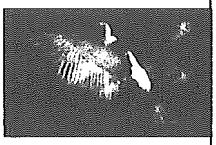
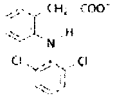
Decline of *Gyps* spp. Vultures in Pakistan & India – Possible Link with Diclofenac



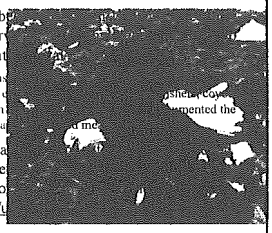
- Beginning in the early 1990s, vultures (especially white-backed vultures such as *Gyps bengalensis*) have experienced dramatic population declines (as great as 95%) in Southern Asia – particularly India and spreading to Pakistan and Nepal.
- Various hypothesized causes have ranged from pathogens to pesticides. The causative agent(s) result in acute renal failure (manifested as visceral gout from accumulation of uric acid), leading to death of the breeding population.
- Prof. J. Lindsay Oaks (Washington State University) et al. present evidence that (at least in Pakistan) the die-offs are strongly linked with diclofenac poisoning ("Diclofenac Residues as the Cause of Vulture Population Decline in Pakistan," *Nature*, 28 January 2004).
- Diclofenac, although primarily a human NSAID, is used in veterinary medicine in certain countries. In India, diclofenac is used for cattle, whose carcasses are a major food source for *Gyps*.



- Diclofenac seems to be selectively toxic to *Gyps* spp. versus other carrion-eating raptors.
- Health hazards grow from the accumulation of uneaten cattle carcasses (as well as human), which now serve to attract growing packs of dangerous feral dogs, which can also carry rabies. As of 2005, India will phase-out the veterinary use of diclofenac.

Animal Euthanasia and Secondary Poisoning of Wildlife

- Various drugs are used to euthanize domestic pets and other animals.
- The principle drug is pentobarbital. High doses are used. Most of the body-burden residue escapes excretion and persists indefinitely. The carcass, if not disposed of according to local regulations, can be consumed by scavenger wildlife. But determined wildlife can even uncover well-buried carcasses.
- Wildlife pentobarbital poisonings have b… mid-1980s. The U.S. Fish and Wildlife Ser… bald and golden eagles as casualties of pent…
- Wildlife vulnerable to accidental pentobarbital pois… euthanasia) include a wide range of birds (especially … lynx, bobcats, cougars, and otters. Domestic dogs can … deaths of tigers, cougars and lions that were accidenta…
- In July 2003, the FDA's CVM required a… to animal euthanasia products ["Environme… Euthanasia Products," U.S. FDA, Center fo… July 2003: http://www.fda.gov/cvm/index/u…

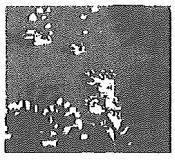


Personal Care Products as Exposure Sources for Conventional Pollutants

- Ayurveda and folk remedies (e.g., litargirio, or litharge): **lead (Pb)** and other metals (upwards of 80% by weight)
- Dermal products: **phthalates** (esp. diethyl and dibutyl), **solvents, dyes, parabens** (4-hydroxybenzoic acid alkyl esters)
- Lice and tick control shampoos: **lindane** and **permethrins**
- Shampoos and soaps: **alkylphenolic surfactants**

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

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



Aquatic organisms — captive to continual, life-cycle chemical exposures

➢ Aquatic Exposure is Key: Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.

➢ Re-evaluation of "Persistence": Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat). These can be referred to as ***pseudo-persistent*** **chemicals (P2's).**

Bioconcentration: New Paradigm ?

➢ Low octanol-water partition coefficients (high polarity) would seem to preclude bioconcentration for most PPCPs.

Examples of those subject to bioconcentration include: synthetic musks, sunscreen filters, parabens, triclosan, triclocarban.

➢ But certain drugs, despite their low lipid solubilities, are being detected in aquatic tissues in concentrations enriched from those in the ambient water. This is perhaps partly a result of drugs being designed to take advantage of gaining intracellular access via active transport :

Examples:

estrogens (concentrated in fish bile 60,000 X)
gemfibrozil (concentrated in fish tissue, 113 X)
diclofenac (concentrated in fish)
fluoxetine (concentrated in muscle, liver, and brain of fish)

Potential for Subtle Effects?

continued >

Potential for Subtle (currently unrecognized) Effects?

➢ Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time? For example, latent damage, only surfacing later in life. The issue of "resiliency".

➢ Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause?

➢ Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological) — e.g., subtle shifts in behavior or intelligence.

➢ Advances required in developing/implementing new aquatic toxicity tests to better ensure that such effects can be detected.

continued >

Subtle, Difficult-to-Detect Effects:

some examples

- Profound effects on development, spawning, and wide array of other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants (ppb levels).
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of efflux pump inhibitors in compromising aquatic health?

Peeking at the Future

Critical Importance of *Futuring* & *Anticipatory Research*

- Important to design and implement a range of mechanisms for providing insight as to those types of pollutants and sources that could emerge in the future.
- Pollution Prevention and Stewardship programs can be less costly than remediation (Precautionary Principle), pollutant "musical chairs" (pollutant diversion), or "pollution postponement" (storage such as in landfills).

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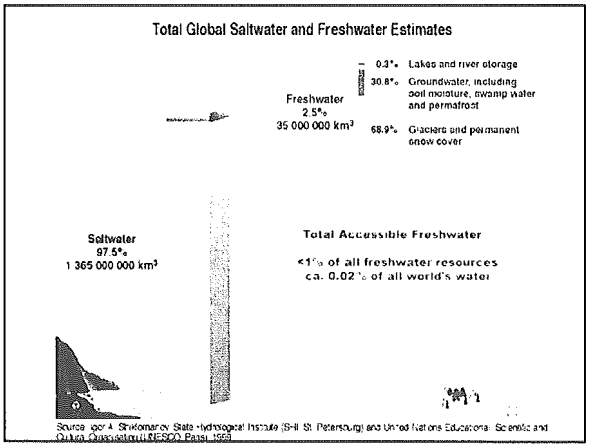
The World's Accessible Freshwater Resources



Critical Importance of Forging Better Linkages between Science and the Public

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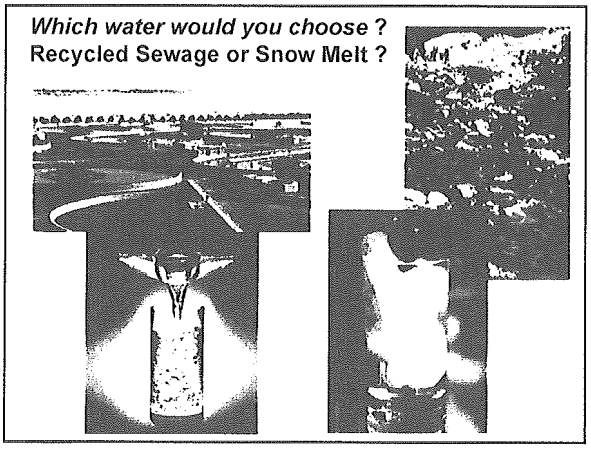

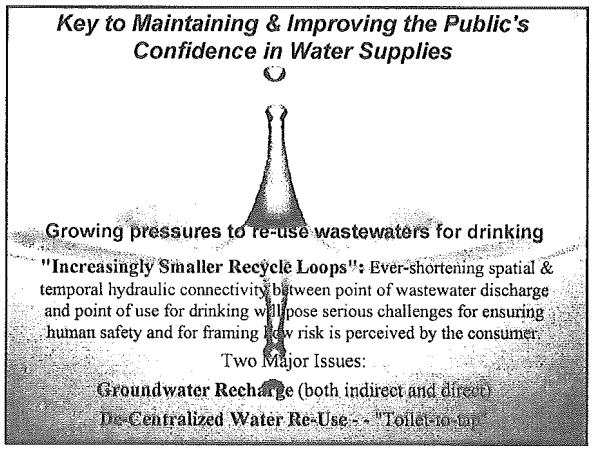

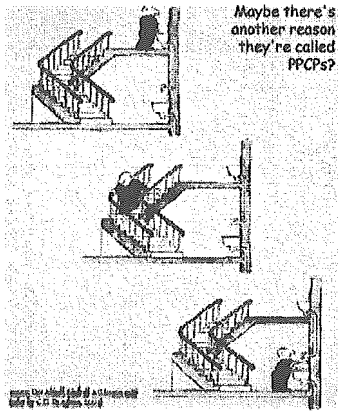

Key Role of Beliefs in Public Acceptance of Recycled Water

- Historically, some water re-use projects have become "branded" with negative images by consumers.
- Negative images cannot necessarily be erased or corrected by more or even better science. In fact, studies show that additional supportive data often serves to exacerbate already-formed negative images.
- Instead, we must involve social psychologists to bridge the communications gap between science and the public.
- The "yuck factor" associated with so-called "toilet-to-tap" programs, for example, derives from beliefs that have long been imbedded in social belief constructs, and these beliefs are refractory to being influenced by positive findings of science.

continued >

Risk Communication and Water Re-Use

An examination in new light of the problems with communicating risk, especially with regard to groundwater injection and water reuse:

Daughton C.G. "Groundwater Recharge and Chemical Contaminants: Challenges in Communicating the Connections and Collisions of Two Disparate Worlds," In Fate and Transport of Pharmaceuticals and Endocrine Disrupting Compounds (EDCs) During Ground Water Recharge (special issue), *Ground Water Monitoring & Remediation*, **2004**, 24(2): 127-138.

http://www.epa.gov/nerlesd1/chemistry/ppcp/images/water-reuse.pdf

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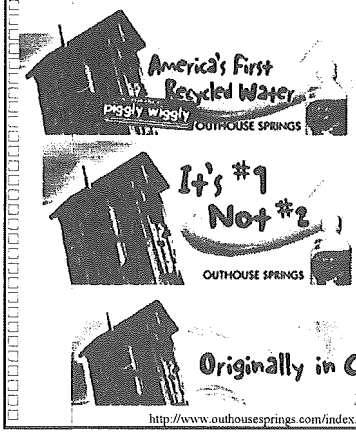


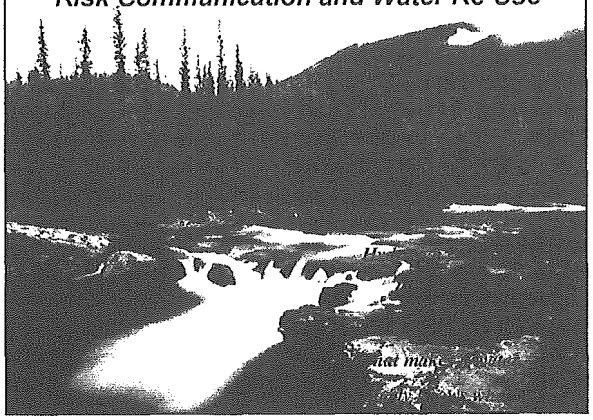
Real-world lesson in communicating:

***Outhouse Springs* Bottled Water**

Experiment by: *Adams Outdoor Advertising*, South Carolina, 2002

concluded

Risk Communication and Water Re-Use



Questions

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prepared: 8 August 2005

Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?

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During the last three decades, the impact of chemical pollution has focused almost exclusively on the conventional "priority" pollutants, especially those acutely toxic/carcinogenic pesticides and industrial intermediates displaying persistence in the environment. This spectrum of chemicals, however, is only one piece of the larger puzzle in "holistic" risk assessment. Another diverse group of bioactive chemicals receiving comparatively little attention as potential environmental pollutants includes the pharmaceuticals and active ingredients in personal care products (in this review collectively termed PPCPs), both human and veterinary, including not just prescription drugs and biologics, but also diagnostic agents, "nutraceuticals," fragrances, sun-screen agents, and numerous others. These compounds and their bioactive metabolites can be continually introduced to the aquatic environment as complex mixtures via a number of routes but primarily by both untreated and treated sewage. Aquatic pollution is particularly troublesome because aquatic organisms are captive to continual life-cycle, multigenerational exposure. The possibility for continual but undetectable or unnoticed effects on aquatic organisms is particularly worrisome because effects could accumulate so slowly that major change goes undetected until the cumulative level of these effects finally cascades to irreversible change—change that would otherwise be attributed to natural adaptation or ecologic succession. As opposed to the conventional, persistent priority pollutants, PPCPs need not be persistent if they are continually introduced to surface waters, even at low parts-per-trillion/parts-per-billion concentrations (ng-µg/L). Even though some PPCPs are extremely persistent and introduced to the environment in very high quantities and perhaps have already gained ubiquity worldwide, others could act as if they were persistent, simply because their continual infusion into the aquatic environment serves to sustain perpetual life-cycle exposures for aquatic organisms. This review attempts to synthesize the literature on environmental origin, distribution/occurrence, and effects and to catalyze a more focused discussion in the environmental science community. *Key words*: aquatic, drugs, ecologic health, ecologic risk assessment, emerging risk, pharmaceuticals, pollution, sewage. — *Environ Health Perspect* 107(suppl 6):907–938 (1999).
http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/907-938daughton/abstract.html

Summary

Risks associated with previously unknown, unrecognized, unanticipated, or unsuspected chemical pollutants in the environment have long been a major concern of environmental scientists. The importance of identifying such emerging risks is reflected in one of the top five goals of the Strategic Plan 2000 for the U.S. Environmental Protection Agency's (U.S. EPA) Office of Research and Development. Early identification and investigation of potential environmental pollution issues before they worsen are critical for protecting ecologic and human health. It is also important to rule out issues that could be of concern but prove otherwise, so that limited resources can be redirected. Ecosystem change is effected by human activities primarily via three routes: habitat fragmentation, alteration of community structure (e.g., via nonindigenous species), and chemical pollution. The scope of the former two is highly delineated and obvious compared with the latter. During the last three decades, the impact of chemical pollution has focused almost exclusively on the conventional "priority" pollutants. This group of chemicals, however, is only one piece of the larger puzzle.

One large class of chemicals receiving comparatively little attention comprises the pharmaceuticals and active ingredients in personal care products (PPCPs), which are used in large amounts throughout the world; quantities of many are on par with agrochemicals. Escalating introduction to the marketplace of new pharmaceuticals is adding exponentially to the already large array of chemical classes, each with distinct modes of biochemical action, many of which are poorly understood. In contrast to agrochemicals, most of these products are disposed or discharged into the environment on a continual basis via domestic/industrial sewage systems and wet-weather runoff. The bioactive ingredients are first subjected to metabolism by the dosed user; the excreted metabolites and unaltered parent compounds can then be subjected to further transformations in sewage treatment facilities. The literature shows, however, that many of these compounds survive biodegradation, eventually being discharged into receiving waters; metabolic conjugates can even be converted back to their free parent forms. Many of these PPCPs and their metabolites are ubiquitous and display persistence in, and bioconcentration from, surface waters on par with those of the widely recognized organochlorine pollutants. Additionally, by way of continual infusion into the aquatic environment, those PPCPs that might have low persistence can display the same exposure potential as truly persistent pollutants since their transformation/removal rates can be compensated by their replacement rates.

Although certain biochemical actions of many drugs in humans have been elucidated, these actions are not necessarily always the ones responsible for the purported physiologic target effects. Sometimes the known pathways of action may have nothing to do with the actual desired effect, as the actual mechanism remains totally unknown. Understanding of the complex biochemical signaling pathways is currently too limited to design drugs that act only via targeted routes, and even then, if their activity can be limited to a single type of receptor, the tissue distribution of the receptor may not be fully known. Unpredicted and unknown side effects are often the norm. The possible actions and biochemical ramifications on nontarget aquatic biota are even less understood; many are totally unknown. The few that are known to elicit subtle but dramatic effects on aquatic life at very low concentrations, however, may point to an ill-defined vulnerability in aquatic ecosystems. A major concern is not necessarily acute effects to

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nontarget species (effects amenable to monitoring once they are understood), but rather the manifestation of perhaps imperceptible effects that can accumulate over time to ultimately yield truly profound changes—those whose causes would be obscured by time and that would not be distinguishable from natural events. The specter of subtle, cumulative effects could reduce the usefulness of current toxicity-directed screening methods in testing waste effluents for toxicologic end points due to PPCPs. Subtle effects, from low concentrations of bioactive PPCPs, whose continual expression over long periods of time in certain nontarget populations, could lead to cumulative, insidious, adverse impacts that would otherwise be attributed to natural change/adaptation or ecologic succession—any "signal" would be lost among the noise. Current comprehensive environmental risk assessments and epidemiologic studies do not factor in exposures/body burdens from PPCPs and therefore may be flawed by over simplicity.

It is useful to note that the data reported and evaluated in this review reflect the diverse and uneven nature of the PPCP literature published for source/origin, occurrence, distribution, transport, transformation, ecologic exposure and effects, risk assessment, and test strategies. The comprehensiveness of the published literature in each of these areas and across the broad spectrum of PPCP classes is very unequal. This review therefore does not present an exhaustive and rounded view of this emerging topic but rather summarizes most of the significant papers in an integrated, comprehensive manner, and thereby elucidates many of the questions that still need to be addressed by the environmental science community. This review aims to catalyze a discussion on the potential importance of PPCPs in the environment and presents recommendations for focusing further research (Table 1).

Introduction

For the purposes of this discussion, pharmaceutical (and veterinary and illicit) drugs (and the ingredients in cosmetics, food supplements, and other personal care products), together with their respective metabolites and transformation products, will collectively be referred to as pharmaceuticals and personal care products. PPCPs are continually infused into the environment via sewage treatment facilities and wet weather runoff. In many instances, untreated sewage is discharged into receiving waters (e.g., flood overload events, domestic "straight-piping," or sewage waters lacking municipal treatment). In the United States alone, possibly more than a million homes do not have sewage systems but instead rely on direct discharge of raw sewage into streams by straight-piping or by outhouses not connected to leach fields (*1*). A number of Canadian cities are reported to discharge 3.25 billion liters per day (over 1 trillion liters per year) of essentially untreated sewage into surface waters and the ocean (*2*). Raw/treated sewage is also disposed of from some locales in the deep ocean where it may possibly remix with upper waters.

We hope that this overview of PPCPs in the environment will *a*) catalyze a concerted effort among environmental chemists and ecotoxicologists to survey sewage treatment effluents, surface waters/groundwaters, and potable water for the presence of PPCPs and their bioactive transformation products and to determine their origins; *b*) elucidate the spectrum of possible physiologic effects of PPCPs on nontarget species, especially those that are aquatic; and *c*) promote discussion of whether this is an environmental issue deserving further investigation. We believe that a scientific debate on this topic is warranted given the evidence that has been accumulating over the last two decades on the occurrence of various pharmaceuticals in sewage effluent and in both surface waters and groundwaters. The big unknown is whether the combined low concentrations from each of the numerous PPCPs and their transformation products have any significance with respect to ecologic function, while recognizing that immediate effects could escape detection if they are subtle and that long-term cumulative consequences could be insidious. Another question is whether the pharmaceuticals remaining in water used for domestic purposes poses long-term risks for human health after lifetime ingestion via potable waters multiple times a day of very low, subtherapeutic doses of numerous pharmaceuticals; this issue, however, is not addressed in this review.

The hypothesis is further complicated by the fact that while the concentration of individual drugs in the aquatic environment could be low (sub-parts per billion or sub-nanomolar, often referred to as micropollutants), the presence of numerous drugs sharing a specific mode of action could lead to significant effects through additive exposures. It is also significant that drugs, unlike pesticides, have not been subjected to the same scrutiny regarding possible adverse environmental effects. They have therefore enjoyed several decades of unrestricted discharge to the environment, mainly via sewage treatment works. This is surprising especially since certain pharmaceuticals are designed to modulate endocrine and immune systems and cellular signal transduction and as such (as opposed to pesticides and other industrial chemicals already undergoing scrutiny as endocrine disruptors) have obvious potential as endocrine disruptors in the environment. Exposure to PPCPs in the environment, especially for aquatic organisms, may differ from that of pesticides and other industrial chemicals in one significant respect—exposures may be of a more chronic nature because PPCPs are constantly infused into the environment wherever humans live or visit, whereas pesticide fluxes are more sporadic and have greater spatial heterogeneity. It is quite apparent that little information exists from which to construct comprehensive risk assessments for the vast majority of PPCPs having the potential to enter the environment.

Although little is known of the occurrence and effects of pharmaceuticals in the environment, more data exist for antibiotics than for any other therapeutic class. This is a result of their extensive use in both human therapy and animal husbandry, their more easily detected effects end points (e.g., via microbial and immunoassays), and their greater chances of introduction into the environment, not just by sewage treatment plants, but also by run-off and groundwater contamination, especially from confined animal feeding operations (CAFOs). The literature on antibiotics is much more developed because of the obvious issues of direct effects on native microbiota (and consequent alteration of microbial community structure) and development of resistance in potential human pathogens. Because of the considerably larger literature on antibiotics, this review only touches on the issue; for the same reason, this discussion only touches on steroidal drugs (those purposefully designed to modulate endocrine systems).

For the purposes of this document, pharmaceuticals will refer to nonbiologic drugs (i.e., those that do not comprise proteinaceous or nucleotide material). The number of biologics approved by the U.S. Food and Drug Administration (FDA) is growing, and their fate in the environment is unknown. This overview covers only a subset of the commercially available classes of pharmaceuticals and active ingredients in personal care products. The subset of classes discussed in this review comprises the primary classes for which the limited data on environmental occurrence and effects on nontarget species can be found, in a highly fragmented, disjointed, and disparate literature.

Pharmaceutical drugs are chemicals used for diagnosis, treatment (cure/mitigation), alteration, or prevention of disease, health condition, or structure/function of the human body. The definition is extended to veterinary pharmaceuticals and can also be applied to illicit (recreational) drugs. It also must be noted that the active ingredient in a drug may or may not be the actual formulated parent compound. For example, prodrugs such as the esters of clofibric acid, a metabolite of certain lipid regulators, are converted from pharmacologically inactive parent

Table 1. Conclusions, potential research needs, and recommendations.

Conclusion/finding	Research needs and recommendations
Chemical identification	
Of all the aspects of pharmaceuticals in the environment, the one that is perhaps the best developed is chemical identification and quantitation.	A feature distinguishing PPCPs from the currently recognized persistent organic pollutants (POPs) is the higher polarity of the parent PPCPs. This, coupled with their low concentrations, necessitates more work in the area of analysis, especially preconcentration. More development is also required for sensitive chemical analysis approaches to polar pollutants, which are not directly amenable to conventional protocols.
The trend in pharmaceuticals toward higher potency (e.g., enantiomerically pure drugs) while serving to reduce the burden of pharmaceuticals in the environment will add an additional challenge to the analytical effort required to characterize environmental samples because the required detection levels will be even further lowered from the current ppt-ppb levels.	The environmental monitoring community would benefit from additional analytical methods, including improved cleanup/preconcentration techniques, possibly based on highly specific approaches such as immunochemical or molecular imprinting [a highly sensitive, specific, and cost-effective technique that has already shown promise for nerve gas hydrolysis products, e.g., (*147*)].
Identification of nontarget (unsuspected) toxicants in complex waste streams by toxicity-directed assay of fractions is insufficient (because of the exponential complexity of stressor-receptor combinations). Direct, rigorous chemical characterization of problematic samples must play a role in identifying toxicants that might present previously unrealized (e.g., subtle) effects in nontarget organisms.	In the absence of comprehensive ecotoxicity tests that can accommodate the wide range of PPCPs and broad spectrum of possibly subtle effects, screening must also rely on rigorous chemical characterization—often for nontarget analytes. The results can then be used to direct subsequent toxicologic testing.
	Standard reference materials for pharmaceuticals and their metabolites need to be made more widely available at lower cost to environmental researchers to aid in monitoring activities. The NIST/EPA/NIH Mass Spectral Library (*148*) needs to be expanded to encompass a larger set of pharmaceuticals (those that are directly amenable to gas chromatography) as well as their derivatives; these spectra are currently available only in specialty databases such as Pfleger/Maurer/Weber (*3,4*). Non-EI (electron ionization) spectra need to be produced for the nonvolatile PPCPs (e.g., see *http://www.chemicalsoft.de/a.htm*).
Source and occurrence	
Wide arrays of PPCPs representing a diverse spectrum of modes of action are used throughout the world in large quantities, rivaling those of agrochemicals.	A systematic survey of potential drugs in waterways (especially those receiving hospital effluents) and their sources should be undertaken for those PPCPs that are most persistent or that elicit effects on aquatic life at very low concentrations (e.g., clofibric acid, antineoplastics, amino-nitro musks, SSRIs, chemosensitizers). To date (and very roughly), occurrence data for only about 50 nonantibiotic drugs (of the thousands in use today) have been published; numerous others may be present in the aquatic environment.
The major sources of PPCPs in the environment are primarily STW effluent and, secondarily, terrestrial run-off (e.g., from CAFOs).	Screening: Given the large numbers of pharmaceuticals that could be present in receiving waters, a rough screening approach is needed for assessing the potential of pharmaceuticals to occur. Samples with high potential could then be subjected to more rigorous analysis for individual targets. A possible approach might rely on analyses for only two widely used PPCPs/metabolites/inactive ingredients. The first would serve as a "conservative" indicator, one that is relatively easily biodegraded and whose presence would indicate that the possibility is high that many other (less degradable drugs) are also present. The second would also be ubiquitously used in large quantities but would be relatively persistent and relatively easily analyzed (e.g., musks). By monitoring its presence in receiving waters (and determining subsequent concentration gradients), the dilution of any drug (from the source) could be determined.
Some PPCPs (e.g., blood lipid regulators such as clofibric acid, X-ray contrast media, and musks) are ubiquitous and extremely persistent in the environment.	
Only a very small percentage of commercially used PPCPs have even been investigated for their occurrence in the environment. Drug classes that will experience huge usage rates (e.g., impotence drugs such as sildenafil citrate) have no associated environmental occurrence or exposure data.	
Although the genotoxic potency of industrial wastewaters is often the highest, the overall loadings of genotoxic compounds to surface waters are far greater (up to several orders of magnitude) from municipal treatment plants—and antineoplastic drugs might play the largest role.	
Aquatic monitoring efforts that focus on accumulation of pollutants in filter feeders may be grossly underestimating the levels of many pollutants, simply because functional MXR systems keep these pollutants at abnormally low concentrations within their cells. The corollary to this is that many aquatic organisms may be more susceptible to more hydrophilic toxicants (those that MXR systems are less effective at dealing with).	Monitoring programs focusing on aquatic systems should consider that bioaccumulated tissue concentrations may be aberrant, depending on the degree of MXR induction or inhibition.
Fate	
The low concentrations of individual PPCPs (possibly exceeding the catabolic enzyme affinities of sewage microbiota), coupled with their metabolic "novelty," leads to incomplete removal from STWs.	The nearly unknown ramifications of PPCPs in the environment (fate, transport, effects) warrant a more precautionary view on their environmental disposition. Environmental scientists need to focus more attention on this concern. An effort similar to that which was invested in elucidating the environmental transformation and fate of pesticides and industrial "toxics" (especially POPs) may need to be made for PPCPs.
Compared with POPs, there is a paucity of information on the fate, especially, biotransformation and phototransformation, of PPCPs.	
The low volatility of PPCPs means that their distribution through the environment will primarily occur through aqueous transport and food-chain dispersal. The polar, nonvolatile nature of most drugs prevents their escape from the aquatic realm. ("Global distillation" presumed to occur with POPs would not be a factor.)	Fate studies that simply follow disappearance (removal) of a PPCP will underestimate the level of parent compound (e.g., because of reservoirs of conjugates) and completely miss any bioactive metabolites.
Drug conjugates potentially act as storage "reservoirs" from which the free parent drug can later be released (e.g., via hydrolysis) in the environment.	

Table 1. *Continued.*

Conclusion/finding	Research needs and recommendations
Exposure	
An extreme diversity of stressor–receptor possibilities (most of which have yet to be identified) exists for nontarget species exposed to PPCPs and their metabolites entering the environment and serves to exacerbate an already complex problem.	Guidance is needed to determine those aquatic (and to a lesser extent, certain nonaquatic) organisms most susceptible to exposure to PPCPs.
The bioconcentration/bioaccumulation potential for at least some PPCPs (e.g., nitro musks) matches that for many of the more persistent organohalogen POPs.	Although little is known regarding nontarget effects in the aquatic environment, the SSRIs have the most data pointing to the potential for subtle behavioral/reproductive effects (at low concentrations), and the musks (nitro/amino) for acute effects, but nothing is known about their occurrence or fate in the environment. Much more research is needed to establish whether aquatic exposures are significant for PPCPs.
Because the main source of PPCPs in the environment (STWs) allows for continual, year-long introduction of these chemicals into the environment, outright persistence of an individual PPCP does not play the overwhelming role ordinarily found in governing exposure. Even relatively short-lived PPCPs could effect significant chronic exposures, as they are continually infused to the aquatic environment. Aquatic organisms are captives of their environment and therefore suffer perpetual exposure.	Although the introduction of PPCPs to STWs might remain relatively constant, wet weather and seasonal transitions (leading to overflows or upsets) can lead to increased aquatic exposures that must be accounted for in determining exposure ranges.
Organisms in less polluted waters may be at more risk from newly introduced chemicals than those in more polluted areas simply because their levels of MXR are not as fully developed.	Monitoring MXR activity in aquatic organisms should be pursued as a means of measuring overall health due to exposure.
Even naturally occurring PPCPs (e.g., nutraceuticals) could present risks to nontarget species because their usage serves to redistribute and extend their normal occurrence in the environment, promoting exposure to nontarget organisms that otherwise would never occur, and possibly resulting in higher concentrations in surface waters than would normally occur at their geographic sites of origin.	Perhaps more concern should be directed at exposure of organisms in more pristine aquatic locations than those in areas receiving established, known pollutant loads because the former are more at risk to effects from the introduction of a new pollutant since they have lower MXR activity. Similarly, the introduction of a pollutant to a pristine aquatic environment may pose more toxicological significance than for a more polluted environment.
Aquatic exposure can be increased in receiving waters having lower flows (e.g., smaller streams or during dry weather). On the other hand, wet weather and seasonal transitions can disrupt STWs and lead to poor removal efficiencies.	Detection of exposure of fish to many drugs can be facilitated through the analysis of bile.
Discharge of untreated sewage maximizes exposure.	
Effects	
Some PPCPs (e.g., nitro and amino-nitro musks) show very high acute aquatic toxicity. Others (e.g., SSRIs) can elicit constellations of significant but subtle effects across numerous species. These effects are not necessarily readily detectable but have the potential to lead to ecologic change that would be erroneously attributed to natural change.	Practically no aquatic toxicity data, especially behavioral effects, exists for PPCPs, even for those known to occur ubiquitously (e.g., blood lipid regulators, musks). This is a major unaddressed area. Although some studies have been done peripherally (e.g., MEIC) (*125*), none have been dedicated to PPCPs in the aquatic environment.
Although pharmaceuticals with broad modes of action (e.g., antineoplastics) may pose cause for concern in nontarget species, recent evidence shows that those with highly specific mechanisms (e.g., SSRIs) can elicit profound effects at extremely low concentrations.	Ecotoxicity tests need to better accommodate subtle end points (e.g., behavioral/genetic modifications), whose continued expression over long periods of time in certain populations could lead to adverse impacts that would otherwise be attributed to natural change. These tests need to address the higher levels of organization as expressed on the population/community structure level.
It is clear that aquatic life can be exquisitely sensitive to at least some PPCPs (e.g., SSRIs). Between-species, between-sex, and between-drug effects can also vary widely.	Ecotoxicity screening procedures must be developed that take into consideration the modes of action (currently largely unknown) of PPCPs on nontarget species.
Gross within-class differences regarding aquatic effects possibly make the approach of assessing ecologic risk on a class-by-class basis untenable. For example, some SSRIs are extremely potent, whereas others have almost no effect. A trend among individual drugs of a given class concerning effects on one species may not hold for other end points in the same species.	Research is particularly needed to identify those PPCPs that act as chemosensitizers for aquatic organisms. Quick assays for multixenobiotic resistance/inhibition (e.g., those using dyes) (*34*) would be particularly valuable.
Simple extrapolations of aquatic effects from higher concentrations do not necessarily have any predictive value for lower concentrations.	More attention is required to identify those PPCPs that modulate the endocrine systems of, or act as behavioral/developmental signaling agents in, aquatic species (e.g., retinoid receptors).
Antineoplastics harbor potential concern for environmental effects, not just for their acute toxicity but for their ability to effect subtle genetic changes, the cumulative impact of which over time could lead to more profound ecologic change.	
Chemosensitizers—those chemicals that inhibit multixenobiotic transporters—may play key roles in potentiating the effects of PPCPs. Little is known, however, as to how prevalent this ability is among pollutants.	
The capacity of MXR can be overwhelmed by nonspecific agents that simply competitively overwhelm the MXR mechanism, but which otherwise would not be toxic.	
Since many drugs are relatively polar (in contrast to most "conventional" pollutants), the defensive utility of MXR may not be effective for many PPCPs.	
The EDSTAC screening strategy will focus initially on only the three primary hormone systems—estrogen, androgen, and thyroid—hormone systems of relatively unknown importance to invertebrates.	

Table 1. *Continued.*

Conclusion/finding	Research needs and recommendations
Risk assessment	
The approach of assessing ecologic risk on a class-by-class basis (either by chemical or by mode of action) may not be feasible given that some drugs within the same class (e.g., SSRIs) display effects at concentrations differing by many orders of magnitude.	The approval of pharmaceuticals needs to be better coupled with meaningful ecologic risk assessments (and followed up with confirmatory environmental survey ERA studies after market introduction).
	When determining ecologic risk, consideration must be given to both additive effects (drugs of like-mode of action) and to synergistic effects (adverse interactions between drugs of different classes).
Evidence that the persistence and bioaccumulative potential of at least some PPCPs can be similar to the problematic organohalogen POPs should necessitate their consideration in comprehensive risk assessments. Over the decades, innumerable epidemiologic studies have purported correlations of various disease states with the body burdens of particular pesticides/industrial pollutants. The findings of these studies may well be flawed, as they made no attempt to also consider the possible effects of PPCP body burdens. Any comprehensive risk assessment must factor in the exposures/body burdens of all pollutants, regardless of origin—and PPCPs are perhaps the most ignored remaining major class of pollutants.	Even though the concentration of any one drug might be very low, the additive effects of multiple drugs sharing a like mode of action must be considered. This approach is already adopted under the Food Quality Protection Act (FQPA), in which the exposure risks for humans from pesticides having common mechanisms of action must be combined in calculating total risk; dioxins and PCBs are also assessed this way (e.g., via TEFs).
	Epidemiologic studies (both ecologic and human) should start to give equal consideration/weight to the body burdens/fluxes of PPCPs. Comprehensive risk assessments may not be possible without considering the simultaneous presence of pesticides, PPCPs, and other industrial chemicals.
	Assessment of risk should proceed on two fronts: *a)* studies focused on PPCPs already in wide use, and *b)* requirement for studies prior to registration of new PPCPs.
Mitigation, pollution prevention, and regulation	
The removal efficiencies of most PPCPs from STWs is poorly understood. And then, in those instances where efficiencies have been determined, only the disappearance of the parent compound has been tracked—this approach ignores the issue of fate (e.g., bioactive metabolites, and conjugates of the parent PPCP).	Prevention of direct discharge of untreated sewage to the environment would have the greatest impact on reducing the discharge of less persistent PPCPs. Small, unregulated sources (e.g., "straight-piping") may have the largest impacts (analogous to the overall smog impact of exhaust emissions from a small number of vehicles not in compliance). Reuse of treated wastewater would reduce impacts on surface waters.
Direct discharge of untreated sewage to surface waters would probably be the major source in the environment for those PPCPs that are otherwise easily removed by conventional STW processes. As such, individual direct discharge sources possibly have the most profound impact on the loading of the more easily degraded PPCPs in the environment.	The disposal of pharmaceuticals (e.g., unwanted/expired drugs) to the domestic waste system (sewage and garbage) should be discouraged (this could be addressed with a new labeling requirement).
Highly bioactive nonprescription chemicals are used in huge quantities and represent an unregulated source of (hormonally) active agents.	More attention may be needed in ensuring that the degradation of pharmaceuticals to innocuous products in waste treatment plants is maximized. This could entail the development of new or improved treatment technology.
The continued development of optically pure pharmaceuticals may eventually serve to reduce both the burden of pharmaceuticals in the environment and the exposure to daughter enantiomers that might have untoward effects.	Drugs should be screened for MXR inhibitory activity.
Dosages of drugs could be reduced by the co-administration of inhibitors of microsomal oxidases and multi-drug transporters to enhance intestinal uptake.	Land disposal (or use) of sewage sludge may need to be carefully monitored for release of PPCPs.
The advent of gene therapy might help to ease the use of pharmaceuticals.	Physicians should resist the temptation to over-prescribe in response to unfounded patient demands. Prescriptions should be written for no more than the requisite course. More emphasis should be placed on patient education with respect to prescribing unneeded medications.
	Sales of prescription drugs over the Internet may need to be regulated.
Research planning	
No coordinated effort aimed at studying PPCPs in the environment yet exists.	The multifaceted nature of PPCPs in the environment will require the collaborative efforts of different regulatory and scientific agencies, such as the U.S. EPA, the FDA, the National Institute of Environmental Health Sciences, and the OECD. A single agency should be responsible for research coordination and facilitating interorganization communication.
While resources continue to be focused on environmental fate/toxicology of conventional POPs, yielding only incremental enhancement of our knowledge base, a fraction of these same resources could yield significant advancements in the analogous understanding of PPCPs in the environment.	An interagency strategic research plan covering occurrence, exposure, and effects for nontarget species, ecologic risk assessment, and mitigation would be very useful. The PPCP industry, university partners, and other stakeholders should be actively involved.
	The literature on the occurrence, fate, and effects of PPCPs in the environment is sometimes hard to access and is highly fragmented, uneven, and difficult to assess and integrate . A concerted effort will be required to bring this disparate literature together into a useful body of knowledge.
	A web-based electronic database on occurrence, concentrations, and ecotoxicologic data (peer reviewed) for PPCPs in the environment would be highly useful.

compounds to the physiologically active form. With the exception of antibiotics and antineoplastics, the objective for most drug classes is simply to control symptoms and not to actually cure conditions. As such, many drugs are taken for very long periods, sometimes a good portion of the user's lifetime.

Although drugs are usually designed with a specific mode of action in mind (e.g., methotrexate universally affects all organisms in the same manner—by inhibiting nucleic acid synthesis), they can also have numerous effects on nontarget, or as yet unknown, receptors and possibly cause side effects in the target organism. Furthermore, and of equal importance, nontarget organisms can have receptors, or receptor tissue distributions, that do not exist in the target organisms, and therefore unexpected effects can result from unintentional exposure. This is a primary basis for the hypothesis of this paper.

Pharmaceuticals in the Environment

Sources and Origins

The possibility that pharmaceuticals can enter the environment from a number of different routes and possibly cause untoward effects in biota has been noted in the scientific literature for several decades, but its significance has gone largely unnoticed. This probably results in large part from the international regulation of drugs by human health agencies, which usually have limited expertise in environmental issues. Traditionally, drugs were rarely viewed as potential environmental pollutants; there was seldom serious consideration as to their fates once they were excreted from the user. Then again, until the 1990s, any concerted efforts to look for drugs in the environment would have met with limited success because the requisite chemical analysis tools with sufficiently high separatory efficiencies, to resolve the drugs from the plethora of other substances—native and anthropogenic alike, and low detection limits (i.e., nanograms per liter or parts per trillion), were not commonly available. Other obstacles, which still exist to a large degree, are that many pharmaceuticals and cosmetic ingredients and their metabolites are not available in the widely used environmentally oriented mass spectral libraries. These are available in specialty libraries such as Pfleger (e.g., *3,4*), which are not frequently used by environmental chemists. Analytical reference standards, when available, are often difficult to acquire, and are quite costly. The majority of drugs are also highly water soluble. This precludes the application of straightforward, conventional sample clean-up/preconcentration methods, coupled with direct gas chromatographic separation, that have been used for years for "conventional" pollutants, which tend to be less polar and more volatile.

Drugs in the environment did not capture the attention of the scientific or popular press until the last couple of years, with some significant overviews/reviews presented by Halling-Sørenson et al. (*5*), Montague (*6*), Raloff (*7*), Roembke et al. (*8*), Ternes et al. (*9*), and Velagaleti (*10*), among others. The evidence supports the case that PPCPs refractory to degradation and transformation [see Halling-Sørenson et al. (*5*) for summary of published transformation studies] do indeed have the potential to reach the environment. What is not known, however, is whether these chemicals and their transformation products can elicit physiologic effects on biota at the low concentrations (ng-µg/L) at which they are observed to occur. Another unknown is the actual quantity of each of the numerous commercial drugs that is ingested/disposed. With respect to determining the potential extent of the problem, this contrasts sharply with pesticides in which usage is much better documented and controlled.

A list of the PPCPs covered in this review, together with their chemical names, structures, and some representative environmental occurrence/effects data, is presented in Table 2. These chemicals, together with their synthetic precursors and transformation products, are continually released into the environment in enormous quantities as a result of their manufacture, use (via excretion, mainly in urine and feces), and disposal of unused/unwanted drugs and those that have expired, both directly into the domestic sewage system and via burial in landfills. Although largely unknown, there is evidence that large quantities of prescription and nonprescription, "over-the-counter" (OTC) drugs are never consumed (for any number of reasons) (*11*), and many of these are undoubtedly eventually disposed down toilets or via domestic refuse.

A striking difference between pharmaceuticals and pesticides with respect to environmental release is that pharmaceuticals have the potential for ubiquitous direct release into the environment worldwide—anywhere that humans live or visit. Even areas considered relatively pristine (e.g., national parks) are subject to pharmaceutical exposures, especially given that some parks have very large, aging sewage treatment systems, some of which discharge into park surface waters and some of which overflow during wet weather events and infrastructure failures (e.g., Yellowstone National Park) (*12,13*). Other possible sources include disposal of unwanted illicit drugs and synthesis byproducts into domestic sewage systems by clandestine drug operations; disposal of raw products and intermediates (e.g., ephedrine) via toilets is not uncommon in illegal laboratories. Also, in contrast to pesticides, pharmaceuticals in any stage of clinical testing (not yet approved for dispensing by the FDA) are subject to release into the environment, although their overall concentrations would be very low.

Some drugs are excreted essentially unaltered in their free form (e.g., methotrexate and platinum antineoplastics), often with the help of active cellular "multidrug transporters" for moderately lipophilic drugs. Others are metabolized to various extents, which is partly a function of the individual patient and the circadian timing of the dose (the P450 microsomal oxidase system is a major route of formation of more polar, more easily excreted metabolites). Still others are converted to more soluble forms by formation of conjugates (with sugars or peptides). The subsequent transformation products—metabolites and conjugates from eukaryotic and prokaryotic metabolism, and from physicochemical alteration—add to the already complex picture of thousands of highly bioactive chemicals. The FDA refers to all metabolites and physicochemical transformation products, for example, those that range from the dissociated parent compound to photolysis products, for a given drug as structurally related substances (SRSs), which can have greater or lesser physiologic activity than the parent drug.

As in mammals, the metabolic disposition of lipophilic xenobiotics, such as numerous drugs, in vertebrate aquatic species is largely governed by what is referred to as Phase I and Phase II reactions (*14*); less is known about invertebrate metabolism. Phase I makes use of monooxygenases (e.g., cytochrome P450), reductases, and hydrolases (for esters and epoxides) to add reactive functional groups to the molecule. Phase II uses covalent conjugation (glucuronidation) to make the molecule hydrophilic and more excretable. These reactions are catalyzed by glycosyltransferases and sulfotransferases (for hydroxyaromatics and carboxy groups), glutathione *S*-transferases (for electrophilic functional groups such as halogens, nitro groups, or unsaturated/conjugated sites), acetyltransferases (for primary amines or hydrazines), and aminoacyltransferases (for forming peptides from carboxy groups using free amino acids). This metabolic strategy creates metabolites successively more polar than the parent compound, thereby enhancing excretion (Figure 1). Considerable interspecies and intraspecies diversity, however, can be observed in actual metabolic potentials. Many drugs and metabolic products, especially those over 400 Da, are concentrated in the bile of fish (vs blood or fat) (*15*). Although the total amount excreted via the urine may be higher, Guarino and Lech (*15*) recommend bile analysis to maximize the chance of detecting drugs, especially their conjugates, in fish in order to confirm exposure. They also report that the

Table 2. PPCPs identified in environmental samples—or having significance with respect to aquatic life.

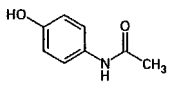
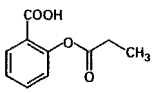
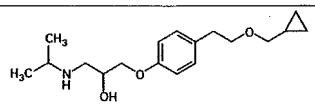
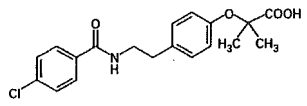
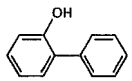
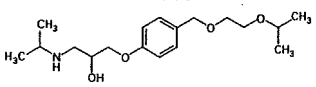
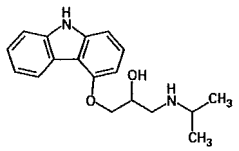
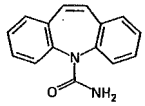
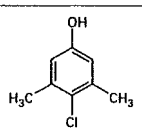
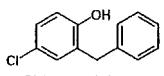
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Acetaminophen	 *N*-(4-Hydroxyphenyl)acetamide; (Paracetamol)	103-90-2 151.17 $C_8H_9NO_2$	Analgesic/anti-inflammatory	Efficiently removed by POTW (*18*); POTW max. effluent: 6.0 µg/L; not detected in surface waters (*18*)	e.g., Tylenol; *Daphnia* immobilization EC_{50} 0.27–0.90 mM (*125*)
Acetylsalicylic acid	 2-(Acetyloxy)benzoic acid; (Aspirin)	50-78-2 180.16 $C_9H_8O_4$	Analgesic/anti-inflammatory	Ubiquitous. One of first pharmaceuticals identified in sewage influent/effluent; POTW removal efficiency 81% (*18*); POTW max. effluent: 1.5 µg/L; max. in surface waters: 0.34 µg/L. Sewage effluent: 1 µg/L (*40*)	Efficiently removed by POTWs; *Daphnia* immobilization EC_{50} 0.9–8.2 mM (*125*)
Betaxolol	 1-[4-[2-(Cyclopropylmethoxy) ethyl]-phenoxy]-3-[(1-methyl-ethyl)amino]-2-propanol	63659-18-7 307.43 $C_{18}H_{29}NO_3$	Beta-blocker (antihypertensive, antiglaucoma)	POTW max. effluent: 0.19 µg/L; max. in surface waters: 0.028 µg/L (*73*)	e.g., Betoptic
Bezafibrate	 2-[4-[2-[(4-Chlorobenzoyl)-amino]ethyl]phenoxy]-2-methylpropanoic acid	41859-67-0 361.82 $C_{19}H_{20}ClNO_4$	Lipid regulator	Loading of ~ 300 g/day in German POTW (18); POTW removal efficiency 83% (18); POTW max. effluent: 4.6 µg/L; max. in surface waters: 3.1 µg/L. Influent concentration of 1.2 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 27–50%	Among highest reported values for occurrence in STW effluent and surface waters; e.g., Befizal
Biphenylol	 2-Biphenylol 2-Hydroxydiphenyl	90-43-7 170.21 $C_{12}H_{10}O$	Antiseptic, fungicide	POTWs in Germany: biphenylol routinely found in both influents (up to 2.6 µg/L) and effluents (*70*), but removal was extensive	e.g., Dowicide A
Bisoprolol	 1-[4-[[2-(1-Methylethoxy)-ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol	66722-44-9 325.45 $C_{18}H_{31}NO_4$	Beta-blocker (antihypertensive)	POTW max. effluent: 0.37 µg/L.; max. in surface waters: 2.9 µg/L (*73*)	e.g., Concor
Carazolol	 1-(9*H*-Carbazol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol	57775-29-8 298.38 $C_{18}H_{22}N_2O_2$	Beta-blocker (antihypertensive, antianginal, antiarrhythmic)	POTW max. effluent: 0.12 µg/L; max. in surface waters: 0.11 µg/L (*73*)	e.g., Conducton
Carbamazepine	 5*H*-Dibenz[*b,f*]azepine-5-carboxamide	298-46-4 236.27 $C_{15}H_{12}N_2O$	Analgesic; antiepileptic	Loading of over 100 g/day in German POTW (*18*); but load in effluent can be 114 g/day; POTW removal efficiency 7% (*18*); POTW max. effluent: 6.3 µg/L; max. in surface waters: 1.1 µg/L	e.g., Tegratal; only 1–2% excreted free (*18*); 10,11-epoxy-carbamazepine major metabolite; also excreted as glucuronides
4-Chloro-3,5-xylenol (Chloroxylenol)	 4-Chloro-3,5-dimethylphenol	88-04-0 156.61 C_8H_9ClO	Antiseptic	POTWs in Germany: 4-chloroxylenol occasionally found in both influents and effluents (< 0.1 µg/L) (*70*)	e.g., Benzytol
Chlorophene	 4-Chloro-2-(phenylmethyl)phenol; (*o*-Benzyl-*p*-chlorophenol)	120-32-1 218.68 $C_{13}H_{11}ClO$	Antiseptic	POTWs in Germany: chlorophene routinely found in both influents (up to 0.71 µg/L) and effluents (*70*); removal not as extensive as for biphenylol.	e.g., Santophen 1

Table 2. *Continued.*

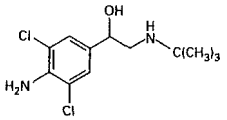
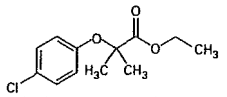
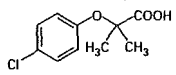
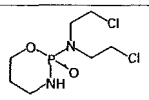
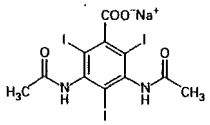
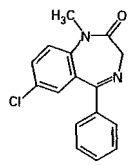
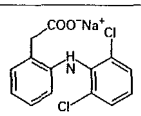
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Clenbuterol	 4-Amino-3,5-dichloro-α-[[(1,1-dimethylethyl)amino]-methyl]benzenemethanol	37148-27-9 277.19 $C_{12}H_{18}Cl_2N_2O$	β_2-Sympathomimetic (bronchodilator)	POTW max. effluent: 0.08 µg/L; max. in surface waters: 0.05 µg/L (*18*)	e.g., Monores
Clofibrate	 2-(4-Chlorophenoxy)-2-methyl-propanoic acid ethyl ester	637-07-0 242.70 $C_{12}H_{15}ClO_3$	Lipid regulator	Not detected in POTW effluent (*18*); not detected in surface waters. River water: ~ 40 ng/L (*40*)	e.g., Bioscleran; rapidly hydrolyzed upon ingestion
Clofibric acid	 2-(4-Chlorophenoxy)-2-methylpropanoic acid; e.g., Regulipid	882-09-7 214.66 $C_{10}H_{11}ClO_3$	Polar, active metabolite of lipid regulators (clofibrate, etofyllin clofibrate [theofibrate], etofibrate)	One of first prescription drugs/metablites ever reported in sewage influent/effluent: Missouri STW effluent avg. 2.1 kg/day (*38*); 0.8–2.0 µg/L in raw sewage and activated sludge effluent (*37*). Loading of over 50 g/day in German POTW (*18*); POTW removal efficiency 51% (*18*); POTW max. effluent: 1.6 µg/L; max. in surface waters: 0.55 µg/L. Swiss rural/urban lakes: 1–9 ng/L (ppt); North Sea (up to 7.8 ng/L) (*67*). Influent concentration of 1 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 15–34%. Up to 270 ng/L in German tap waters (*23*)	Active metabolite of clofibrate; formed via hydrolysis very soon after ingestion; excreted primarily as glucuronide (very little as the free acid); presence in POTWs indicates hydrolysis of conjugate (*18*)
Cyclophosphamide (Cyclophosphane)	 *N,N*-Bis(2-chloroethyl)tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-amine 2-oxide; e.g., Cycloblastin	50-18-0 261.09 $C_7H_{15}Cl_2N_2O_2P$	Antineoplastic	POTW max. effluent: 0.02 µg/L; not detected in surface waters (*18*). Hospital sewage 146 ng/L (*149*) and 19 ng/L–4.5 µg/L (*82*); POTW receiving hospital waste: influent up to 143 ng/L, effluent up to 17 ng/L	Oxazaphosphorine (structural isomer of ifosfamide); high dosages (over 100 mg/kg); up to 50% excreted unaltered; mutagen/carcinogen; resistant to microbial degradation
Diatrizoate (Na)	 3,5-Bis(acetylamino)-2,4,6-triiodobenzoic acid sodium salt	737-31-5 635.90 $C_{11}H_8I_3N_2NaO_4$	X-Ray contrast media (radiopaque medium)	Resistant to biodegradation and yields refractory, unidentified metabolites (*91*). In German surface waters, median concentration of 0.23 µg/L (*92*; isolated maximum values above 100 µg/L indicate that locally very high concentrations can occur, especially in small streams containing a high percentage of STW discharges.	e.g., Hypaque Sodium; very high annual worldwide usage rates
Diazepam	 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	439-14-5 284.74 $C_{16}H_{13}ClN_2O$	Psychiatric drug (anxiolytic; muscle relaxant)	POTW max. effluent: 0.04 µg/L; not detected in surface waters (*18*). Groundwater from a Superfund site near Atlantic City, New Jersey: 10–40 µg/L (*88*).	e.g., Valium; *Daphnia* immobilization EC_{50} 0.015–0.049 mM (*125*)
Diclofenac-Na	 2-[(2,6-Dichlorophenyl)-amino]benzeneacetic acid-Na	15307-79-6 318.13 $C_{14}H_{10}Cl_2NO_2Na$	Analgesic/anti-inflammatory	Loading of ~100 g/day in German POTW (*18*); POTW removal efficiency 69% (*18*); POTW max. effluent: 2.1 µg/L; max. in surface waters: 1.2 µg/L. Influent to Swiss STWs 500–1800 ng/L and effluents more than 50% as much; Swiss lakes/rivers 1–12 ng/L, with lower order streams 11–310 ng/L (*71*). Influent concentration of 0.8 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 9–75%.	e.g., Voltaren; lab data show rapid and extensive photodegradation to multiple products (*71*)

Table 2. *Continued.*

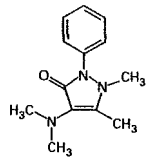
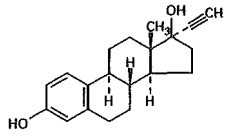
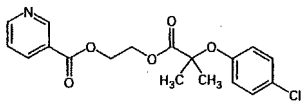
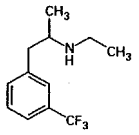
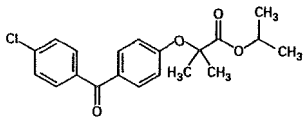
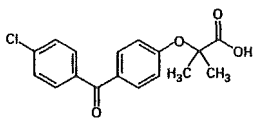
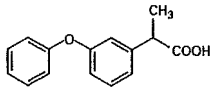
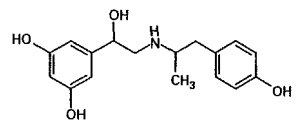
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Dimethylamino-phenazone (Aminopyrine)	 4-Dimethylaminoantipyrine	58-15-1 231.30 $C_{13}H_{17}N_3O$	Analgesic/anti-inflammatory	Loading of over 50 g/day in German POTW (*18*); POTW removal efficiency 38% (*18*); POTW max. effluent: 1.0 µg/L; max. in surface waters: 0.34 µg/L	e.g., Piridol
17α-Ethinyl estradiol	 (17α)-19-Norpregna-1,3,5 (10)-trien-20-yne-3,17-diol	57-63-6 296.41 $C_{20}H_{24}O_2$	Oral contraceptive (in combination with progestogens)	Up to 7 ng/L in POTW effluent (*26*). Not detected in German surface water above 0.5 ng/L (*9*), but found in Dutch Rhine water up to 4.3 ng/L (*150*).	Prime synthetic suspect regarding estrogenic effects in fish; the natural estrogen is 17β-estradiol; e.g., Oradiol
Etofibrate	 3-Pyridinecarboxylic acid 2-[2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy]ethyl ester	31637-97-5 363.80 $C_{18}H_{18}ClNO_5$	Lipid regulator	Not detected in POTW effluent (*18*); not detected in surface waters.	e.g., Lipo-Merz; rapidly hydrolyzed upon ingestion
Fenfluramine	 *N*-Ethyl-α-methyl-3-[trifluoro-methyl] benzeneethanamine	458-24-2 231.26 $C_{12}H_{16}F_3N$	Sympathomimetic amine (anorexic)	While no one has looked for fenfluramine in sewage, it is known to enhance the release of serotonin (5-HT), and in the crayfish, 5-HT in turn triggers release of ovary-stimulating hormone—resulting in larger oocytes with enhanced amounts of vitellin (consequences unknown) (*74*). Similarly, in fiddler crabs, fenfluramine (dose of 125 nmol) stimulates (through 5-HT) the production of gonad-stimulating hormone—accelerating testicular maturation (*75*).	Popular diet (anorectic) drug removed from the U.S. market in 1998 by the FDA because of heart valve damage; e.g., hydrochloride: Pondimin
Fenofibrate	 2-[4-(4-Chlorobenzoyl)-phenoxy]-2-methylpropanoic acid 1-methylethyl ester	49562-28-9 360.84 $C_{20}H_{21}ClO_4$	Lipid regulator	Efficiently removed by POTW (*18*); POTW max. effluent: 0.03 µg/L; not detected in surface waters.	e.g., Fenobrate; rapidly hydrolyzed upon ingestion
Fenofibric acid	 2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid	42017-89-0 318.84 $C_{17}H_{15}ClO_4$	Polar, active metabolite of fenofibrate	Loading of over 50 g/day in German POTW (18); POTW removal efficiency 64% (18); POTW max. effluent: 1.2 µg/L; max. in surface waters: 0.28 µg/L. Influent concentration of 0.4 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 6–45%.	Formed via hydrolysis very soon after ingestion; excreted primarily as glucuronide (very little as free acid); presence in POTWs indicates hydrolysis of conjugate (*18*)
Fenoprofen	 α-Methyl-3-phenoxy-benzeneacetic acid	31879-05-7 242.27 $C_{15}H_{14}O_3$	Analgesic/anti-inflammatory	Not detected in POTW effluent or surface waters (*18,69*).	e.g., Fenopron
Fenoterol	 5-[1-Hydroxy-2-[[2-(4-hydroxy-phenyl)-1-methylethyl] amino]ethyl]-1,3-benzenediol	13392-18-2 303.36 $C_{17}H_{21}N_4O$	β_2-Sympathomimetic (bronchodilator)	POTW max. effluent: 0.06 µg/L; max. in surface waters: 0.061 µg/L (*18*)	e.g., Airum

Table 2. *Continued.*

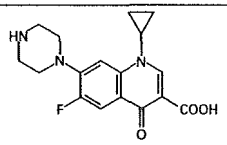
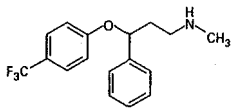
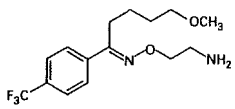
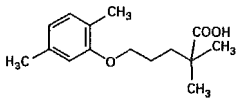
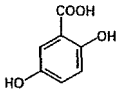
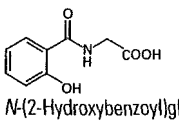
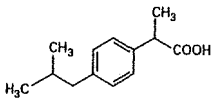
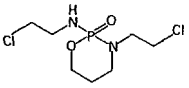
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Fluoroquinolone carboxylic acids	 Large class; e.g., ciprofloxacin	e.g., 85721-33-1 331.35 $C_{17}H_{18}FN_3O_3$	Antibiotics	As one of only many classes of pharmaceuticals, antibiotics in general have been investigated for their occurrence in the environment more than any other class of PPCPs. Their ubiquitous occurrence in the environment is a leading proposed cause of the rise in resistance among pathogenic bacteria. Strongly sorbs to soil (*151,152*). Highly active in hospital wastewaters (*62,153*)	Gyrase inhibitors (needed for DNA replication); excreted mainly as parent compound
Fluoxetine	 *N*-Methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine	54910-89-3 309.33 $C_{17}H_{18}F_3NO$	Antidepressant (SSRI)	Not yet searched for in environmental samples	e.g., Prozac; Fluoxetine elicits significant spawning in male mussels at 10^{-7} M (~150 µg/L) and in females at 10^{-6} M (*76*)
Fluvoxamine	 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone *O*-(2-aminoethyl)oxime	54739-18-3 318.34 $C_{15}H_{21}F_3N_2O_2$	Antidepressant (SSRI)	Not yet searched for in environmental samples	e.g., Luvox; Fluvoxamine elicits significant spawning in male mussels at 10^{-9} M (~0.318 µg/L) and in females at 10^{-7} M. Fluvoxamine is the most powerful spawning inducer ever identified for bivalves (*76*)
Gemfibrozil	 5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid	25812-30-0 250.34 $C_{15}H_{22}O_3$	Lipid regulator	Loading of over 50 g/day in German POTW (*18*); POTW removal efficiency 69% (*18*); POTW max. effluent: 1.5 µg/L; max. in surface waters: 0.51 µg/L. Influent concentration of 0.3 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 16–46%	e.g., Lopid
Gentisic acid	 2,5-Dihydroxybenzoic acid	490-79-9 154.12 $C_7H_6O_4$	Hydroxylated metabolite of acetylsalicylic acid	Efficiently removed by POTW (*18*); POTW max. effluent: 0.59 µg/L; max. in surface waters: 1.2 µg/L. Average gentisic acid concentrations in POTW influents of 4.6 µg/L (*70*) with no detectable amounts in the effluents	A minor ultimate metabolite
o-Hydroxyhippuric acid	 *N*-(2-Hydroxybenzoyl)glycine	487-54-7 195.17 $C_9H_9NO_4$	Metabolite of acetylsalicylic acid	Efficiently removed by POTW (*18*); not detected in POTW effluent or surface waters (*18*); average *o*-hydroxyhippuric acid concentrations in POTW influents of 6.8 µg/L; no detectable amounts in effluents (*70*)	
Ibuprofen	 α-Methyl-4-(2-methylpropyl)-benzeneacetic acid	15687-27-1 206.28 $C_{13}H_{18}O_2$	Analgesic/anti-inflammatory	Loading of over 200 g/day in German POTW (*18*); POTW removal efficiency 90% (*18*); POTW max. effluent: 3.4 µg/L; max. in surface waters: 0.53 µg/L. Influent concentration of 0.3 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 22–75%. STW influents up to 3.3 µg/L, POTW removal >95%, surface waters up to 8 ng/L; one of few studies to look at metabolites (*72*)	e.g., Advil; excreted substantially by humans in free form or conjugated (*72*)
Ifosfamide	 *N*,3-bis(2-chloroethyl)tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-amine 2-oxide; e.g., Holoxan	3778-73-2 261.09 $C_7H_{15}Cl_2N_2O_2P$	Antineoplastic	POTW max. effluent: 2.9 µg/L; not detected in surface waters (*18*). Hospital sewage 24 ng/L (*149*). Hospital effluent: max 1.91 µg/L, median 109 ng/L; POTW influent/effluent max 43 ng/L, median 6.5–9.3 ng/L (*83*). Found to be totally refractory to removal by POTW (*83*)	Oxazaphosphorine (structural isomer of cyclophosphamide); high dosages (over 100 mg/kg). Up to 50% excreted unaltered, but generally ~20%; fate of metabolites unknown (*83*)

Table 2. *Continued.*

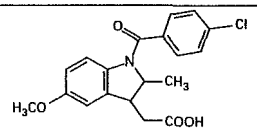
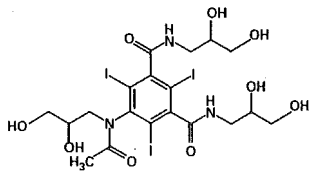
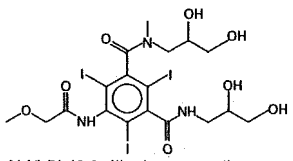
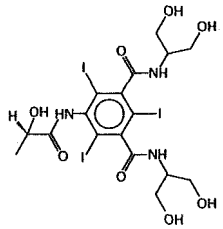
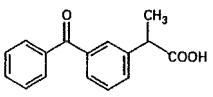
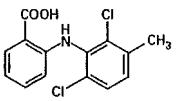
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Indomethacine	 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid	53-86-1 357.79 $C_{19}H_{16}ClNO_4$	Analgesic/anti-inflammatory	Loading of ~10 g/day in German POTW (*18*); POTW removal efficiency 75% (*18*); POTW max. effluent: 0.60 µg/L; max. in surface waters: 0.20 µg/L. Influent concentration of 0.95 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 71–83%	e.g., Amuno
Iohexol	 5-[Acetyl(2,3-dihydroxypropyl)-amino]-*N,N*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide	66108-95-0 821.14 $C_{19}H_{26}I_3N_3O_9$	X-Ray contrast (radiopaque) media; e.g., Omnipaque	Very low aquatic toxicity reported by Steger-Hartmann et al. (*93*)	
Iopamidol	*N,N*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide	60166-93-0 777.09 $C_{17}H_{22}I_3N_3O_8$	X-Ray contrast (radiopaque) media; e.g., Isovue	Concentrations as high as 15 µg/L in municipal STW effluents (*92*), and median concentration of 0.49 µg/L	
Iopromide	 *N,N*-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methyl-1,3-benzenedicarboxamide	73334-07-3 791.12 $C_{18}H_{24}I_3N_3O_8$	X-Ray contrast (radiopaque) media; e.g., Ultravist	Resistant to biodegradation and yields refractory, unidentified metabolites (*91*). Reported by Ternes et al. (*92*) in rivers. Concentrations as high as 11 µg/L in municipal STW effluents (*92*)	Very high annual worldwide usage rates. Parent compounds possibly low toxicity (*93*). Metabolites have unknown aquatic toxicology. Extremely persistent
Iotrolan	 5,5'-[(1,3-Dioxo-1,3-propanediyl)*bis*(*methylimino*)]-*bis*[*N,N'*-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide]	79770-24-4 1626.2 $C_{37}H_{48}I_6N_6O_{18}$	X-Ray contrast (radiopaque) media; e.g., Isovist	Very low aquatic toxicity reported by Steger-Hartmann et al. (*93*)	
Ketoprofen	 3-Benzoyl-α-methylbenzeneacetic acid	22071-15-4 254.28 $C_{16}H_{14}O_3$	Analgesic/anti-inflammatory	POTW max. effluent: 0.38 µg/L; max. in surface waters: 0.12 µg/L (*18*). Influent concentration of 0.5 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 48–69%	e.g., Oruvail
Meclofenamic acid	 2-[(2,6-Dichloro-3-methylphenyl)amino]benzoic acid	644-62-2 296.15 $C_{14}H_{11}Cl_2NO_2$	Analgesic/anti-inflammatory	Not detected in POTW effluent or surface waters (*18,69*)	Used mainly in veterinary medicine; e.g., Arquel

Table 2. *Continued.*

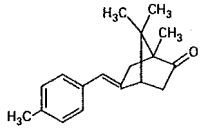
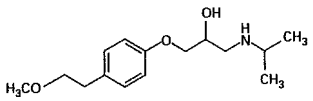
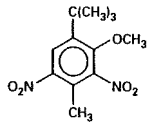
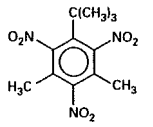
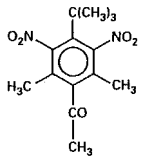
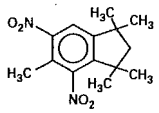
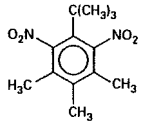
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Methylbenzylidene camphor	 3-(4-Methylbenzyliden) camphor	36861-47-9 254.37 $C_{18}H_{22}O$	Sunscreen agent	Bioconcentrated in roach from German lakes (*115*)	e.g., Eusolex 6300
Metoprolol	 1-[4-(2-Methoxyethyl) phenoxy]-3-[(1-methylethyl) amino]-2-propanol	37350-58-6 267.37 $C_{15}H_{25}NO_3$	Beta-blocker (antihypertensive)	Loading of nearly 400 g/day in German POTW (*18*); POTW removal efficiency 83% (*18*); POTW max. effluent: 2.2 µg/L; max. in surface waters: 2.2 µg/L	Tartrate: e.g., Lopressor; principal metabolite: metaprolol acid
Musk ambrette (a nitro musk)	 2,6-Dinitro-3-methoxy-4-*tert*-butyl toluene	83-66-9 268.27 $C_{12}H_{16}N_2O_5$	The first of two major classes of synthetic musks–the "nitro" musks. Widely used in a wide array of fragrances for cosmetics and other personal care products. Introduced to commerce in late 1800s	Synthetic musks first began to be identified in environmental samples almost 20 years ago. Yamagishi et al. (*100,101*) performed the first comprehensive monitoring effort, identifying musk xylene and musk ketone in freshwater fish, marine shellfish, river water, and STW wastewater. Musk xylene was found in all samples, and musk ketone was found in 80% of the 74 samples analyzed. Concentrations in STW effluents ranged from 25 to 36 ng/L (musk xylene) and from 140 to 410 ng/L (musk ketone). Concentrations of musk xylene in fish muscle were in the tens of ppb, while those for musk ketone were less than 10 µg/kg, with highest values in fish downstream of STWs. In contrast, for shellfish, the concentrations ranged lower, between 1 and 5.3 µg/kg, presumably because of their lower lipid contents. In river water, musk xylene occurred in all samples, whether upstream or downstream of STWs, and ranged from 1 to 23 ng/L; musk ketone was generally in the same range, but in distinct contrast, was not detectable in upstream samples Winkler et al. (*104*) measured musks in 31 particulate matter and water samples from the Elbe River (Germany). In all particulate matter samples were found musk ketone (4–22 ng/g), Galaxolide (148–736 ng/g), and Tonalide (194–770 ng/g); Celestolide was found in 23 of the particulate matter samples (4–43 ng/g). The values for the three most prevalent musks were within the same magnitude as	The nitro musks are being phased out of use in many parts of the world because of toxicity concerns. Musk xylene was introduced in 1888
Musk xylene (a nitro musk)	 1-*tert*-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene (MX)	81-15-2 297.27 $C_{12}H_{15}N_3O_6$			
Musk ketone (a nitro musk)	 1-*tert*-Butyl-3,5-dimethyl-2,6-dinitro-4-acetylbenzene (MK)	81-14-1 294.31 $C_{14}H_{18}N_2O_5$			
Musk moskene (a nitro musk)	 4,6-Dinitro-1,1,3,3,5-pentamethylindane	116-66-5 278.31 $C_{14}H_{18}N_2O_4$			
Musk tibetene (a nitro musk)	 1-*tert*-Butyl-2,6,-dinitro-3,4,5-trimethylbenzene	145-39-1 266.30 $C_{13}H_{18}N_2O_4$			

Table 2. *Continued.*

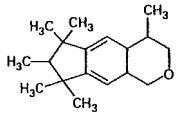
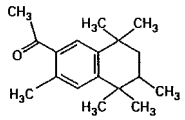
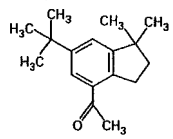
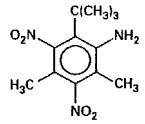
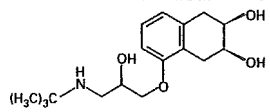
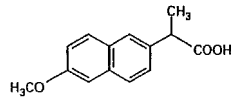
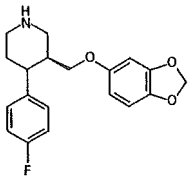
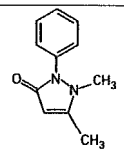
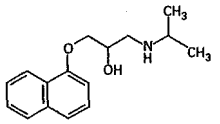
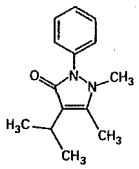
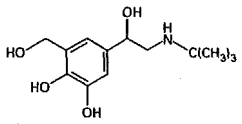
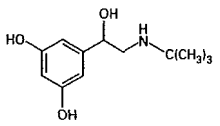
Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Galaxolide (HHCB) (a polycyclic musk)	 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-(g)-2-benzopyrane	1222-05-5 258.40 $C_{18}H_{26}O$	The second of two major classes of synthetic musks—the "polycyclic" musks. Widely used in a wide array of fragrances for cosmetics and other personal care products. Introduced to commerce in 1950s	that for 15 PAHs, and exceeded those for 14 common polychlorinated organic pollutants (only HCB and *p,p'*-DDT were of similar concentration). Also found in all the water samples were musk ketone (2–10 ng/L), Galaxolide (36–152 ng/L), and Tonalide (24–88 ng/L); Celestolide was only found at 2–8 ng/L. These higher values exceeded those for all the polychlorinated organics and the PAHs Draisci et al. (*106*) examined freshwater fish in Italy and identified two of five targeted musks in most fish samples; Galaxolide and Tonalide were identified at levels ranging from less than 4 ng/g to 105 ng/g (ppb) in fish muscle tissue. Eschke et al. (cited in *107*) identified Galaxolide, Tonalide, and Celestolide in the fatty tissue of bream and perch from the Ruhr River (Germany) at average concentrations ranging from 2.5 to 4.6 mg/kg (ppm). Müller et al. (*98*) identified in the Swiss river Glatt, Galaxolide, Tonalide, and Celestolide at ng/L concentrations (136, 75, and 3.2, respectively); they also found the nitro-musks (tibetene, ambrette, moskene, ketone, xylene) at ng/L concentrations (0.04, < 0.03, 0.08, 8.3, and 0.62, respectively)[a]	
Tonalide (AHTN) (a polycyclic musk)	 7-Acetyl-1,1,3,4,4,6-hexa-methyltetraline	1506-02-1 258.40 $C_{18}H_{26}O$			
Celestolide (ADBI) (a polycyclic musk)	 4-Acetyl-1,1-dimethyl-6-*tert*-butylindane	13171-00-1 244.38 $C_{17}H_{24}O$			The nitro musks are being phased out of use in many parts of the world because of toxicity concerns. Musk xylene was introduced in 1888
Musk xylene derivatives reduced (aminated)	 1-*tert*-Butyl-3,5-dimethyl-2-amino-4,6-dinitrobenzene 1-*tert*-Butyl-3,5-dimethyl-4-amino-2,6-dinitrobenzene 1-*tert*-Butyl-3,5-dimethyl-2,4-diamino-6-nitrobenzene 1-*tert*-Butyl-3,5-dimethyl-2,4,6-tri-aminobenzene		Transformation products of nitro musks, resulting from microbial reduction of the nitro groups.	Behecti et al. (*111*) tested the acute toxicity of four reduced analogs of musk xylene on *Daphnia magna*. The *p*-aminodinitro compound exhibited the most toxicity of the four, with EC_{50} values averaging 0.25 µg/L (0.25 ppb). Gatermann et al. (*96*) identified in sewage influent/effluent and in Elbe River (Germany) musk xylene and musk ketone together with their amino derivatives: 4- and 2-amino-musk xylenes and 2-amino musk ketone. Sewage influent: musk xylene and musk ketone at 150 and 550 ng/L, respectively; in the effluent, concentrations 10 and 6 ng/L, respectively. Amino derivatives not detectable in influent, but concentrations in the effluents dramatically increased: 2-amino musk xylene (10 ng/L), 4-amino musk xylene (34 ng/L), and 2-amino musk ketone (250 ng/L	The amino musks show greater toxicity than the parent nitro musks
Nadolol	 5-[3-[(1,1-Dimethylethyl)-amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-2,3-naphthalenediol	42200-33-9 309.40 $C_{17}H_{27}NO_4$	Beta-blocker (antihypertensive)	POTW max. effluent: 0.06 µg/L; not detected in surface waters (*18*)	e.g., Corgard
Naproxen	 (*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid	22204-53-1 230.26 $C_{14}H_{14}O_3$	Analgesic/anti-inflammatory	Loading of over 50 g/day in German POTW (*18*); POTW removal efficiency 66% (*18*); POTW max. effluent: 0.52 µg/L; max. in surface waters: 0.39 µg/L. Influent concentration of 0.6 µg/L in Brazilian STWs (*69*) with removal efficiencies ranging from 15–78%.	e.g., Naprosyn

Table 2. *Continued.*

Compound	Structure and CAS name	CAS RN MW Formula	Use/origin	Environmental occurrence	Trade names, comments, and nontarget species effects
Paroxetine	 (3*S-trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine	61869-08-7 329.37 $C_{19}H_{20}FNO_3$	Antidepressant (SSRI)	Not yet searched for in environmental samples	Compared with fluoxetine and fluvoxamine, paroxetine does not elicit spawning behavior in molluscs; e.g., Paxil
Phenazone (Antipyrine)	 1,2-Dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one	60-80-0 188.23 $C_{11}H_{12}N_2O$	Analgesic	Loading of ~10 g/day in German POTW (*18*); POTW removal efficiency 33% (*18*); POTW max. effluent: 0.41 µg/L; max. in surface waters: 0.95 µg/L	e.g., Parodyne
Propranolol	 1-[(1-Methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol	525-66-6 259.35 $C_{16}H_{21}NO_2$	Beta-blocker (antihypertensive)	Loading of over 500 g/day in German POTW (*18*); POTW removal efficiency 96% (*18*); POTW max. effluent: 0.29 µg/L; max. in surface waters: 0.59 µg/L	e.g., Avlocardyl; principal metabolite: 4-hydroxypropanolol; *Daphnia* immobilization EC_{50} 0.01–0.06 mM (*125*)
Propyphenazone	 4-Isopropylantipyrine	479-92-5 230.31 $C_{14}H_{18}N_2O$	Analgesic/anti-inflammatory	Grinsted (Denmark) landfill leachates: 0.3–4.0 mg/L directly beneath and declining depending on depth and distance along plume (*21*); prevalent in Berlin waters (*23*)	e.g., Isoprochin
Salbutamol albuterol (in U.S.)	 α^1-[[(1,1-Dimethylethyl)-amino]methyl]-4-hydroxy-1,3-benzenedimethanol	18559-94-9 239.31 $C_{13}H_{21}NO_3$	β_2-Sympathomimetic (bronchodilator)	POTW max. influent: 0.17 µg/L; max. in surface waters: 0.035 µg/L (*18*)	e.g., sulfate: Ventolin
Salicylic acid	 2-Hydroxybenzoic acid; e.g., Duofilm	69-72-7 138.12 $C_7H_6O_3$	Primary hydrolytic metabolite of acetylsalicylic acid, keratolytic, dermatice, preservative of food	Up to 54 µg/L in POTW effluent but efficiently removed in effluent (*18*); POTW max. effluent: 0.14 µg/L; max. in surface waters: 4.1 µg/L. Average salicylic acid concentrations in POTW influents of 55 µg/L and in effluents of 0.5 µg/L (*70*)	Efficiently removed by POTWs; the free form of salicylic acids represents only one (minor) of several ultimate metabolites
Sulfonamides	Large class	NA	Antibiotics	Grinsted (Denmark) landfill leachates: 0.04–6.47 mg/L directly beneath and declining depending on depth and distance along plume (*21*)	
Terbutaline	 5-[2-[(1,1-Dimethylethyl) amino-1-hydroxyethyl]-1,3-benzenediol	23031-25-6 225.29 $C_{12}H_{19}NO_3$	β_2-Sympathomimetic (bronchodilator)	POTW max. effluent: 0.12 µg/L; not detected in surface waters (*18*)	e.g., sulfate: Brethaire