and personal care products (PPCPs) in the environment. This poster will summarize the discussions of the workshop, with an emphasis on how federal-level collaborations can advance the current knowledge and future research directions of this topic. Other themes may include taking a holistic approach to addressing PPCPs in the environment and future federal research directions.

Advanced Tools for Assessing Selected Prescription and Illicit Drugs in Treated Sewage Effluents and Source Waters

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[1]National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Las Vegas, NV; [2]U.S. Geological Survey, Columbia, MO

Poster Abstract

The purpose of this poster is to present the application and assessment of advanced technologies in a real-world environment—wastewater effluent and source waters—for detecting six drugs (azithromycin, fluoxetine, omeprazole, levothyroxine, methamphetamine, and methylenedioxymethamphetamine [MDMA]).

Methods were developed and compared using solid-phase extraction cartridges and time-weighted polar organic chemical integrative samplers (POCIS). Both extraction techniques were coupled with micro-liquid chromatography-electrospray/ion trap mass spectrometry, which was used for detection.

Azithromycin was detected at concentrations ranging from "not detected" to 77 ng/L in the effluent from wastewater treatment plants (WWTP) and in source waters. Also detected and confirmed in the effluent from two WWTPs, as well as one source water, were two illicit drugs, methamphetamine and MDMA, at an average of 5 ng/L and 0.5 ng/L, respectively.

Although the ecotoxicological significance of drugs in environmental matrices, particularly water, has not been closely examined, it only can be surmised that these substances have the potential to adversely affect biota that are continuously exposed to them even at very low levels. The potential for chronic effects on human health also is unknown but of increasing concern because of the multi-use character of water, particularly in densely populated arid areas.

The next phase of this project is underway in which POCIS was deployed throughout a large urban stream and recreational body of water to map the source, flow, and concentration of selected pharmaceuticals.

Lethal and Sublethal Effects of Simvastatin on Grass Shrimp (*Palaemonetes pugio*)

Peter Key, Jennifer Hoguet, Lou Ann Reed, and Michael Fulton
National Oceanic and Atmospheric Administration, Charleston, SC

Poster Abstract

Urbanized estuarine watersheds may contain elevated contaminant levels in sediments and waters. Recently, concerns have emerged about the potential impacts associated with pharmaceutical products, which may enter estuaries by means of sewage treatment effluents, septic tank and landfill seepage, and agricultural run-off. This study investigated the effects of simvastatin, the main ingredient in Zocor®, a highly prescribed lipid-regulating drug, on larval and adult grass shrimp, *Palaemonetes pugio*, an important estuarine species. Sublethal effects (changes in glutathione [GSH] levels, lipid peroxidation [LPx] levels, and cholesterol levels) and lethal effects (survival) were determined. GSH, a ubiquitous tripeptide, has been shown to help maintain a normal immune system and reduce oxidative damage, whereas LPx, often caused by oxyradicals, can impart cellular damage. There were no significant differences in GSH levels in either larval or adult exposures, although GSH levels in larvae were significantly lower than in adults. LPx levels were significantly higher than controls at 1.0 mg/L in both larvae and adults. Cholesterol levels in adult shrimp were not affected by simvastatin exposure, but levels in larvae were significantly lower at the highest exposure level. Although adult survival was slightly affected (30% mortality at 10 mg/L), larvae were more susceptible with 100 percent mortality at 10 mg/L after 48 hours and a 96-hour lethal concentration, 50 percent of 1.18 mg/L. Lower levels of GSH in larvae may have contributed to increased mortality and increased LPx levels associated with simvastatin exposure.

Concentrated Animal Feeding Operations as a Source of EDCs and Their Management

Marc A. Mills[1], Steve Hutchins[2], James Lazorchak[3], and Gary Ankley[4]
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Poster Abstract

In the United States, there is an estimated 376,000 animal feed operations, generating approximately 128 billion pounds of waste each year. A facility is an animal feed operation (AFO) if animals are stabled/confined, or fed/maintained, for 45 days or more within any 12-month period, and the facility does not produce any crops, vegetation, or forage growth. Concentrated animal feed operations (CAFOs) are the largest of these and are regulated under the Clean Water Act. CAFOs are generally considered to be operations with more than 1,000 animal units. Endocrine-disrupting chemicals (EDCs) are known to be used or naturally produced by the three major categories of CAFOs. Cattle CAFOs use growth hormones, estrogens (i.e., estradiol, estradiol benzoate) and androgens (i.e., trenbolone acetate, testosterone propionate). Poultry CAFOs can contain natural hormones, such as estradiol, estrone, and testosterone. Swine contain no added growth hormones but produce natural hormones.

The U.S. Environmental Protection Agency's (EPA) National Risk Management Research Laboratory (NRMRL), National Health and Environmental Effects Research Laboratory (NHEERL), and National Exposure Research Laboratory (NERL) have been developing analytical and biological tools to assess the extent, exposure, and effects of these estrogens in ground and surface waters. NHEERL has developed an analytical chemistry method for 17-α and 17β-trenbolone in cattle feedlot discharge and in river water and has measured *in vitro* androgenic activity of the discharge using CV-1 cells that had been transiently cotransfected with human androgen receptor and reporter gene constructs. NERL has applied a vitellogenin gene expression assay to trenbolone in cattle CAFO discharges. NRMRL has been working on developing gas chromatogramphy/ tandem mass spectrometry and liquid chromatography/tandem mass spectrometry protocols for analyzing swine lagoon effluent and ground water for estrogens and estrogen conjugates at environmentally relevant levels (ng/L). NRMRL has been applying these methods to determine whether swine CAFOs contribute estrogens to ground and surface waters at land application sites and downstream of CAFO facilities. In addition, NERL is collaborating with the U.S. Geological Survey and the State of West Virginia to look at potential linkages of poultry wastes to high incidences of ova-testis in male smallmouth bass.

Currently, the Office of Research and Development is developing analytical and biological approaches to measure and detect EDCs in ground and surface waters and assess the potential exposures to aquatic life. With these approaches, various field sites will be selected where these tools can be used to further assess the potential exposure and effects of EDCs from CAFOs on ground water and surface water communities. This information will then be provided to EPA Regions and Program Offices for decisions on best management practices for controlling EDCs.

Wastewater Treatment and Its Management of Endocrine Disrupting Chemicals

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National Risk Management Research Laboratory, Office of Research and Development,
U.S. Environmental Protection Agency, Cincinnati, OH

Poster Abstract

Research has shown that wastewater treatment (WWT) can be a significant source of endocrine disrupting chemicals (EDCs) to the environment. WWT can include centralized wastewater treatment plants (WWTPs) or onsite WWT technologies. EDCs found in WWT effluents (aqueous and biosolids) include estrogenic and androgenic hormones, detergent metabolites, and plasticizers. Many questions exist as to why some WWT technologies have higher or lower removal efficiencies. Little research has been conducted to demonstrate how technology or plant operations contribute to the EDCs removal. The efficacy of the unit processes within the plant is not well characterized. In addition, no significant research has been conducted to evaluate onsite WWT for the management of EDCs.

One focus of the EDCs and wastewater research is to characterize the performance of existing risk management strategies. This research has been started at the bench and pilot scale. Research has been conducted on the fate of alkylphenols and to characterize their biodegradation rates under redox conditions typically found in WWTPs. Additionally, research is being initiated to evaluate estrogenic and androgenic hormones under similar conditions.

At the pilot scale, two pilot plants were constructed and operated to simulate a municipal WWTP. The plants were fed a simulated wastewater with constant dosing of EDCs to allow a mass balance analysis of the plant and the individual unit processes. Research also has been initiated at the full plant scale. A project evaluating the digesters efficacy has been initiated to study alkylphenols, hormones, and bisphenol A. This project is a collaborative effort between U.S. Environmental Protection Agency (EPA) Office of Research and Development laboratories, EPA Region 5, and a regional wastewater utility.

A second focus of this research is to determine techniques to optimize existing management strategies or develop alternative management strategies. Once unit operations and technology performance are understood, engineering solutions can be developed to reduce the discharge of EDCs. Additional research is being developed in the area of onsite WWT technologies. These technologies include septic systems, constructed wetlands, and other onsite technologies.

The results of this research can be used to help WWT operators understand the capability of their plants to remove EDCs, how process variables influence performance, and how to improve the operation of their plants to minimize effluent levels of EDCs. In the future, if EPA concludes that EDCs in effluents must be regulated, the Office of Water will require performance information on conventional and innovative treatment to make regulatory determinations.

Liquid Chromatography/Mass Spectrometry Library Development and Strategy for Identifying Harmful Organics in Drinking Water

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Poster Abstract

The screening of water samples for harmful organic pollutants not amenable to gas chromatography/mass spectrometry (GC/MS) has increased interest. Pollutants can affect drinking water usage and limit acceptable sources of ground and reservoir supplies. Water is our most abundant and most important natural resource, so it is vital that we develop strategies to detect and react to harmful chemicals in our water supply.

In light of this issue, the U.S. Environmental Protection Agency Region 5 Central Regional Laboratory is collaborating with the Waters Corporation, under a Cooperative Research and Development Agreement, to develop a quick and robust method that will detect specific harmful agricultural, industrial, and pharmaceutical compounds in drinking water. This method is based on developing a searchable mass spectral library system for liquid chromatography (LC)/MS and LC/MS/MS analysis. Many harmful organic compounds of interest, such as pesticides, pharmaceuticals, and drugs of abuse, are nonvolatile and therefore not amenable to GC/MS, for which MS libraries are in widespread use. There are currently no transferable LC/MS libraries available for practical use.

Aside from GC/MS, there are LC methods using various detection systems available wherein chromatographic resolution is critical for identification and quantification. These LC non-MS methods, however, are not well suited for the important task of screening for a large variety of potentially co-eluting harmful organic compounds in drinking water simultaneously. Data will be presented to validate the use of a library system that has been verified by a few laboratories to demonstrate that transferable LC/MS libraries are practical and possible.

資　料　－　Ⅲ　　目　次

米国 EPA（国立環境暴露試験場）クリスチャンドートン博士からの情報

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

EPA

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

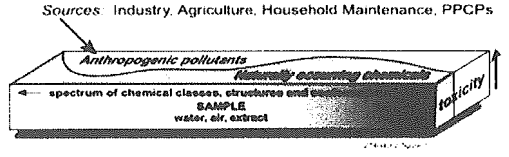
The *POTENTIAL* Universe

- 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.

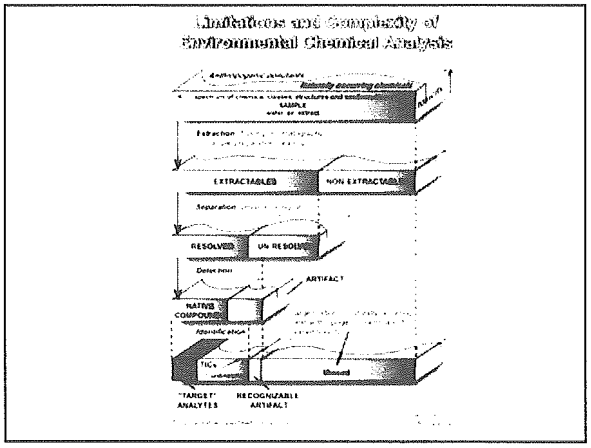
How many distinct organic chemical entities could hypothetically be synthesized and added to a seemingly limitless, ever-expanding chemical universe?

- 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".

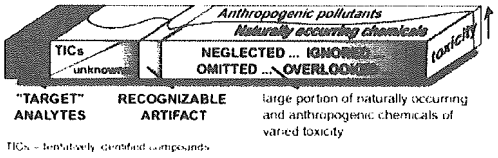
Universe of Chemicals in the Environment



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



Chemical Analysis Output for a Typical Environmental Sample



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.

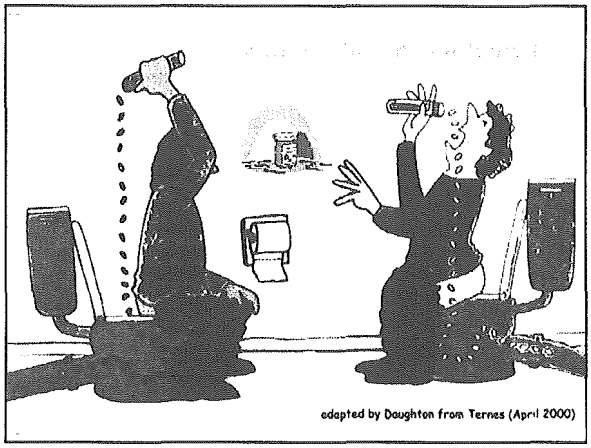
further truisms regarding *Environmental Monitoring*

- 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."



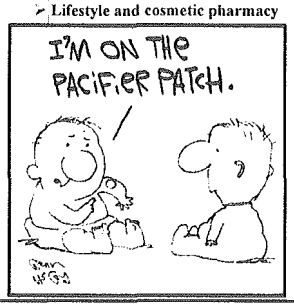
Origins of PPCPs in the Environment

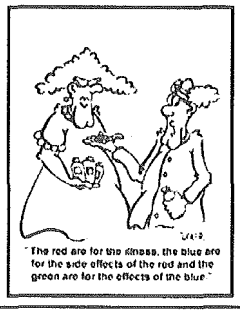
- Other potential routes to the environment include leaching from municipal landfills, runoff from confined animal feeding operations (CAFOs) and medicated pet excreta, loss from aquaculture, spray-drift from agriculture, direct discharge of raw sewage (storm overflow events & residential "straight piping"), 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.

continued >

Expanding Uses and Escalating Usage

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





Expanding Uses and Escalating Usage

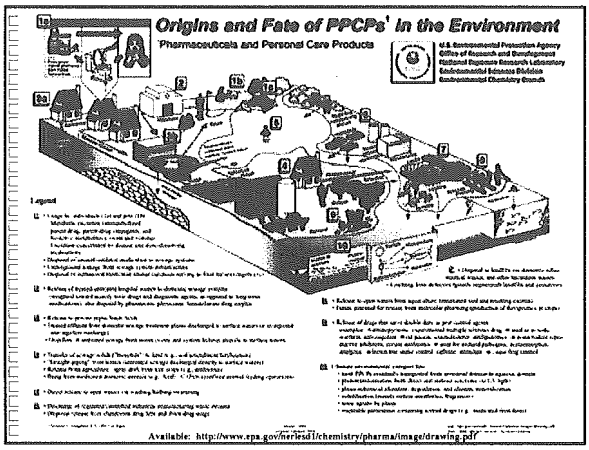
Geriatric Medicine: Unforeseen routes for increase in medication usage, especially among the elderly

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.



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 (μ 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.

continued >

Potential Toxicological Significance as a Result of:

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

(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:

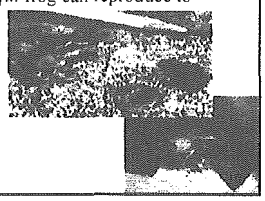
- **4-aminopyridine**: experimental multiple sclerosis drug and an avicide
- **warfarin**: anticoagulant and a rat poison
- **triclosan**: general biocide and gingivitis agent used in toothpaste
- **azacholesterols**: antilipidemic drugs and avian/rodent reproductive inhibitors [e.g., Ornitrol]
- **antibiotics**: 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].