

Pharmaceuticals, Personal Care Products, Endocrine Disruptors (PPCPs) and Microbial Indicators of Fecal Contamination in Ground Water in the Helena Valley, Montana,



Montana Bureau of Mines and Geology Open-File Report 532

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Introduction

- 22 PPCPs detected in ground water in the Helena Valley, both private and public supplies
- Associated with discharge from domestic wastewater
- Little is known :
 - Mobility or persistence in ground water or surface water
 - Human health or aquatic ecosystems effects
- Proposed Ground Water Rule: Multiple Microbial Fecal Indicators for public water supplies
 - Possible future monitoring coliphage, *E.coli*, enterococci



Residential Development on the Valley Fringe





Selected Previous Investigations on PPCPs and Coliphage in Ground Water

■ Hinkle et al, 2005, LaPine, OR

- Of 45 compounds found in wastewater only 9 found in GW - too reactive to serve as GW tracers
- Also found sulfamethoxazole (SMX), acetaminophen and caffeine in GW
- Coliphage detected 8 samples (considered to be field or lab contamination) but absent in replicate and repeat samples; probably attenuated before reaching sampled wells

■ Heberer, 2004, Berlin, Germany

- PPCPs are likely attenuated in ground water
- Loading rates between wastewater systems could be highly variable

■ Seiler, 1999, Reno, NV

- Caffeine (up to 0.23 ug/L) and PPCPs as fecal indicators in GW– unambiguous evidence of fecal contamination
- But caffeine is not conservative; probable nearly complete catabolism of caffeine in bacteria-rich septic system...
- Also found carbamazepine (anti-seizure), chlorpropamide (treats diabetes) and phensuximide (anti-seizure)

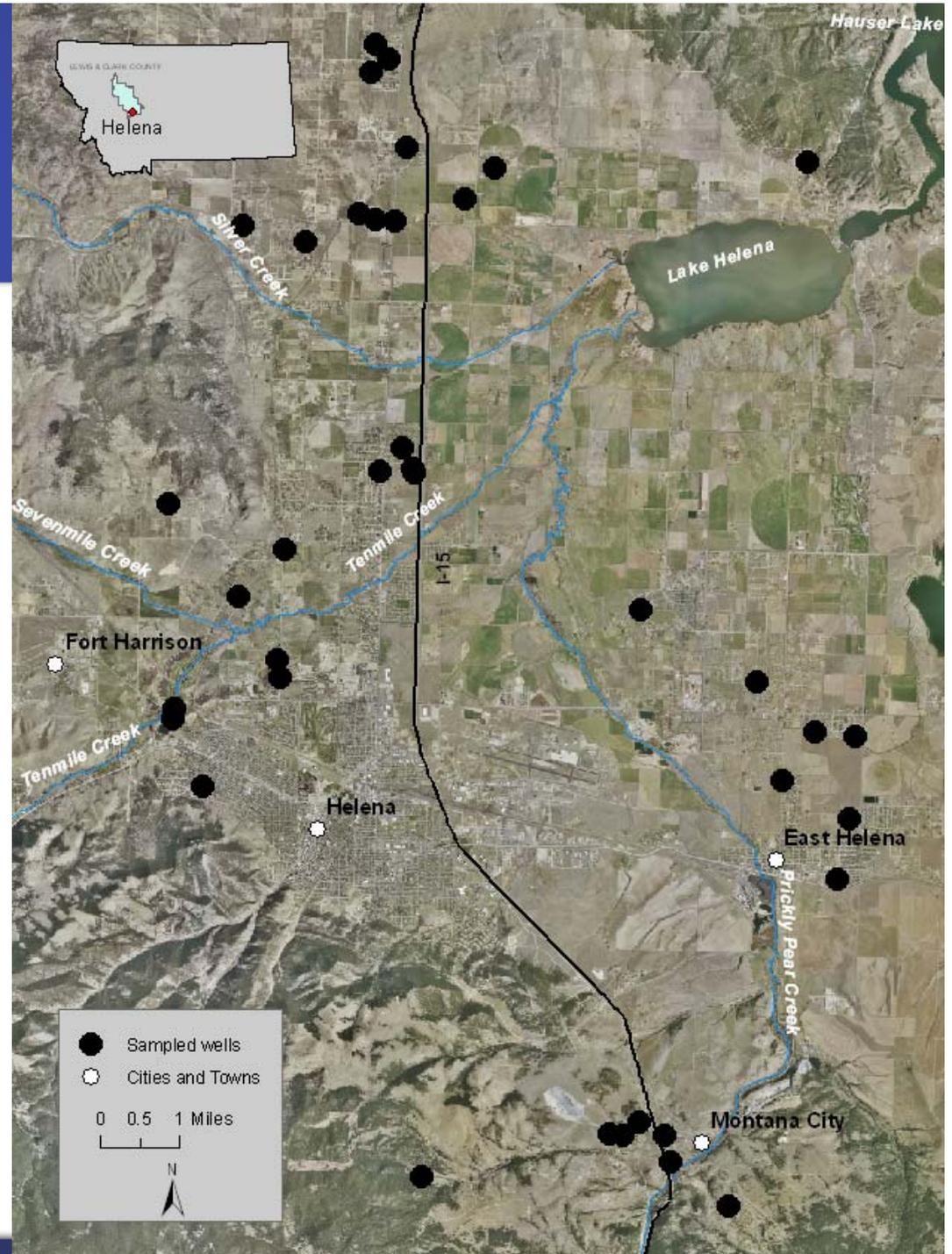
■ Godfrey and Woessner, 2004, Missoula MT

- Acetaminophen, caffeine, nicotine, codeine, trimethoprim (antibiotic) and carbamazepine in wastewater



The Helena Valley

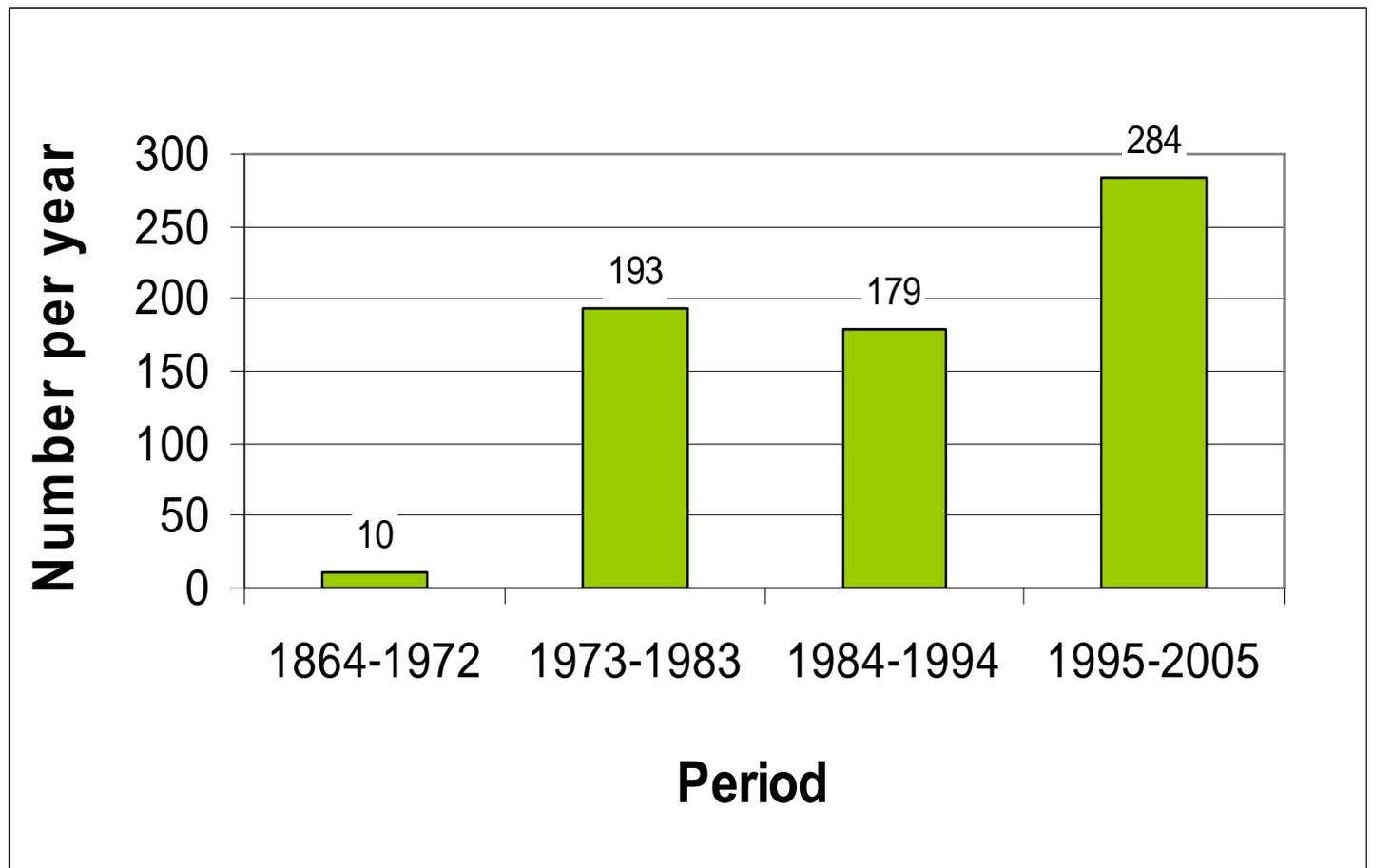
- Rocky Mountain Foothills
- 330 sq. mi.
- City Limits pop. 28,000
- State Capital
- Previous investigators:
 - coliphage in 10 of 19 samples
- Mixed-use
 - Previous: Agriculture and metals-mining
 - Current: residential





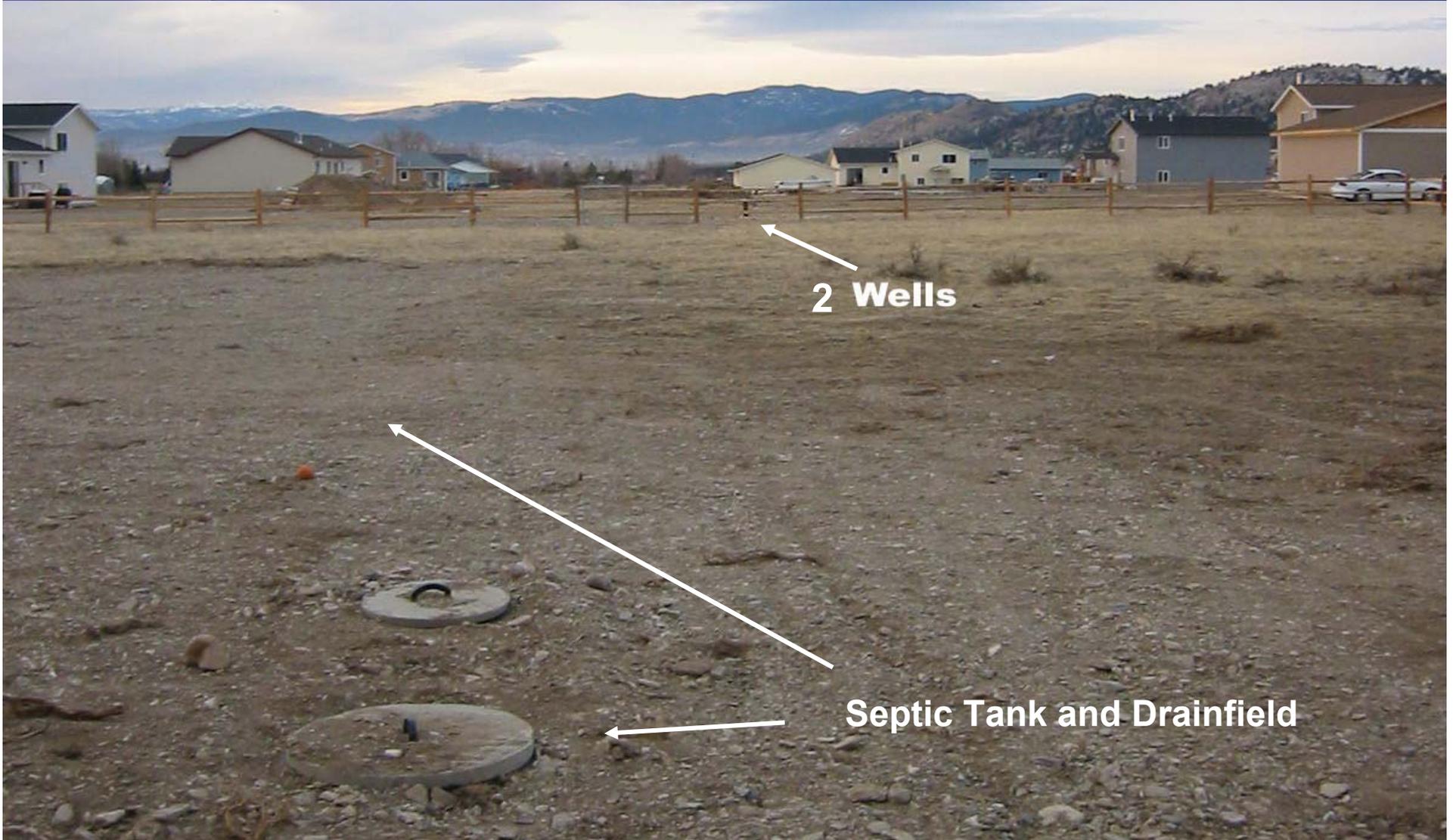
Number of New Well Installations Per Year

- Residential development into areas with no central water or sewer





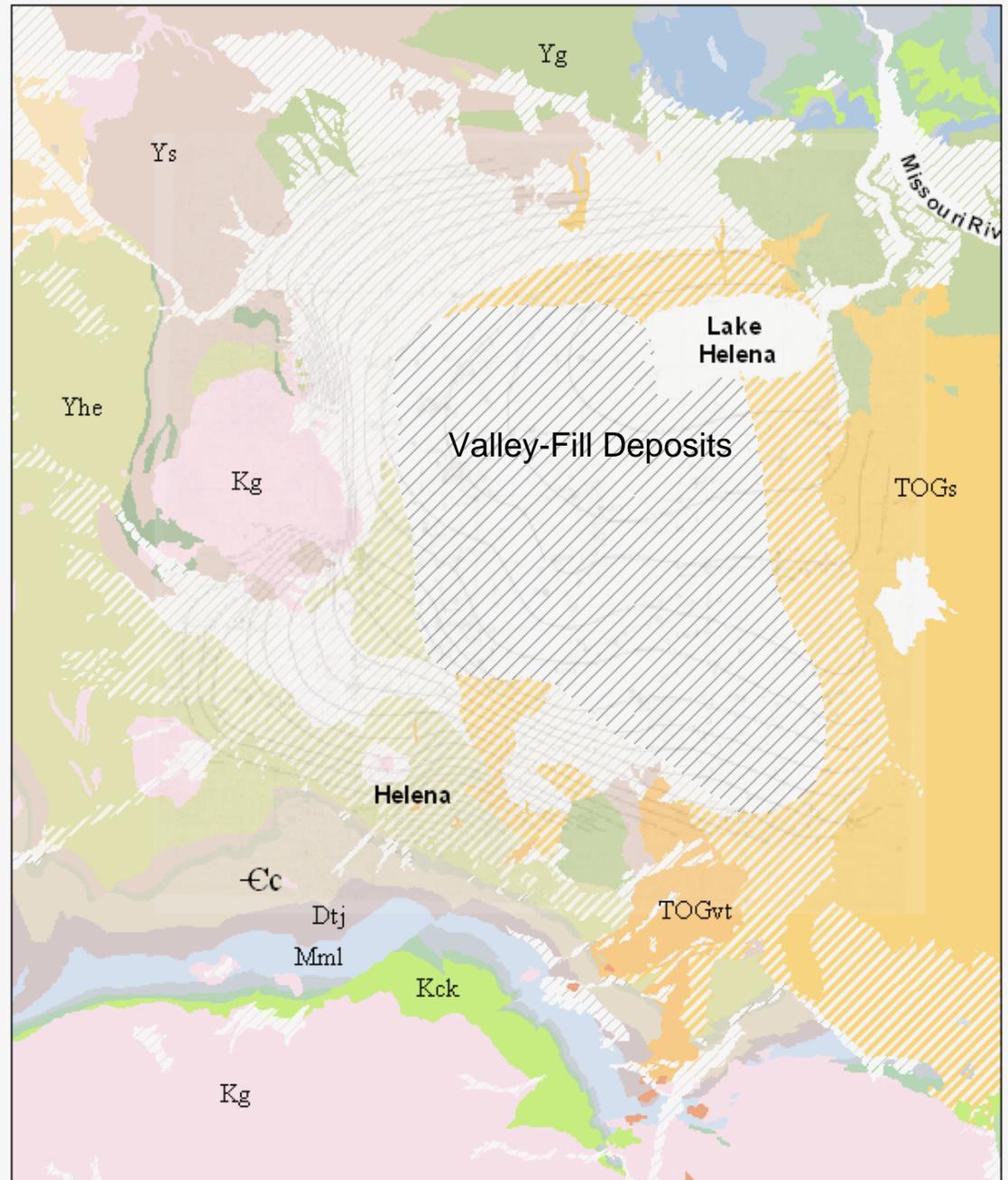
Onsite Wastewater Systems and Drinking-Water Wells





Helena Valley Hydro-geology

- Bedrock is Precambrian to Cretaceous age, folded and fractured, sedimentary, metamorphic and igneous
- Valley-fill deposits (Q/T age) function as one complex aquifer system
- Irrigation with imported Missouri River water
- Ground-water flow from south, west, and north margins to Lake Helena
- Calcium bicarbonate type ground-water quality





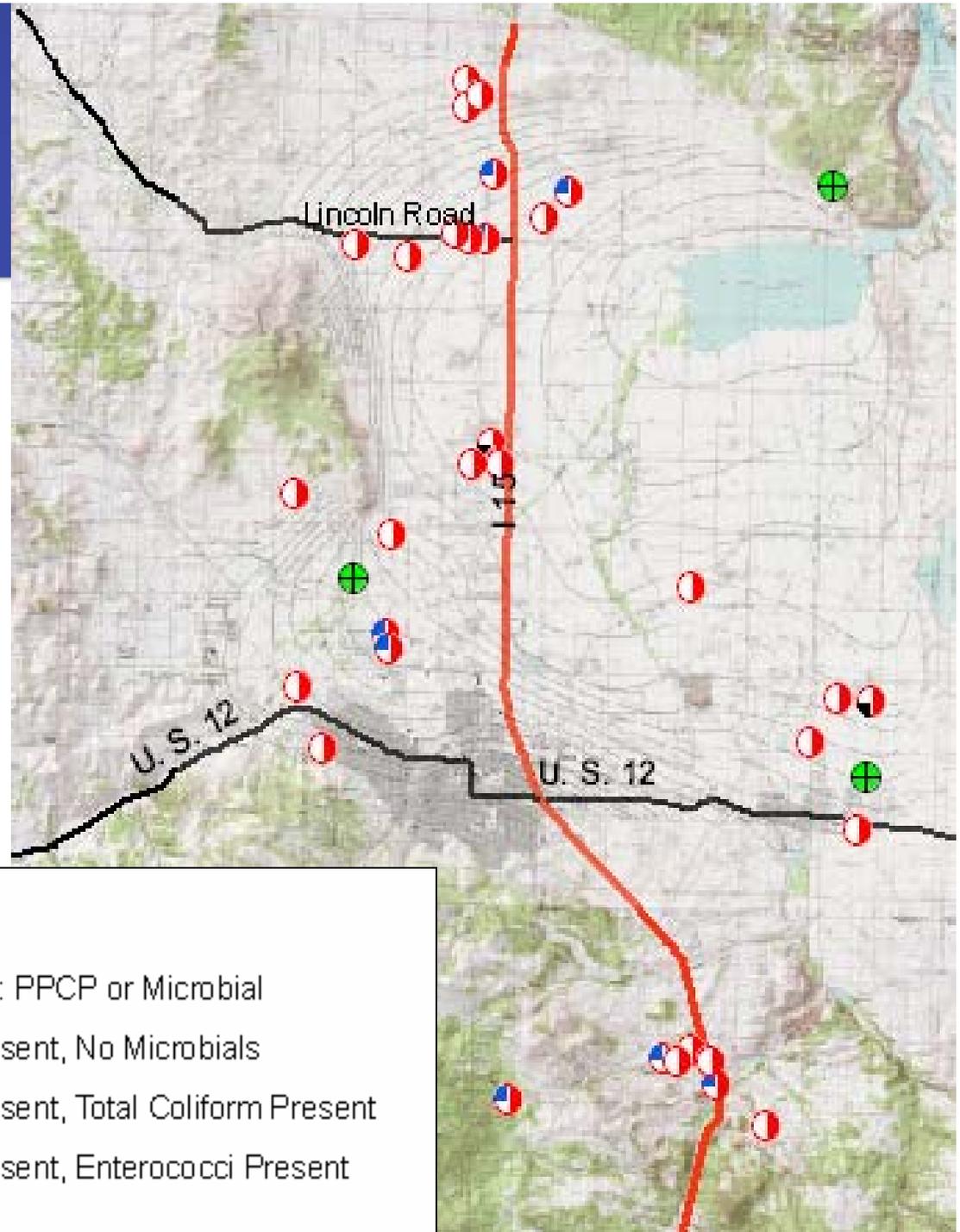
Methods

- April, June, November 2005
- 35 wells sampled for PPCPs
- 38 wells sampled for microbial indicators
 - 12 wells completed in bedrock aquifers
 - 26 wells completed in valley fill deposits
- 18 public water supplies
- Wells flushed until stable field parameters
- Analytical;
 - Coliphage – EPA 1601 Male specific and somatic coliphage by two-step enrichment procedure
 - PPCPs – Sample prep by EPA Method 3535, used LC/MS/MS
- Each well site assigned unique GWIC ID number referenced to the Montana Ground-Water Information Center
- Well depths range from 39 – 425 ft



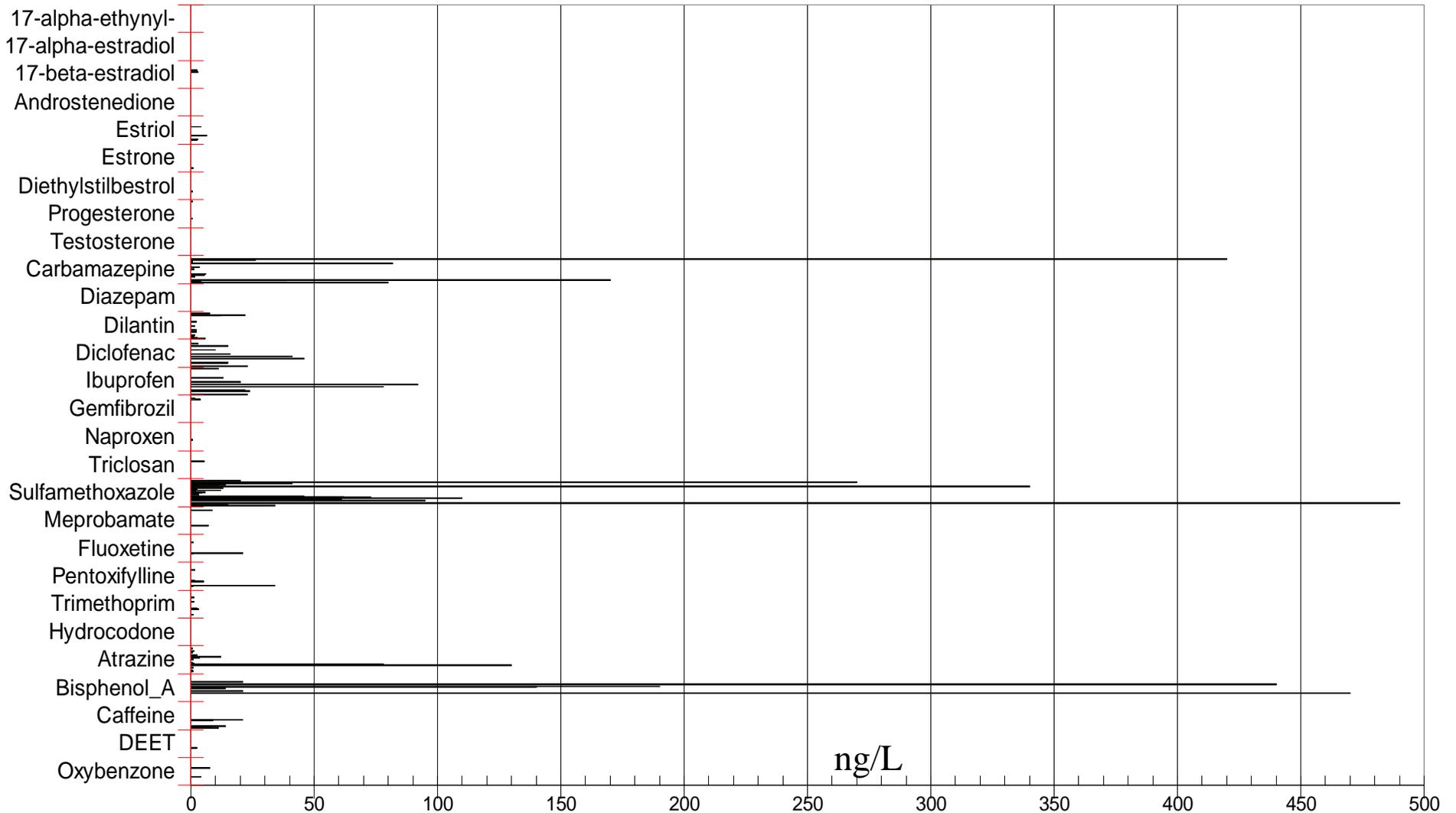
PPCP and Microbial Results

- PPCPs detected at 32 of 35 sites
- Zero coliphage detected
- Zero *E.Coli* detected
- 8 sites positive for total coliform in the presence of PPCP
- 2 sites positive for enterococci in the presence of PPCP



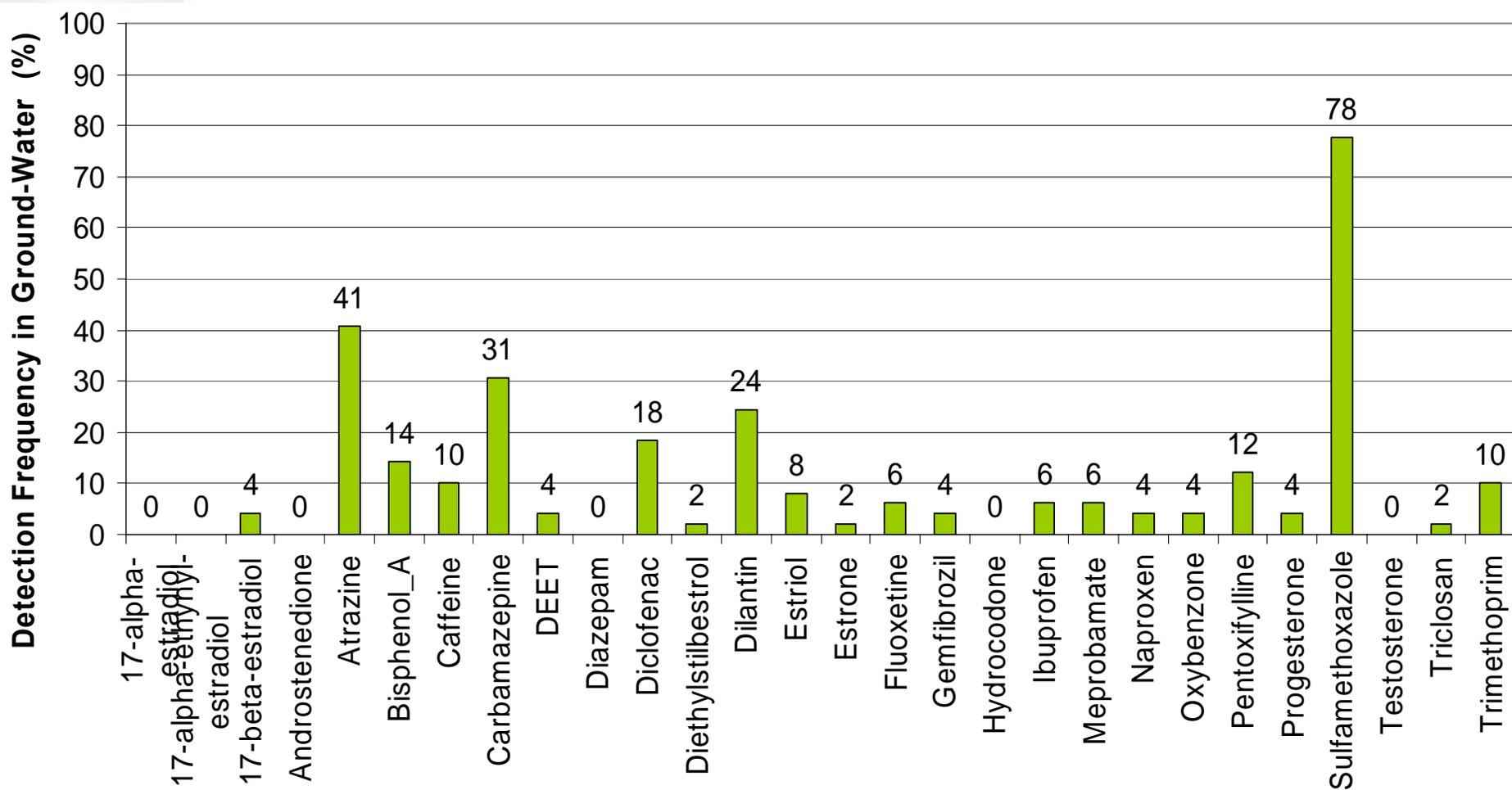


PPCP Concentrations in Helena Valley Ground Water, 2005





Detection Frequencies of 28 PPCPs





PPCP Concentrations

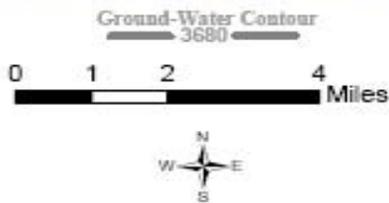
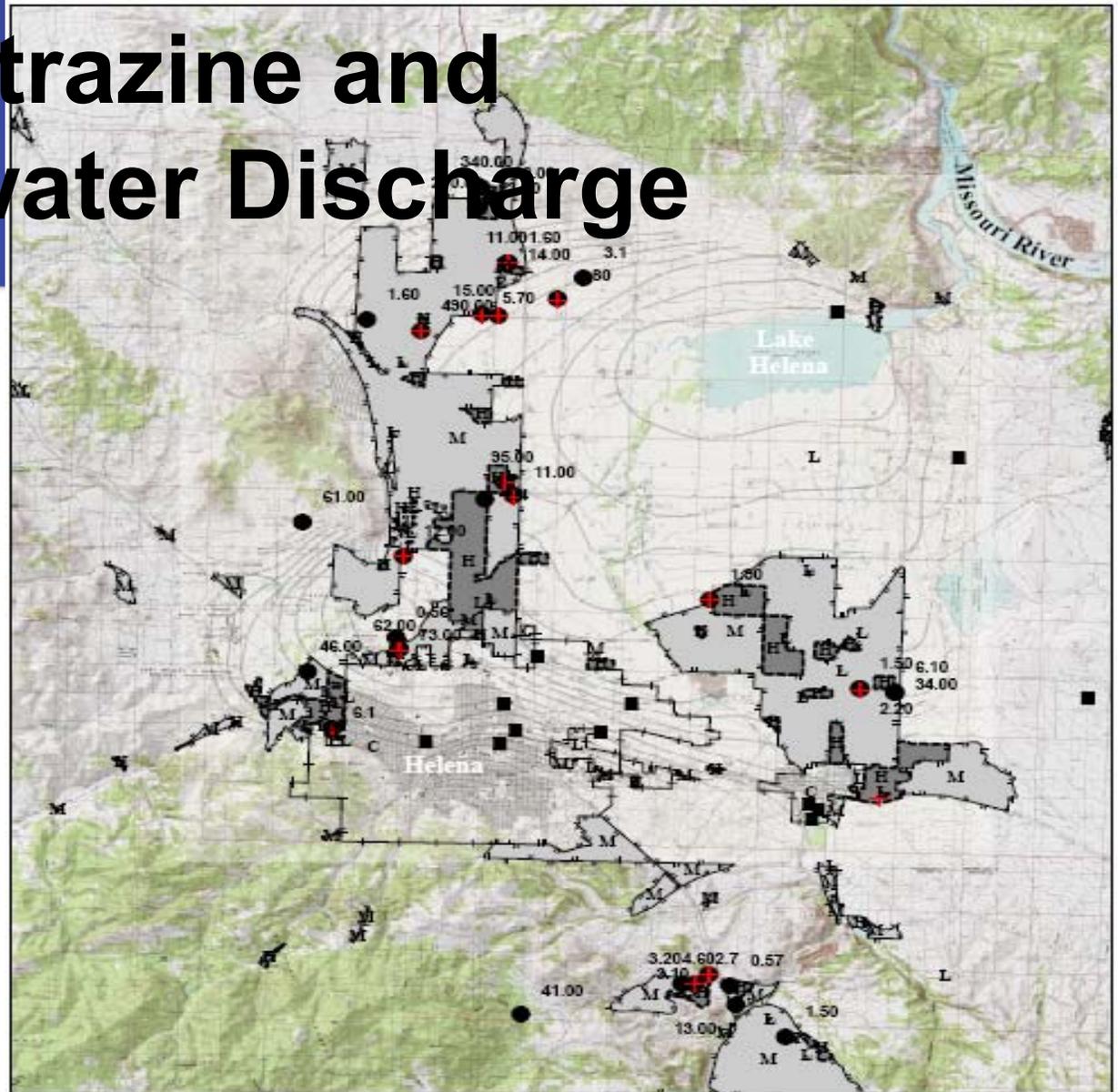
Five Most Frequently-Detected PPCPs	Maximum Concentration ($\eta\text{g/L}$)
Sulfamethoxazole (SMX)	490
Atrazine	130
Carbamazepine	420
Dilantin	22
Diclofenac	46



SMX, Atrazine and Wastewater Discharge

Septic Tank Density

- **High:**
 - >300 septic tanks /mi²
- **Moderate:**
 - 50-300 septic tanks /mi²

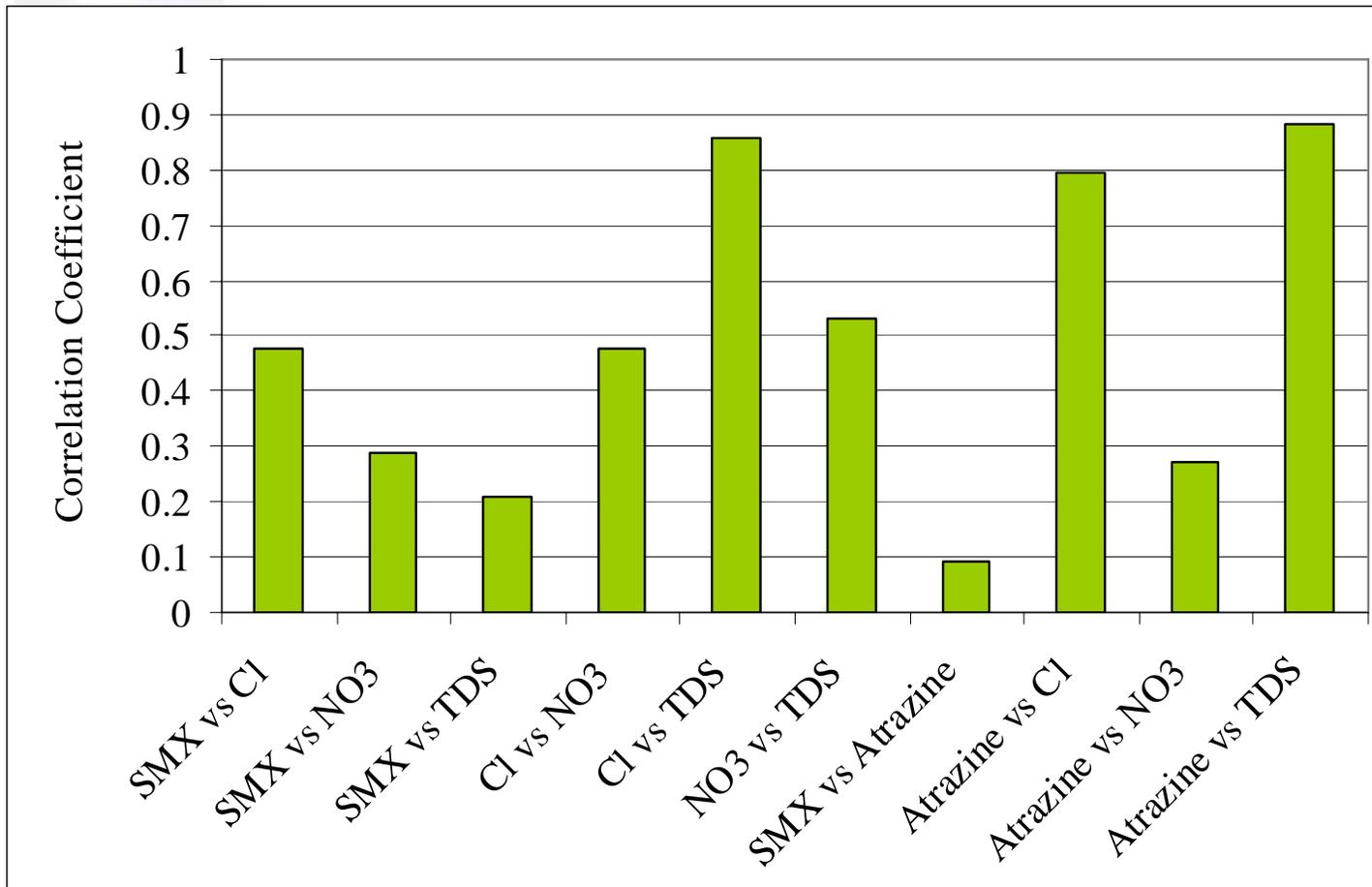


Legend

- Endocrine Disrupting Compounds
- Atrazine
 - Sulfamethoxazole
11.48 (Concentration in micrograms per liter)
- Septic Density
- C = City Sewer
 - H = High
 - M = Moderate
- Wastewater Discharge Sites
- Wastewater Discharge Sites



Correlation Between Sulfamethoxazole (SMX), Atrazine, Chloride (Cl), Total Dissolved Solids (TDS) and Nitrate (NO₃)



Question:

- Is atrazine present in domestic wastewater?



Research Summary

- PPCP findings are consistent with those of other investigators of ground water receiving onsite wastewater discharge
- Coliphage results present implications for suitability as indicators of fecal contamination in ground water
- We are left with questions:
 - Human and aquatic health effects
 - Potential synergistic or additive effects of exposure
 - *Role of aquifer properties and water quality in controlling sorption, degradation and coliphage survival and attenuation in subsurface*



General Notes - Environmental Exposure to Pharmaceuticals

Drug Portal to the World



adapted by Daughton from Ternes (April 2000)



■ **Basic Information**

- In the last decade, the scientific community has become increasingly concerned that humans experience health problems and wildlife populations are adversely affected following exposure to chemicals that interact with the endocrine system. The endocrine system is made up of glands throughout the body, hormones which are synthesized and secreted by the glands into the bloodstream, and receptors in the various target organs and tissues which recognize and respond to the hormones. The function of the system is to regulate a wide range of biological processes, including control of blood sugar, growth and function of reproductive systems, regulation of metabolism, brain and nervous system development, and development of an organism from conception through adulthood and old age. Disruptions in hormonal balance at critical life stages may have long-lasting effects. Because of the potential global scope of the Endocrine Disrupting Chemical (EDC) problem, the possibility of serious problems in humans and wildlife, and the persistence of some suspected EDCs in the environment, research on EDCs is a high priority in EPA's Office of Research and Development's (ORD). Research & Development's National Risk Management Research Laboratory (NRMRL) is conducting research to investigate sources of suspected EDCs that impact the environment. Risk management strategies are being developed to minimize exposure of humans and wildlife to suspected EDCs. Risk management EDC research efforts focus on areas such as waste water treatment, drinking water treatment, and pollution prevention making it the only such program in the world. The program's overarching research questions are:
- Using current available approaches, can the risk of EDCs be managed in a cost-effective manner in cases where the known or highly suspected EDCs appear to be causing impacts on the environment?
- As more information is generated from effects, exposure and assessment research, what new tools are needed to manage likely and unacceptable risk associated with EDCs?



- **In simple terms, what is the overall scientific concern?**

- Large quantities of a wide spectrum of PPCPs (and their metabolites) can enter the environment following use by multitudes of individuals or domestic animals and subsequent discharge to (and incomplete removal by) sewage treatment systems. PPCP residues in treated sewage effluent (or in terrestrial run-off or directly discharged raw sewage) then enter the environment. All chemicals applied externally or ingested (and their bioactive transformation products) have the potential to be excreted or washed into sewage systems and from there discharged to the aquatic or terrestrial environments. Input to the environment is a function of the efficiency of human/animal absorption and metabolism and the efficiency of the waste treatment technologies employed -- if any (sewage is sometimes discharged without treatment by storm overflow events, failure of systems, or "straight piping"). Removal efficiencies from treatment plants vary from chemical to chemical and between individual sewage treatment facilities (because of different technologies employed and because of operational fluctuations and "idiosyncracies" of individual plants). Obviously, discharge of untreated sewage maximizes occurrence of PPCPs in the environment. No municipal sewage treatment plants are engineered for PPCP removal. The risks posed to aquatic organisms (by continual life-long exposure) and to humans (by long-term consumption of minute quantities in drinking water) are essentially unknown. While the major concerns to date have been the promotion of pathogen resistance to antibiotics and disruption of endocrine systems by natural and synthetic sex steroids, many other PPCPs have unknown consequences. The latter are the focus of the ongoing U.S. EPA Office of Research and Development (ORD) work summarized here.
- Although the concern with regard to the potential for environmental impact focuses on the "active" ingredients in PPCPs, some attention should also be devoted to those ingredients used to formulate the active ingredients in consumer products. These so-called "inert" ingredients (such as propellants and solvents) are becoming to be established as a larger source of air pollution than previously recognized. While the active ingredients in PPCPs (with the exception of certain anaesthetic gases and synthetic musk fragrances; see item 10 at: <http://www.epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf>) [PDF, 307 KB] are almost without impact on air (the aquatic and terrestrial environmental compartments serve as the ultimate sinks), the more heavily used "inert" ingredients, especially those in many personal care products (and which are referred to as "excipients" in drug formulation), can contribute to general indoor air pollution and serve as precursors to smog. Regulators in California, for example, began to recognize in 2003 that the "inert" ingredients in personal care products are in part responsible for significant air pollution (including smog). These regulators also began to note that the individually minuscule contributions from each individual when combined can yield a significant impact. For more information, see LA Times news story "Chemicals in Home a Big Smog Source" (9 March 2003); also see the California Air Resources Board's "Consumer Products Program" (<http://www.arb.ca.gov/consprod/consprod.htm>). More information on excipients can be found in part #2 of the [Overview Slide Presentation](#). [PDF, 2.2 MB]



- Briefly, here's a summary of the overall issue:
- **Background** EPA's historic focus over the last 30 years on chemical pollutants in water has been limited to a small set of industrial pollutants (mainly "persistent pollutants" and a small set of NPDES criteria pollutants) The focus of sewage treatment works (STWs), as stipulated by law, is solely on a small subset of "criteria" pollutants -- but the effluents from STWs contain a wide spectrum of numerous other chemicals, and for few of which is much known with regard to potential environmental effects. With the ingenuity of synthetic chemists, useful chemicals from an ever-expanding universe of possibilities are introduced to consumers yearly. Few are understood with respect to their environmental impacts (if any). PPCPs are only one broad group of newly considered pollutants. 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; see discussion regarding [analytical chemistry](#). *There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.* In addition to antimicrobials and steroids, over 50 individual PPCPs (from more than 10 broad classes of therapeutic agents and personal care products) had been identified (up to year 1999) in environmental samples (mainly in sewage, surface waters, ground waters, and to a very limited extent, limited drinking waters). While this list is expanding, it is important to note that most PPCP classes have yet to be searched for as of the year 2000. Since 2000, the number of studies that have characterized the occurrence of PPCPs in a wide variety of environmental compartments has grown greatly; many of these can be found [here](#). Those PPCPs that have been identified in waters tend to occur in concentrations ranging from 100's of ppb ($\mu\text{g/L}$) to sub-ppt (ng/L) (see [explanation of measurement terminology](#)). Most research to date has been conducted in Europe, with North American studies only recently coming on line. **The Issue** PPCPs are known to gain entry to the environment through their end uses by consumer consumption and disposal and via use in domestic animals. While these routes to the environment have gained general recognition amongst scientists in the last decade, one can safely surmise that as long as drugs have been in use, their excretion has carried them to the environment. The two aspects of the overall issue that have gained the most attention to date are: (1) hormone disruption in fish by natural and pharmaceuticals estrogens, and (2) the mis(over)use of antibiotics, leading to release of resistant pathogens (from excreta) as well as to their natural selection in the wild (from exposure to sub-lethal levels). But these two major classes of PPCPs represent only a small portion of the large number of PPCPs in use today. The pertinent environmental issues could be as varied and diverse as the number of chemical classes in use Numerous PPCPs or metabolites/breakdown products are introduced to the environment through their use and disposal While their concentrations are very low (ppb-ppt), the fact that they are **continually** introduced to the aquatic environment lends those with short half-lives a quality of persistence (because of a pseudo-steady-state -- breakdown is balanced by replacement); certain others are truly persistent because of resistance to breakdown. Continual, multi-generational exposure of aquatic life to multiple PPCPs has unknown consequences. Human consumption of tap water with ppt levels (and below) has completely unknown consequences; regardless, the occurrence of minute traces of PPCPs in drinking water can pose a number of [problems that derive from the perception of risk](#) [PDF, 13 pp., 562 KB]. The overall topic generates a multitude of questions, few of which have definitive answers.



- **Are PPCPs considered an "emerging" environmental issue?**

- This issue is considered "emerging" simply because it has witnessed most of its development only during the last 5-10 years. The conventional priority pollutants had captured most of our attention for the previous 30 years. The greatly accelerating development of new PPCPs and the escalating prescription of drugs will only serve to increase the prevalence of PPCPs in the environment. Indeed, one can safely conclude that as long as a particular PPCP has been available for public consumption, it has had the potential to enter the environment. While it is true that this issue has only recently become topical in the U.S., much research has already been accomplished over the last decade by a number of European and Scandinavian investigators. Previously unidentified or under-appreciated aspects of chemical pollution often involve chemical classes not before recognized as pollutants -- there is nothing rigorous or definitive about the established lists of pollutants. One of the primary goals of the U.S. EPA's Office of Research and Development is to identify and foster investigation of "hidden" or potential environmental issues/concerns before they become critical ecological or human health problems -- pollution prevention being preferable to remediation/restoration (to minimize public cost and to minimize human and ecological exposure -- the fuel oxygenate methyl-tert-butyl ether is a recent case in point). A major route to achieving this end is to highlight potential environmental issues, thereby fostering further research, and to compile and integrate the resulting data so that the scientific community and the public can reach informed decisions -- ensuring that science provides the foundation for any eventual discussion/decisions regarding guidance/regulation. The work on PPCPs addresses one of the 10 goals that compose the U.S. EPA's Draft Strategic Plan 2000 (<http://www.epa.gov/ocfopage/plan/plan.htm>); this plan is partly driven by the Government Performance Results Act. Among these goals, is one that deals with "Research to Detect Emerging Risk Issues: By 2008, establish capability and mechanisms within EPA to anticipate and identify environmental or other changes that may portend future risk, integrate futures planning into ongoing programs, and promote coordinated preparation for and response to change. We will also build institutional capacity to forecast and prepare for emerging problems. To prevent damage to both human and ecosystem health, it is critical to detect, describe, evaluate, and mitigate or eliminate stressors before damage occurs." See the more extensive discussion of this topic at the Web site bullet: "[PPCPs and One Approach of EPA/ORD's to "Emerging" Science Issues](#)". For an expanded perspective on the topic of emerging contaminants, see: "[Non-Regulated Contaminants: Emerging Issues](#)". An excellent example of a complex class of emerging PPCPs is those based on nanomaterials and nanotechnology.



- **Although antibiotics and steroids are not part of the scope of this web site, what are their major environmental concerns?**
- The (over)use of antibiotics in humans and especially domestic animals introduces these agents to the terrestrial and aquatic environments leading to the potential for accelerated development of resistance among naturally occurring pathogens (e.g., see: http://www.who.int/multimedia/antibiotic_res/index.html/). Antibiotics can also change the community structure/diversity of native bacteria, which constitute a fundamental aspect of the environment; a discussion of some of the less-appreciated aspects of antimicrobials in the environment can be found in [this slide presentation](#). [PDF, 1.9 MB] Sex steroids (e.g., from oral contraceptives) can feminize male fish and change the behaviors of either sex -- all with unknown consequences (e.g., see: <http://www.tmc.tulane.edu/ecme/eehome>; <http://www.nap.edu/books/0309064198/html/>.)
- This is not to say, however, that the estrogenic hormones are the only ones of concern. Evidence exists that other hormone classes play possible roles in aquatic effects. An interesting example is the bacterial synthesis of the anabolic steroid androstenedione from the naturally occurring sterols in pulp mill effluents; the androgens have potent masculinizing effects. For a summary of this issue, see "Macho Waters: Some river pollution spawns body-altering steroids," J. Raloff, *Science News*, 2001, 159(1): 8-10 (available: <http://www.sciencenews.org/20010106/bob7.asp>)



- **What pharmaceuticals or classes of PPCPs are of greatest concern?**

- The major concerns to date have been the promotion of pathogen resistance to antibiotics and disruption of endocrine systems by natural and synthetic sex steroids. These two topics have been the focus of the vast majority of the published research on PPCPs. But these two classes of PPCPs represent only a portion of the potential environmental issues faced by PPCPs. The focus of the work covered at this web site **excludes** the antimicrobials and steroidal estrogens -- it instead focuses on the myriad of other chemical classes, each with its own potential distinct effects with currently unknown environmental consequences. Only a very limited subset of these other PPCPs have been looked for in the aquatic environment to date (in the aquatic environment, this serves as "exposure" data for those PPCPs that are known to occur). To begin any type of risk evaluation, one also needs effects data. Unfortunately, but a paucity of work has ever been done to evaluate the potential effects of PPCPs on aquatic life (after all, before now, there was little reason to explore aquatic toxicology for chemicals that were designed for human and domestic animal use). Of these few studies, the antidepressant selective serotonin reuptake inhibitors (SSRIs), calcium-channel blockers, and efflux-pump inhibitors (anti-depressants) seem to have obvious potential for untoward effects (especially since they each impart effects on metabolic pathways that are central to aquatic life). This does not discount the possibility, however, as toxicologists begin to evaluate other PPCPs, especially for non-conventional subtle effects, that other classes could be found with profound effects, even at low concentrations. There are other suites of PPCPs for which occurrence data exists as well as significant human toxicity but not aquatic effects data. An example is the antiepileptics, some of which are known human neuroteratogens. The acutely genotoxic chemotherapeutic agents are also of concern. With specific toxicologic concerns aside, there are a number of [other concerns that derive from the way in which risk is communicated and perceived](#) [PDF, 13 pp., 562 KB]. As of 2004, the most extensive compilation of materials relevant to the ecotoxicology of PPCPs was presented at the Fourth SETAC World Conference (14-18 November 2004); the abstracts for this meeting can be found by locating the relevant SETAC meeting at [Completed Scientific Conferences Devoted to PPCPs in the Environment](#).



- **In what types of places and in what geographic locales have PPCPs been identified?**
- PPCPs have been identified in most places where they have been looked for. Up until 2002 with the first publication from the [USGS nationwide monitoring program](#), followed shortly thereafter with investigations in [Canada](#), the range of places that have been investigated for PPCPs were primarily in Europe and Scandinavia. The major ultimate disposition for PPCPs in the environment is the aquatic environment because of their higher water solubility and lower volatility than conventional pollutants; but another route is to the terrestrial environment from the use of treated sewage sludge ("biosolids") to soil (e.g., see NRC report at: <http://www.nap.edu/books/0309084865/html>). The sources/origins of PPCPs in the environment are illustrated [here](#). [PDF, 307 KB] There is no reason to believe that similar data will not be found anywhere that PPCPs are used. The types of locations where they have been found include:
- MANY German surface waters (rivers, streams), some German [drinking waters](#) (in older, east Berlin sectors), as well as some new, limited data for U.S. [drinking water](#) and Canada, and the raw influents and treated effluents from MANY sewage treatment plants (in Europe, Brazil); note that the very first reports of drugs in the environment were for clofibric acid in U.S. sewage, Swiss lakes, certain very large bodies of natural water, hospital waste streams, fish (musk fragrances), leachate from landfills (e.g., in Denmark), and ground waters



- **In what quantities are PPCPs consumed or introduced to the environment?**

- It is important to keep in mind that "quantities" consumed are only one part of a more complicated suite of factors that determine what amounts can end up in the environment. Certain PPCPs that are manufactured in very large quantities might find little exposure to the environment if they are easily metabolized or degraded quickly in the environment. Conversely, some PPCPs made in small quantities could get efficiently transferred to the environment if they are poorly metabolized and efficiently excreted to domestic sewers. Quantities of PPCPs sold/consumed are very difficult to locate and verify. This is partly because these data are highly complex (and there are numerous sources to consider) and partly because the data are proprietary to the industry. According to IMS Health, there has been 10% growth in drug sales through retail pharmacies in 12 key markets in the 12 month period from March 1999 through to February 2000. These sales were about \$210.7 billion worldwide. The top therapeutic markets were cardiovascular, alimentary, CNS (e.g., antidepressants), anti-infectives, and respiratory. In the 12 months to Feb. 2000, U.S. sales were about \$92 billion, Europe \$54B, and Japan \$49B (the three largest markets); so it looks like U.S. sales are about half of worldwide sales. According to PhRMA's "Industry Profile 2000" report, sales of ethical pharmaceuticals (by U.S. and foreign companies) in the U.S. for 1999/2000 were roughly one-half of worldwide (ca. \$100 of \$200B total); veterinary sales being roughly 1-2% of total, and OTC sales ca. 2% of total. In 1997, the U.S. per capita expenditures on drugs was the third highest in the world (\$319); with Belgium, Japan, and France being the top three with \$321-\$351, respectively. Pharmaceutical sales for 1997 in the U.S. were 1.4% of gross domestic product. The most recent data can be found in the current PhRMA's "Industry Profile" report (<http://www.phrma.org/publications/publications/>); the 2003 report can be found here: <http://www.phrma.org/publications/publications/profile02/index.cfm>. One can safely conclude that these sales figures represent very large quantities of actual chemical product. The yearly worldwide production of some individual drugs amounts to hundreds of tons, while others are merely kilograms. Personal care products tend to be made in extremely large quantities - thousands of tons per year.



- **What are the major sources of PPCPs in the environment?**

- Some obvious sources for PPCPs as environmental pollutants include residues from pharmaceutical manufacturing and from hospitals. The discharge of pharmaceuticals and synthesis materials and by-products from manufacturing are already well defined and controlled. For more information regarding manufacturing discharges, see: U.S. EPA "Development Document for Final Effluent Limitations Guidelines and Standards for the Pharmaceutical Manufacturing Point Source Category," Office of Water, EPA-921-R-98-005, September 1998 (available: <http://epa.gov/ostwater/guide/pharm/techdev.html> or <http://epa.gov/ostwater/guide/pharm/techdev/tdd.pdf>) [PDF, size not available, 468 pages] . While these are indeed sources, they are not the main focus of the work covered at this web site, which focuses on the importance of the activities, actions, and behaviors of individuals. The importance and significance of the individual in directly contributing to the combined load of chemicals in the environment has been largely overlooked. PPCPs in the environment illustrate the immediate, intimate, and inseparable connection of the actions/activities of the individual with their environment. Furthermore, the importance of dispersed, diffuse, non-point "discharges" of anthropogenic chemicals to the environment has been overshadowed for decades by the more obvious point sources. These diffuse sources include the excretion of ingested drugs and bioactive metabolites, the washing of externally applied drugs and personal care products (e.g., see: Eriksson et al. "[Household Chemicals and Personal Care Products as Sources for Xenobiotic Organic Compounds in Grey Wastewater](#)," 2004 [PDF, 69 KB] , and EWG "[Skin Deep](#)," 2004), and the direct disposal of PPCPs to terrestrial sites and domestic sewage. Excretion of parent, unmetabolized drugs is a function of the pharmacokinetic profile of the individual drug, its formulation (certain excipients -- i.e., inert ingredients -- can minimize absorption and therefore maximize excretion), and the metabolic profile of the individual (age, sex, health, and individual metabolic "idiosyncracies"). Previously unrecognized sources must also be considered; illicit drugs are but one example (see: "[Illicit Drugs in Municipal Sewage](#)"). Many of the issues pertaining to the introduction of drugs to the environment from human usage also pertain to veterinary use as well, especially for antibiotics and steroids. A generalized synopsis of the sources of PPCPs in the environment can be viewed here: <http://www.epa.gov/nerlesd1/chemistry/pharma/images/drawing.pdf>. [PDF, 307 KB]



- **What are the major issues with respect to occurrence, distribution, and exposure?**
- The Larger Puzzle: PPCPs are one large group of highly bioactive chemicals that have been long-ignored with respect to their contribution to the larger risk assessment puzzle.
- Limited View of Persistence: Our view of pollutant "persistence" might not be sufficiently encompassing being that the continual introduction of PPCPs to the aquatic environment via sewage outfalls could potentially lead to continual aquatic exposure even though a pollutant may not be truly "persistent" (as currently defined by environmental chemists).
- Existing Data Set for Occurrence of PPCPs Is Too Limited: In the U.S., the types, concentrations, and geographic profile for PPCPs in the aquatic realm and in drinking water needs to be vastly expanded. This will require an integrated monitoring program.
- Data to Establish Trends Present a Major Challenge: Aquatic trends data (for types and concentrations) are perhaps central to the argument as to whether PPCPs in the environment are significant. This is because the major thrust of the argument is that they occur at concentrations that are significantly below therapeutic doses. If trends data proved to show increasing types and concentrations of PPCPs in aquatic environment, then we would be positioned to take action well ahead of any time (before the cusp) when these chemicals and their quantities might prove significant.
- As of 2004, the most extensive compilation of materials relevant to the ecotoxicology of PPCPs was presented at the Fourth SETAC World Conference (14-18 November 2004); the abstracts for this meeting can be found by locating the relevant SETAC meeting at [Completed Scientific Conferences Devoted to PPCPs in the Environment.](#)



- **What are the major issues with respect to effects?**

- Contrast with Conventional Pollutants: Drugs are purposefully designed to interact with cellular receptors at low concentrations and to elicit specific biological effects. Unintended adverse effects can also occur from interaction with non-target receptors.
- Traditional Toxicology: Environmental toxicology has long focused on the more obvious, acute effects of exposure rather than less-obvious chronic effects.
- Toxicity Out of Context: Environmental toxicologists are usually forced to look at exposure issues "out of context" because of the extreme complexity of factoring in exposure from all potential toxicants that may be present in any given exposure situation (and the lack of comprehensive chemical analysis data); see the imitations faced by [analytical chemistry](#).
- Effects on Aquatic Life the Major Concern: Exposure risks for aquatic organisms are much larger than those for humans, given the fact that aquatic organisms can suffer continual, multi-generational exposures to any chemical in their domain and that concentrations in treated drinking water are likely to be much lower. The limited data that have been published so far at least show the potential for subtle effects (that could escape our immediate attention) at low concentrations.
- Exposure of Humans via Drinking Water Poses Problems Deriving from Risk Perception: Should PPCPs occur even in [trace concentrations in drinking water](#), water reuse/recycling programs have the potential to experience a number of problems with respect to consumer acceptance. [These problems mainly derive from the way that risk is communicated and perceived](#) [PDF, 13 pp., 562 KB].
- **Shift of Focus to Subtle Effects:** Any concern with PPCPs in the environment (and if/when present, they would be expected to be at very low concentrations) points to the need for development of tests that detect more subtle end-points (neurobehavioral effects and inhibition of efflux pumps being two examples). Subtle effects that accumulate unnoticed may be significant.
- **Limited Effects Data:** While sparse aquatic/terrestrial toxicology data exists for PPCPs, the little that has been published shows the potential for subtle effects (that could escape our immediate attention) at low concentrations. While only very sparse data has been generated so far on the subtle ways in which drugs can affect aquatic life, this line of concern is bolstered by the substantially more data that is available for pesticides. For example, brief exposure of salmon to 1 ppb of the insecticide diazinon is known to affect signaling pathways (via olfactory disruption), leading to alteration in homing behavior (with obvious implications for predation, feeding, and mating).
- **Example drug classes posing concern:** The consequences of antibiotics are actively being debated and researched (e.g., promotion of antibiotic resistance in pathogens from the (over/mis)use of antimicrobials in people, animals, and agriculture); note, however, that there are a number of under-appreciated issues (discussed [here](#)) surrounding the importance of antimicrobials as pollutants. With antibiotics and estrogenic steroids aside, the limited literature points to several other classes of potential concern. Profound effects on spawning and other behaviors in shellfish can occur with antidepressant **selective serotonin reuptake inhibitors (SSRIs)**. Dramatic inhibition of sperm activity in certain aquatic organisms can be effected by **calcium-channel blockers**. **Antiepileptic drugs** (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain, leading to neurodegeneration. Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota -- possible significance of **efflux pump inhibitors (EPIs)** in compromising aquatic health. **Musk fragrances** are bioaccumulative and persistent. **Genotoxic drugs** (primarily used at hospitals) are also worrisome.



- **In the absence of definitive environmental or human health effects data resulting from actual exposure to trace environmental levels of drugs (which, after all, are far below therapeutic dosages) why should we be concerned about this issue?**
- Although concentrations in drinking water may be low (parts per billion or trillion), concerns cannot be discounted for a number of reasons:
- Epidemiological studies ascribing effects to traditional pollutants do not factor in exposure to other, unconventional pollutants such as PPCPs (because they are not measured in those studies).
- Epidemiological studies on potential effects of inadvertent PPCP exposures are not yet possible.
- Recommended therapeutic dosages are often higher than the therapeutic dose actually required (a dual consequence of not adjusting doses downward from those set in clinical trials and of not individualizing therapy).
- Non-target, unintended effects cannot be discounted at sub-therapeutic dosages (unintended effects can occur at lower concentrations than therapeutic effects, especially during long-term maintenance therapy).
- Drugs are designed to be biologically active, and it may be possible that non-target, unintended effects occur at lower concentrations than therapeutic effects.
- Additive/synergistic effects from simultaneous consumption of numerous drugs are unknown; plus the unknown of added burdens to patients already taking a low-therapeutic index medication.
- Continual, life-long exposure to trace levels -- an unexplored domain of toxicology.
- Relevant to these points regarding exposure to low environmental concentrations is the very important fact that trends data are lacking. Even where/if PPCP concentrations are currently low, no data sets exist for revealing long-term trends. For any particular PPCP at a given geographic location, is its concentration over time decreasing, remaining constant (steady state), or possibly increasing? So regardless of whether a problem exists now, it is important to at least keep a watchful eye (through trends monitoring), so as to have the ability to supply an early warning of an emerging problem before it becomes significant.

The occurrence of trace levels of human drugs in drinking waters can pose problems with regard to risk perception. This poses challenges with regard to the growing need to reuse/recycle wastewater for domestic purposes, eventually including drinking. This topic is covered in the publication: [Ground Water Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds.](#)

- The documented occurrence of PPCPs in the environment may or may not eventually prove to have any implications with regard to either ecological or human health – primarily because their known concentrations are so low. [But the issue of ecological effects in particular cannot be resolved until aquatic toxicologists begin evaluating the effects on non-target organisms by simultaneous exposure to multiple PPCPs at low doses.] Regardless of the outcome with the current generations of PPCPs, however, the very fact that many members of this large, diverse universe of bioactive chemicals have the demonstrated potential to enter the environment gives us the opportunity to proactively investigate (ahead of time) whether each of the myriads of new drugs under development (many of which exert their known effects by totally new mechanisms of action and are ever more potent) poses adverse risks to the aquatic environment (or humans). This knowledge essentially serves as an early-warning to direct more attention to unintended ramifications of introducing new drugs to commerce.
- **Several considerations point to trends of increasing numbers (types/classes) and concentrations of individual drugs in the environment:**
- Drug use can be expected to continue to rise due to a confluence of drivers: Continually expanding uses for existing drugs, increased per capita consumption, expanding population, expanding potential markets (partly due to mainstream advertising/marketing), expiration of patents (availability of cheaper generics), increased use of physician samples, government subsidies for lower-income patients, and new target age groups (e.g., antidepressants for children being a case in point). Old therapeutics are being used



- **If there are indeed health risks, should we be worried more about ecological or human health?**
- The two major sources of PPCPs in the environment are from domestic sewage and terrestrial runoff. Since PPCPs (unlike conventional industrial/agrochemical pollutants) are generally much less volatile, they tend to end up in aquatic environments. Since those that are introduced to the environment (some are completely degraded metabolically and never enter or leave sewage treatment plants), they are continually replenished. This means that aquatic organisms can suffer continual life-long exposures (albeit to very low concentrations, e.g., parts-per-billion or parts-per-trillion -- [see explanation of measurement terminology](#)). Human exposure, in contrast, would come mainly from drinking water, which is usually further treated to remove pollutants after it is taken from surface or ground water. Drinking water, consequently, contains even lower concentrations. Regardless of whether trace levels of PPCPs in drinking water pose any human health concern, a number of interesting problems can arise as a result of how risk is perceived. The issues surrounding how risk is communicated and perceived with regard to the reuse and recycling of water are discussed in [an article published in Ground Water Monitoring and Remediation](#) [PDF, 13 pp., 562 KB].



- **Can pharmaceuticals be monitored and why aren't they regulated?** There are several factors that make PPCP analysis difficult. The major factors are the very low (trace) concentrations, the numerous chemical interferences in environmental samples, the different chemical nature of PPCPs compared with the "conventional" pollutants, and the confounding issues of "non-target analysis" [see further discussion at: "[The Critical Role of Analytical Chemistry](#)"]. Trace analysis involves time-consuming sample "cleanup," and "pre-concentration" or "enrichment" of the pollutant (analyte), so that the analyte can be detected apart from the interferences and the detection limit of the instrumentation (frequently mass spectrometry) can be met. In general, the chemistry analysis techniques required for PPCPs are more advanced than for the "conventional" pollutants. The more polar nature of PPCPs requires the use of non-standard instrumentation that is not as commonly available to non-research laboratories and requires additional skill to use. Finally, the plethora of possible PPCPs that could be in the environment means that a monitoring program would have to target certain ones - and the potential for ecological and human health effects is just not sufficiently understood for the many hundreds of PPCPs that are used commercially. See discussion regarding [analytical chemistry](#). NERL-Las Vegas continues to develop new approaches to identification of "non-target" pollutants with [high-resolution mass spectrometry](#).
- The largest target-based monitoring study ever conducted, was published in March 2002 by the USGS when they released data from its ongoing, nation-wide water monitoring program. This is the most comprehensive water quality monitoring program in the U.S. This particular data set comes from the first phase of targeted PPCP [monitoring in natural waters](#). See: Environmental Science & Technology (by Britt Erickson, 1 April 2002, pp. 140A-145A) "[Analyzing the Ignored Environmental Contaminants](#)" [PDF, 400 KB] http://pubs.acs.org/subscribe/journals/esthag-w/2002/mar/science/be_usgs.html
- With respect to the possibility for future regulation of PPCPs in the environment, little has been written in the legal literature. Perhaps one of the first attempts to expose the legal profession to the topic was a three-part series of articles published in the California Water Law & Policy Reporter: Huizar, Jose "[Unintended Consequences: The Effects of Pharmaceuticals in the Water Supplies—Part I](#)," [PDF, 26 KB] California Water Law & Policy Reporter, December 2000, vol. 11, 72-73. [subscription available: www.Argentco.com] Huizar, Jose "[Part II—Pharmaceuticals in the Water Supplies: Regulations and Works-in-Progress](#)," [PDF, 29 KB] California Water Law & Policy Reporter, January 2001, vol. 11, 95-97. [subscription available: www.Argentco.com] Huizar, Jose "[Part III—Pharmaceuticals in the Water Supplies](#)," [PDF, 24 KB] California Water Law & Policy Reporter, February 2001, vol. 11, 129-130. [subscription available: www.Argentco.com] This series of articles was followed by more extensive examinations by: Campbell, Holly V. "Pharmaceuticals in the Environment: Regulatory and Nonregulatory Approaches," [PDF, 148 KB] Environmental Law Reporter, Environmental Law Institute, October, 2002, 32 ELR 11200-11211 (subscription available: <http://www.eli.org>). Nidel, C.T. "Regulating the Fate of Pharmaceutical Drugs: A New Prescription for the Environment," Food and Drug Law Journal 2003, 58:81-102 (available: http://www.fdi.org/pubs/Journal%20Online/jour_toc/vol58_1.html#7). Electronic reprints can be obtained from [Christopher Nidel](#).
- Finally, it is important to not be misled by the appearance that current regulatory monitoring efforts fail to report PPCPs in the environment or in STP effluents. First, routine monitoring does not target any PPCP, and even if the collected data were examined for PPCPs, few would be found because the analytical methodologies that are used are generally inappropriate for (i) recovering these compounds from samples (e.g., via solvent extraction) or (ii) detecting them via gas chromatography – because of their usually higher polarity than conventional pollutants. With respect to regulation, there simply is not sufficient evidence to warrant regulation; certain representative PPCPs, however, might prove appropriate to eventually add to the EPA Office of Water's Drinking Water Contaminant Candidate List (CCL: <http://www.epa.gov/safewater/ccl/ccdfs.html>) under the EPA's "Unregulated Contaminant Monitoring Rule" (see: <http://www.epa.gov/safewater/ucmr.html>); also see the 2001 NRC publication "Classifying Drinking Water Contaminants for Regulatory Consideration," available at: <http://www.nap.edu/catalog/10080.html>. The European Union and the U.S. FDA have guidance for environmental assessments of new pharmaceuticals (esp. veterinary pharmaceuticals; e.g., see: U.S. FDA CVM (Center for Veterinary Medicine) "Environmental Assessments (EAs), Findings of No Significant Impact (FONSI), and Environmental Impact Statements," <http://www.fda.gov/cvm/efoi/ea/ea.htm>). It is debatable, however, whether the conventional toxicological procedures that are employed in these ecotoxicology assessments can screen for the types of subtle effects that might occur from low-level aquatic exposures.
- The absence of any nationwide requirement for monitoring PPCPs in various waters does not mean that individual states are not pursuing their own requirements or guidance. As an example, in 2002, California proposed language requiring monitoring for the occurrence of drugs in water intended for groundwater recharge. See: "CA DHS Groundwater Recharge Reuse DRAFT Regulations 8-2-02" <http://www.dhs.ca.gov/ps/dwem/publications/waterrecycling/recycledraftreg8-2-02.PDF>: [PDF, 54 KB] "Section 60320.040. Control of Nonregulated Contaminants." "(g) The GRRP shall conduct the following monitoring and report any positive results to the Department and the RWQCB in the next monthly report."
"(2) Each year, the GRRP shall monitor the recycled water for endocrine disrupting chemicals and pharmaceuticals specified by the Department, based on a review of the GRRP engineering report and the affected groundwater basin(s)."
- One area of environmental concern receiving renewed attention with respect to the potential for regulation is that of land application of sewage [biosolids](#). [PDF, size not available, 81 pp.] The National Research Council published a report (commissioned by the EPA) in July 2002 that reassesses the environmental disposition of sewage biosolids: "Biosolids Applied to Land: Advancing Standards and Practices," Committee on Toxicants and Pathogens in Biosolids Applied to Land, National Research Council, 2002 (<http://www.nap.edu/books/0309084865/html/>). Some of the findings and highlights of this report that pertain to PPCPs include the following: (i) Pharmaceuticals and musks are mentioned repeatedly, in Chapter 5 ("Evaluation of EPA's Approach to Setting Chemical Standards"). (ii) The NRC Committee recommends that a new national survey be considered of chemicals in sewage sludge. PPCPs were highlighted as one class that was not considered in EPA's prior 1993 survey. (iii) The NRC recommends that another chemical selection process be conducted to determine which additional chemicals should be considered for regulation. (iv) In reconsidering the [EPA's Part 503 Biosolids Rule](#), the EPA should consider toxic end points (and chemical interactions) that were not considered in the original assessment. (v) Page 183 states: "Two categories of chemicals deserving special attention are pharmaceuticals and odorants" (e.g., synthetic musks). "Considering the amounts discharged to sewage systems, the presence of pharmaceuticals in biosolids has not been adequately investigated." "For odorants, the need for further evaluation is driven by the high level of public concern, as well as very limited characterization of the odorants present in biosolids and their toxicity." (vi) The NRC recommends: "...that a research program be developed for pharmaceuticals and other



- **How should unwanted/unneeded medications be disposed?**

- Drugs enter the environment by a number of [routes](#). The two general means by which they gain entry are by excretion and disposal. Disposal of drugs that are no longer needed or wanted occurs by discarding to trash (which in turn goes to landfills) and by directly discarding to sewage systems (usually via the toilet). Although the long-accepted means of disposing to sewage by flushing down toilets maximizes the ability of a drug to enter the environment, the rationale behind this approach is to minimize the chances of consumption by others for whom the drug was not intended; poisoning of adults and children by medications discarded by others is a problem of increasing concern to physicians. Unfortunately, there are no widely available alternative means for drug disposal. These other means are also fraught by a number of problems. Drug disposal is a deceptively complex topic. The many issues and dimensions surrounding drug disposal (and pollution prevention) are covered in a 2-part monograph: [Part I](#) [PDF, 18 pp., 482 KB] and [Part II](#) [PDF, 11 pp., 151 KB]. A wide spectrum of associated documents and resources covering drug disposal and pollution prevention [are available here](#). Note in particular the following reference:

Pharmacist's Letter, April 2004, Vol 20 No 4 "[Drug Disposal](#)" [PDF, 5 pp., 296 KB] page 24.

Therapeutic Research Center, Stockton CA. www.pharmacistsletter.com Regardless of whether an optimal approach to drug disposal can be developed - - one that is protective of both the environment and human health and safety - - it is important to keep in mind that the question as to what fraction of drugs in the environment emanates from direct disposal versus excretion is currently not answerable. This question is highlighted as a research need in Part II of the Green Pharmacy monograph (see lower right corner of page 777: "[Determining the relative importance of sources](#)" [PDF, 11 pp., 151 KB]). Indeed very little information has been published on this aspect of drug origins in the environment (see discussion in lower right corner of page 780: "[Sparse literature](#)" [PDF, 11 pp., 151 KB]). Finally, drug disposal is part of the larger issue of environmental stewardship and pollution prevention. An overview of PPCP environmental stewardship can be found [here](#). Two significant events (prior to 2005) relevant to large-scale take-back programs for unwanted drugs in the U.S. were the creation of the first legislated state-wide returns program ([see links to the State of Maine's "Unused Pharmaceutical Disposal Program"](#)) and the creation of the first drug-returns "registry" in the U.S. ([see link to "U.S. National Registry for Unused and Expired Medications"](#)) for the collection of data from returned drugs; the data obtained by the returns registry could prove very valuable in providing insights both for modifying prescribing practices (to improve patient safety and health) and for managing environmental impacts. The many questions associated with the disposal of drugs often raise some of the very same questions for personal care products (sometimes referred to in the literature as "[PCPs](#)"). Personal care products are analogous to pharmaceuticals in that their intended end-use can distribute to the environment the [ingredients that compose their formulations](#), as well as the chemicals contained by their packaging. But unlike most drugs, this occurs primarily not by excretion, but rather by washing the product from skin, hair, and mouth, where its ingredients (both active and inactive ingredients) can then enter the environment via the pathway of sewerage. Packaging used for personal care products, which is usually much more elaborate than for drugs, is discarded to trash where it can eventually weather, with the resulting release of additional chemicals from the combined actions of microbial degradation (especially fungal), UV photolysis, physical deterioration (e.g., action of heat), and chemical processes (e.g., solvolysis by water). With regard to environmental ramifications, PCPs (such as cosmetics) differ from pharmaceuticals in three major respects: (1) the design of the packaging discourages disposal of the contents to sewage (because of the added difficulty of emptying package contents), (2) the "active" ingredients in PCPs are usually not engineered or designed to interact with biological receptors that regulate essential cellular functions, and (3) PCPs are used almost exclusively external to the body. When applied to skin or the mouth, however, those chemicals in PCPs that are lipophilic are subject to absorption through the skin or mucosal membranes (e.g., parabens, phthalates, UV screens, and [synthetic musks](#)). One of the paradoxes of consumer risk perception relates to the relatively high concentrations and types of a plethora of [chemicals formulated in personal care products](#) applied directly to the skin, versus the concentrations of some of these same chemicals that might be found in drinking water at many orders of magnitude lower concentrations; the former is often deemed risk-free but the latter not. Unlike pharmaceuticals, mainly as a result of the packaging design and the way in which they are used, the DISPOSAL of unused or unwanted PCPs (e.g., cosmetics, shampoos) to sewage has not been a concern with regard to the potential for environmental pollution. With this said, the ingredients comprising PCPs (both the active ingredients and the so-called "inactive" ingredients) are used in much larger quantities in end-user commercial products than are pharmaceuticals. These active ingredients and even some of the inactive ingredients used in product formulation pose the potential for exposure to aquatic organisms (from residues discharged by sewage) and to terrestrial animals (by scavengers foraging in municipal refuse). Substantial, sustained exposures pose unknown risks (e.g., subtle effects such as behavioral change) for certain organisms, especially those that are subject to continual exposure, such as aquatic organisms; this is especially true for lipophilic compounds that can bioconcentrate. With regard to the disposition of PCPs in the environment, the principles that could guide the creation of products that are most environmentally friendly would be those that fall under the stewardship concept of "[cradle-to cradle design](#)." These principles apply not just to the ingredients used in formulating these products, but also to the design and composition of the packaging. For example, the types and amounts of materials used in manufacturing the packaging itself could be selected for minimal environmental impact (whether that be the sheer volume of packaging added to landfills, or the chemicals released by weathering, or by combustion of refuse packaging). At the same time, the packaging can be designed to maximize the consumer's ability to use the contents to the fullest extent possible, ensuring that the ingredients are directed to sewage treatment facilities (e.g., during bathing) where they can be degraded, rather than partially empty containers to landfills.

- **Can the occurrence of PPCPs in the environment be capitalized on for other purposes?**

- The fact that PPCPs occur in the environment as a result of human consumption and disposal affords a number of "benefits" that allow these pollutants to be used as "tools" for accomplishing collateral objectives. The occurrence of PPCPs in surface and ground waters can be used as sentinels of sewage intrusion, hydrologic tracers, as a social science "tool," and for geologic "dating." These topics are discussed at the web page: "[Use of PPCPs in the Environment as Analytical Tools](#)"

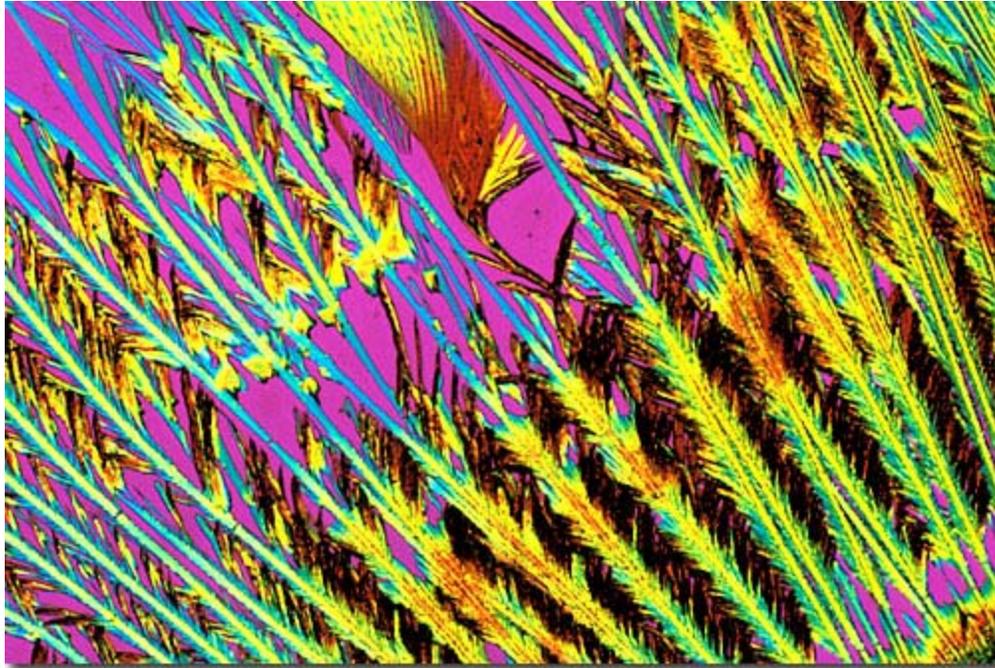


■ Caffeine



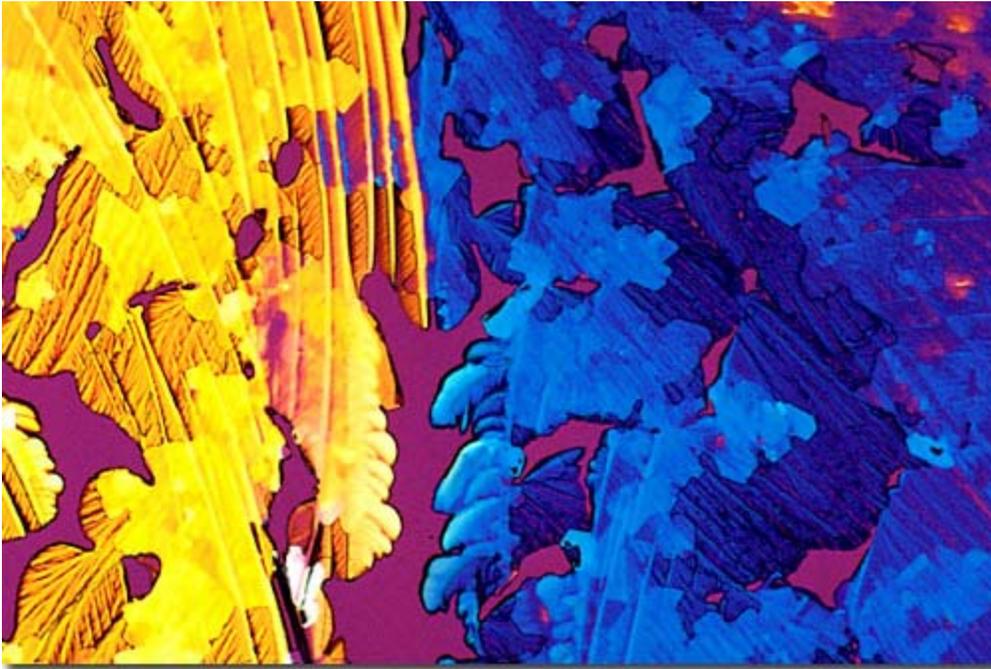


■ Fluoxetine (Prozac)



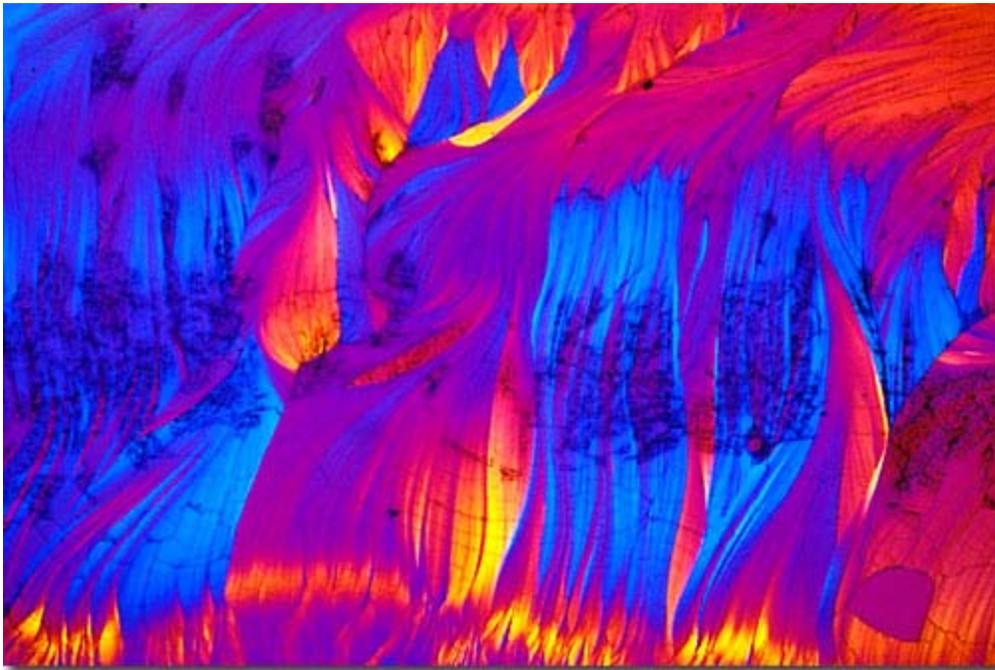


■ Ibuprofen



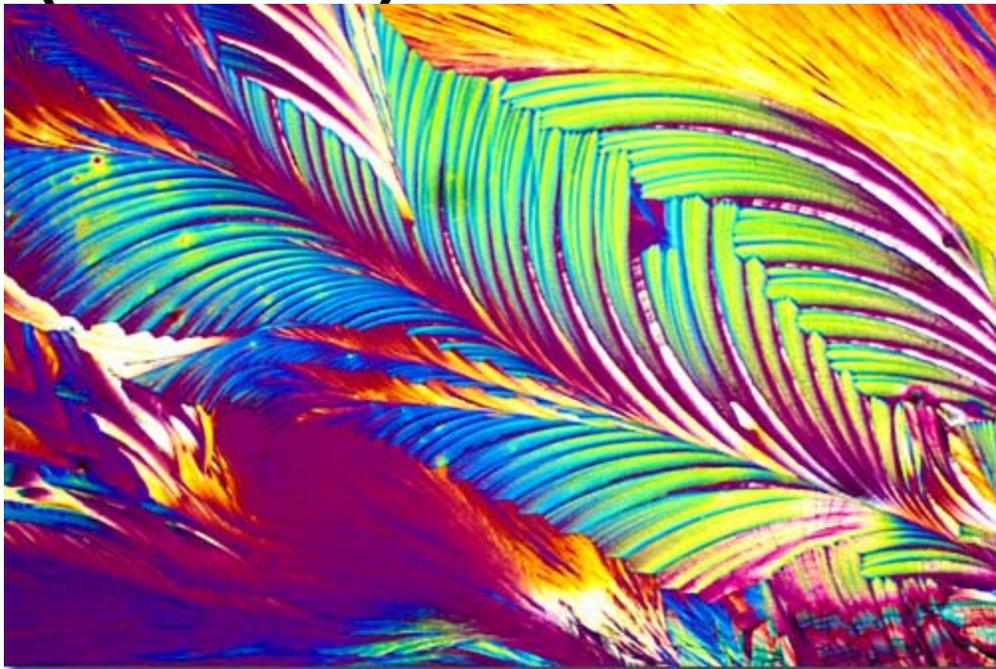


■ Phenytoin (Dilantin)



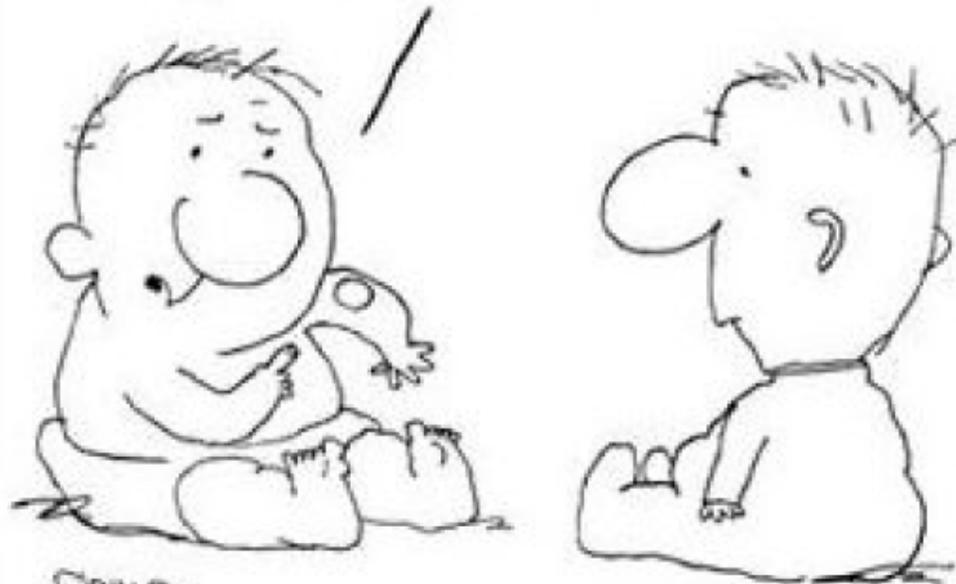


- **Sulfamethoxazole and Trimethoprim
(Bactrim)**





I'M ON THE
PACIFIER PATCH.



Green
MS ©



"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."

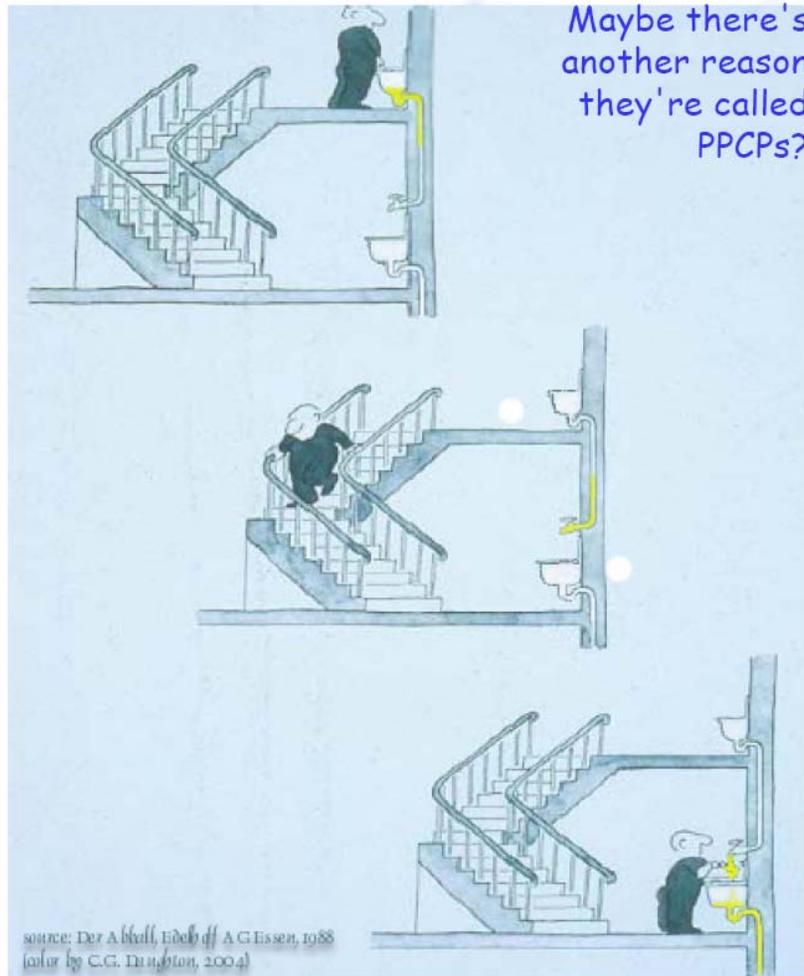


Decline of *Gyps* spp. Vultures in Pakistan & India – Possible Link with Diclofenac

- 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.



An advertisement for Outhouse Springs. On the left is a wooden outhouse with a chimney and a crescent moon cutout. The background is a green and yellow swirl. The text reads "It's #1 Not #2" in a handwritten style. Below that, it says "OUTHOUSE SPRINGS". On the right is a bottle of Outhouse Springs with a label that says "Outhouse Springs" and "TRULY TASTEFUL WATER".

It's #1
Not #2

OUTHOUSE SPRINGS

Outhouse Springs
TRULY TASTEFUL WATER



Pharmaceuticals and Personal Care Products

- **Oriental white-backed vulture, *Gyps bengalensis*** Asia; India, Pakistan, Nepal
- **FACT:** Certain PPCPs occur in the environment, especially the aquatic environment
- **ORIGINS:** Domestic sewage, hospitals, CAFOs
- **ISSUE:** Fate and effects are poorly understood





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 actions (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 (No Observable Effects). Paradoxical “U-shaped” dose-response curves.
4. Dynamic Dose-Response. **Toxicant-Induced Loss of Tolerance (TILT)**: initial exposure sensitizes, and subsequent exposures to levels below those previously tolerated trigger symptoms.
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
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.

Excerpted from Daughton, 2005



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

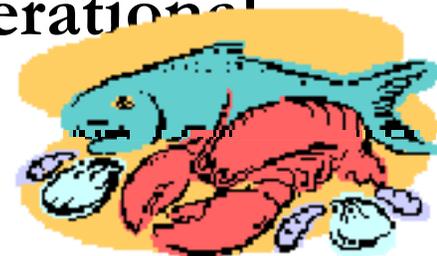
- Important to recognize that **ALL** municipal sewage, regardless of location, will contain PPCPs. Issue is not unique to any particular municipal area.
- Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs.





Aquatic Organisms are Captive to Continual, Life-Cycle Chemical Exposures

- **Aquatic Exposure is Key:**
 - Any chemical introduced by sewage to aquatic realm can lead to continual multigenerational exposure for aquatic organisms.
- **Re-evaluation of “Persistence:”**
 - Chemicals continually infused to the aquatic environmental essentially become “persistent” pollutants even if their half-lives are short- their supply is continually replenished. These can be referred to as *pseudo-persistent chemicals (P2s)*.





Bioconcentration: A New Paradigm?

- High molecular polarity (low octanol-water partition coefficients) would seem to preclude bioconcentration for most PPCPs, **BUT**,
 - Examples of those subject to bioconcentration include: synthetic musks, sunscreen filters, parabens, triclosan, triclocarban.
- But certain drugs despite low lipid solubilities are being detected in aquatic tissues in concentrations higher than those in the ambient water. Because *drugs designed to gain intracellular access via active transport...?*
 - Examples: estrogens (conc. fish bile 60,000 X), gemfibrozil (conc. fish tissue 113 X), diclofenac (conc. in fish) fluoxetine (conc. in muscle, liver and brain of fish)



Subtle, Difficult-to-Detect Effects: *some examples*

- Profound effects on the 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 (regulate blood pressure, etc.)**
- **Antiepileptic drugs** (phenytoin, valproate, carbamazepine) have potential as neuroteratogens, triggering neurodegeneration
- ppm and sub-ppm levels of various drugs [**NSAIDS, glucocorticoids (steroid hormones), anti-fibrotics**] affect collagen metabolism in bony fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps - proteins) are common defensive strategies for aquatic biota – possible significance of **efflux pump inhibitors** (reduce resistance esp. to antibiotics) in compromising aquatic health?



Questions Deserving Attention...

- Low PPCP concentrations in the environment. **Is there cause for concern regarding impact to non-target organisms?**
- Potential effects of PPCPs on non-target species, many of which **do not possess the same suite of receptors as humans**
- Individual PPCPs at low concentrations – **Can multiple PPCPs sharing the same mode of action combine to reach threshold-effects levels?**

continued



Questions Deserving Attention...

- PPCPs that are continually introduced to aquatic environment – **Is this a special exposure case since biota are exposed continually, through multiple generations?**
- Cellular mechanisms in aquatic biota that confer protection from continual exposure (e.g. efflux pumps) - **Can these protective cellular transport systems be inhibited by certain PPCPs, thereby compromising aquatic health?**
- Acute toxicity, carcinogenesis, and mammalian endocrine disruption are highly visible concerns for many environmental pollutants – **Should more attention be paid to other, less overt toxicological endpoints, such as immuno-disruption, neurobehavioral change, and other subtle effects?**

continued



Questions Deserving Attention...

- Practices partly contributing to introduction of PPCPs to the environment include direct disposal of excess/expired PPCPs to domestic sewage and landfills, and over-prescribing of various drugs – **Should these practices be discouraged?**
- Low levels of PPCPs in drinking water, fish, and shellfish – **Can consumption by humans lead to significant exposures?**
- Antibiotic and hormone use in domestic livestock and poultry - **Role of CAFOs?**

concluded



The End

