Pharmaceuticals and Personal Care Products (PPCPs) as Ubiquitous Pollutants from Personal Use and Activities

Christian G. Daughton, Ph.D.

U.S. EPA, Office of Research and Development, National Exposure Research Laboratory,
Environmental Sciences Division, Environmental Chemistry Branch,
P.O. Box 9478, Las Vegas, Nevada 89193-3478
Email: daughton.christian@epa.gov

EPA's research mission in context -- "Anticipatory Research and Emerging Pollutants"

A primary goal of the U.S. EPA's Office of Research and Development is to identify, foster, and perform investigation of potential future environmental issues/concerns before they become critical ecological or human health issues — proactive pollution prevention being preferable to reactive corrective actions.

BACKGROUND

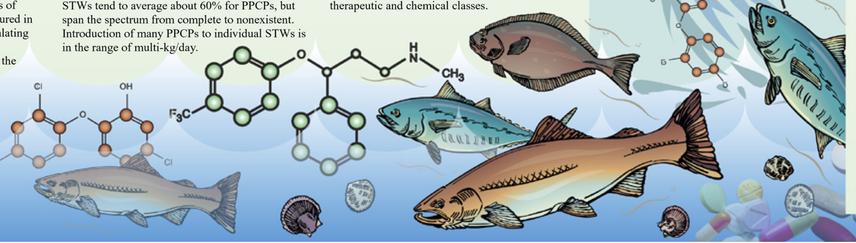
The Issue – Beyond the "Priority Pollutants": Ecosystem change is effected by human activities primarily via three routes — habitat disruption/fragmentation, alteration of community structure (e.g., introduction of alien species), and chemical pollution. The scope of the former two are highly delineated compared with the latter. During the last three decades, the impact of chemical pollution has focused almost exclusively on the very small group of conventional "priority pollutants." This class of chemicals, however, is only one piece of the larger puzzle. A category of potential pollutants receiving very little attention includes **pharmaceuticals and active ingredients in personal care products (PPCPs)**, which are continually introduced to the environment by way of numerous routes. While their immediate biological actions on non-target species (esp. in the aquatic realm) may seem imperceptible, they nonetheless could lead to adverse impacts — as a result of subtle effects (from low, ppb-ppt concentrations — µg-ng/L) whose continual expression over long periods of time could lead to cumulative, insidious changes that would otherwise be attributed to "natural" change or adaptation.

PPCPs comprise a diverse array of potential pollutants manufactured in large quantities: PPCPs are used in large amounts throughout the world — quantities of many are on par with agrochemicals (measured in tons -- sometimes thousands of tons). 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 (most of which are poorly understood, especially in wildlife). While the individual concentrations of particular drugs may be low in the aquatic environment, the combined concentrations of numerous drugs sharing a common mechanism of action could be significant (cumulative exposure).

Sewage and solid waste are the primary sources of PPCPs in the environment: These bioactive compounds are continually introduced to the environment (primarily via surface and ground waters) from human and animal use largely through sewage treatment works (STWs) and wet-weather runoff — directly by washing (via discharge of externally applied PPCPs) and indirectly by excretion of unmetabolized parent compounds; bioactive metabolites (including reconvertible conjugates) are also excreted. Direct disposal of expired PPCPs via sewage and municipal refuse serves as another route of introduction to the environment. While aspirin and caffeine have long been known to occur in sewage, only since the 1980s have other PPCPs been routinely identified in surface and ground waters — even drinking water. The low concentrations of individual PPCPs (possibly below the catabolic enzyme affinities of sewage microbiota), coupled with their metabolic "novelty" to microorganisms, leads to incomplete removal from STWs; in general, removal efficiencies from STWs tend to average about 60% for PPCPs, but span the spectrum from complete to nonexistent. Introduction of many PPCPs to individual STWs is in the range of multi-kg/day.

Ubiquitous, persistent, and sometimes bioaccumulative: Many PPCPs and their metabolites are ubiquitous and display persistence in, and bioaccumulation (e.g., synthetic musk fragrances) from, surface waters on par with that of the widely recognized organochlorine pollutants (e.g., DDT, PCBs). Concentrations in natural surface waters (including oceans) generally range from ppb (µg/L) to ppt (ng/L). Some PPCPs are extremely persistent and introduced to the environment in very high quantities (e.g., X-ray contrast media). Regardless of how short their half-lives in the environment might be, however, all PPCPs can act as persistent pollutants because they are continually replenished by the continual introduction of sewage effluent.

Pollutant classes range from endocrine disruptors, antibiotics, antidepressants ... to synthetic musk fragrances and many others ... Representative classes of PPCPs that may occur in surface waters that receive STW effluents include synthetic estrogens from oral contraceptives (which can feminize fish) ... fluoroquinolone antibiotics (possibly leading to unnecessary development of widespread bacterial resistance) ... antidepressant selective serotonin-reuptake inhibitors (SSRIs) such as Prozac (which can disrupt sexual behavior in shellfish at very low concentrations) ... and nitro musk fragrances (toxic and accumulate in fin and shellfish lipids) — only a few of the representatives from numerous other therapeutic and chemical classes.



COLLABORATORS

This multifaceted issue involves a wide range of disciplines, including analytical/environmental chemistry, toxicology, pharmacology, medical and veterinary sciences, hydrology, sanitary engineering, risk assessment, and policy making. Collaborations are occurring among a wide range of federal scientists in the U.S. (EPA, USGS, FDA, CDC, USFWS), Europe, and Canada (Health Canada) and university researchers (supported by grants from the EPA STAR program and other organizations such as USGS and Sea Grants).

EFFECTS

Effects on aquatic (non-target) species can range from acute to subtle: While the vast majority of PPCPs have poorly understood modes of action in man, their actions/ramifications on non-target biota are practically unknown. Even so, a few PPCPs are already known to elicit profound effects on aquatic life (which cannot escape continual, life-cycle exposure) at very low concentrations. For example, SSRI antidepressants such as Prozac can induce reproductive behavior in certain shellfish at 10^{-10} M.

A major concern is not necessarily acute effects to non-target species (effects which are amenable to monitoring once they are understood), but rather, *the manifestation of perhaps imperceptible effects that can accumulate over time to yield truly profound changes that seem to arise from nowhere.*

Gross within-class differences with respect to aquatic effects possibly makes the approach of assessing eco risk on a class-by-class basis untenable. For example, some SSRIs are extremely potent while others have almost no effect. But the possibility for additive effects (from exposure to multiple PPCPs sharing a common mechanism of action) or synergistic effects is also real.

Subtle effects leading to environmental change? Imperceptible, subtle effects (from low, ppb-ppt concentrations of bioactive PPCPs) whose continual expression over long periods of time in certain non-target (esp. aquatic) species could lead to cumulative, insidious, adverse impacts that would otherwise be attributed to "natural" change/adaptation. Examples of PPCPs that hold the potential to effect long-term change include angiogenesis inhibitors, antineoplastics, antibiotics, sex steroids, SSRIs, calcium channel blockers, and antiepileptics.

Synergistic and potentiated effects could be profound — "Chemosensitizers": A non-specific excretory system called "multixenobiotic transporters" comprises cell proteins that facilitate the active export of potentially toxic substances (primarily those of moderate lipophilicity) from inside cells. Evidence points to the toxicological significance of these non-specific transporters as maintaining a "first line of defense" from exposure to multiple xenobiotics in aquatic species. This "extrusion pump" protein system facilitates the removal of many toxic substances from (and prevents their entry to) aquatic organisms. Unfortunately, these defensive transport systems can be inhibited — by substances loosely referred to as "chemosensitizers." The classic example is verapamil (a cardiac drug — calcium ion influx inhibitor), which at µM concentrations (and lower) greatly increases the toxicity of a number of drugs (or other xenobiotics) for many aquatic organisms. Because these other toxicants cannot be readily removed from the exposed organism, exposure time is thereby lengthened by their intracellular accumulation. Little is known about which xenobiotics can act as "chemosensitizers" in the aquatic environment, or their frequency of occurrence in the environment. But the combined action of many PPCPs (and other toxicants) acting as efflux pump inhibitors could prove significant.

FUTURE NEEDS

Are the current approaches to risk assessment comprehensive? Questions can be raised as to whether the approaches to environmental risk assessments and epidemiological studies sufficiently consider the "universe" of toxic substances involved in exposure or whether the focus on conventional "priority pollutants" gives a narrow perspective. The major unknown in toxicology today is the significance of continual, low-dose exposure to multiple chemicals simultaneously.

The future of research on PPCPs in the environment: The nearly unknown ramifications of PPCPs in the environment (occurrence, fate, transport, effects) warrants a more precautionary view on their environmental disposition. Environmental scientists need to focus more attention on this issue in order to determine with minimal expenditure of resources whether there are any concerns. An effort similar to that which was invested in elucidating the environmental transformation and fate of persistent pesticides and industrial "toxics" (often referred to as POPs or PBTs) needs to be made for PPCPs. Certain PPCPs could eventually be selected for the EPA's Drinking Water Contaminant Candidate List.

Research Gaps: Although the research and monitoring studies to date have added greatly to our understanding of the occurrence and sources of PPCPs as environmental pollutants (and much still needs to be done in this area), those areas that have received no attention are establishing (i) human exposure (esp. fetal and infant) and (ii) the potential effects on non-target organisms (esp. aquatic life). Many proactive actions could also be taken with regard to source reduction (e.g., drug formulation and delivery design, and disposal of expired drugs).

REFERENCES

Daughton, C.G. "Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants: Pollution from Personal Actions, Activities, and Behaviors"; EPA Web Site conceived, designed, established, and maintained by C.G. Daughton (beginning in April 2000): http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm

Daughton, C.G.; Ternes, T.A. "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?" *Environ. Health Perspect.* **1999**, *107*(suppl 6), 907-938.

Daughton, C.G.; Jones-Lepp, T. (eds.) Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues, *Symposium Series 791*; American Chemical Society: Washington, D.C., 2001, 416 pp.

Daughton, C.G. "Pharmaceuticals in the environment: Overarching issues and overview," in *Symposium Series 791*; American Chemical Society: Washington, D.C., 2001, pp. 2-38.

Daughton, C.G. "Illicit Drugs in Municipal Sewage: Proposed New Non-Intrusive Tool to Heighten Public Awareness of Societal Use of Illicit/Abused Drugs and Their Potential for Ecological Consequences," in *Symposium Series 791*; American Chemical Society: Washington, D.C., 2001, pp. 348-364.

Kümmerer, K. Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks, Springer-Verlag Heidelberg, 2001, 265 pp.

Kolpin et al. "Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance," *Environ. Sci. Technol.* **2002**, *36*, 1202-1211.

SUBSET OF PPCPs POTENTIALLY OCCURRING IN THE ENVIRONMENT

Compound (common name)	Structure	Use/Origin	Environmental Occurrence	relevant information regarding the environment
bezafibrate	2-[4-[2-(4-chlorobenzoyl) amino]ethyl]phenoxy]-2-methylpropanoic acid MW 361.82 $C_{19}H_{20}ClNO_4$	lipid regulating agent	loading of ca. 300 g/day in German POTW (Ternes 1998); POTW* removal efficiency 83% (Ternes 1998); 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 (Stumpf et al. 1999) with removal efficiencies ranging from 27-50%. *publically owned treatment works	among highest reported values for occurrence in STW effluent and surface waters
bisoprolol	1-(isopropylamino)-3-[(iso-propoxyethoxymethyl)phenoxy)-2-propanol MW 325.45 $C_{18}H_{31}NO_4$	betablocker (antihypertensive)	POTW max. effluent: 0.37 µg/L; max. in surface waters: 2.9 µg/L (Hirsch et al. 1998)	
carbamazepine	5H-dibenz[b,f]azepine-5-carboxamide MW 236.27 $C_{15}H_{12}N_2O$	antiepileptic drug	loading of over 100 g/day in German POTW (Ternes 1998); but load in effluent can be 114 g/day; POTW removal efficiency 7% (Ternes 1998); POTW max. effluent: 6.3 µg/L; max. in surface waters: 1.1 µg/L	only 1-2% excreted free (Ternes 1998); 10,11-epoxy-carbamazepine major metabolite; also excreted as glucuronides
chlorophene	o-benzyl-p-chlorophenol MW 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 (Ternes et al. 1998); removal not as extensive as for biphenylol.	
clofibric acid	2-(4-chloromethylphenoxy)-propionic acid MW 214.65 $C_{10}H_{11}ClO_3$	polar, active metabolites of lipid regulators (clofibrate, etofyllin clofibrate, etofibrate)	one of first drug/metabolites ever reported in sewage influent/effluent: Missouri STW effluent avg. 2.1 kg/day (Hignite and Azarnoff 1977). Loading of over 50 g/day in German POTW (Ternes 1998); POTW removal efficiency 51% (Ternes 1998); POTW max. effluent: 1.6 µg/L; max. in surface waters: 0.55 µg/L. Swiss rural/urban lakes: 1-9 ng/L (apt); North Sea (up to 78 ng/L) Buser et al. (1998)	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 (Ternes 1998)
17α-ethynyl estradiol	MW 296.41 $C_{20}H_{24}O_2$	oral contraceptive	up to 7 ng/L in POTW effluent (Routledge et al. 1998)	prime synthetic suspect regarding estrogenic effects in fish; the natural estrogen is 17β-estradiol.
fluoroquinolone carboxylic acids	large class; e.g., ciprofloxacin: MW 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 occurence 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.	gyrase inhibitors (needed for DNA replication); excreted mainly as parent compound; strongly sorbs to soil
fluoxetine (Prozac)	*N*-methyl-3(p-trifluoro-methylphenoxy)-3-phenylpropylamine MW 309.33 $C_{17}H_{18}F_3NO$	anti-depressant (selective serotonin reuptake inhibitor, SSRI)	not yet searched for in environmental samples, but effects on shellfish are dramatic.	Fluoxetine elicited significant spawning in male mussels at 10^{-7} M (ca. 150 µg/L) and in females at 10^{-6} M (Fong 1998).
fluvoxamine (Luvox)	5-methoxy-4'-(trifluoromethyl)-valero-phenone-(E)-O-(2-amino-ethyl) oxime maleate MW 318.34 $C_{15}H_{21}F_3N_2O_2$	anti-depressant (selective serotonin reuptake inhibitor, SSRI)	not yet searched for in environmental samples, but effects on shellfish are dramatic.	Fluvoxamine elicited significant spawning in male mussels at 10^{-9} M (ca. 0.318 µg/L) and in females at 10^{-7} M. Fluvoxamine is the most powerful spawning inducer ever identified for bivalves (Fong 1998).
musk ambrette (a nitro musk)	2,6-dinitro-3-methoxy-4-tert-butyl toluene MW 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 personal care products.	Synthetic musks first began to be identified in environmental samples almost 20 years ago. Yamagishi et al. (1983) 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; those of musk ketone were generally in the same range, but in distinct contrast, were not detectable in upstream samples. Winkler et al. (1998) 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 that for 15 PAHs, and exceeded those for 14 common polychlorinated organic pollutants (only HCB and p,p'-DDT were of similar concentrations). Also found in all the 31 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. (1998) 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 (ppb) to 105 ng/g in fish muscle tissue. Eschke et al. (see Mersch-Sundermanno et al. 1998) identified Galaxolide®, Tonalide®, and Celestolide® in the fatty tissue of bream and perch from the Ruhr River (Germany) at average concentrations ranging from 2.5-4.6 mg/kg (ppm). Müller et al. (1996) identified in the Swiss river Glatt Galaxolide®, Tonalide®, and Celestolide® at ng/L concentrations (136 ng/L, 75, and 3.2, respectively); they also found the nitro-musks (tibetene, ambrette, moskene, ketone, and xylene) at ng/L concentrations (0.04 ng/L, <0.03, 0.08, 8.3, and 0.62, respectively).	the nitro musks are being phased out of use in many parts of the world. musk xylene
musk xylene (a nitro musk)	1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene MW 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 MW 294.31 $C_{14}H_{18}N_2O_5$			
musk moskene	4,6-dinitro-1,1,3,3,5-pen-tamethylindane MW 278.31 $C_{14}H_{18}N_2O_4$			
musk tibetene	1-*tert*-butyl-2,6-dinitro-3,4,5-trimethylbenzene MW 266.30 $C_{13}H_{18}N_2O_4$			
Galaxolide® (HHCB) (a polycyclic musk)	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-(g)-2-benzopyran MW 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 personal care products.		Galaxolide
Tonalide® (AHTN) (a polycyclic musk)	7-acetyl-1,1,3,4,4,6-hexa-methyltetraline MW 244.38 $C_{17}H_{24}O$			
Celestolide® (ADBI) (a polycyclic musk)	4-acetyl-1,1-dimethyl-6-tertbutylindane MW 244.38 $C_{17}H_{24}O$			
reduced (aminated) musk xylene derivatives	1-*tert*-butyl-3,5-dimethyl-2-amino-4,6-dinitrobenzene	transformation products of nitro musks, resulting from microbial reduction of the nitro groups.	Gatermann et al. (1998) 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. Behrett et al. 1998 tested the acute toxicity of four reduced analogs of musk xylene on Daphnia magna. The p-amino-ditions 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).
	1-*tert*-butyl-3,5-dimethyl-2,4-diamino-6-nitrobenzene			
	1-*tert*-butyl-3,5-dimethyl-2,4,6-*tri*-aminobenzene			
naproxen	e.g., Naproxyn; (+)-2-(6-methoxy-2-naphthyl)-propionic acid MW 230.26 $C_{14}H_{14}O_3$	analgesic/anti-inflammatory	loading of over 50 g/day in German POTW (Ternes 1998); POTW removal efficiency 66% (Ternes 1998); POTW max. effluent: 0.52 µg/L; max. in surface waters: 0.39 µg/L	
paroxetine	e.g., Paxil; (-)-trans-4R-(4'-fluorophenyl) -3S-((3',4'-methylenedioxy-phenoxy)methyl)piperidine MW 329.37 $C_{19}H_{20}FNO_3$	anti-depressant (selective serotonin reuptake inhibitor, SSRI)	not yet searched for in environmental samples, but effects on shellfish are dramatic.	Compared with fluoxetine and fluvoxamine, paroxetine does not elicit spawning behavior in molluscs
propyphenazone	1,2-dihydro-1,5-dimethyl-4-(iso-propyl)-2-phenyl-pyrazol-3-one MW 230.31 $C_{14}H_{18}N_2O$	analgesic	Grinsted (DEN) landfill leachates: 0.3-4.0 mg/L directly beneath and declining depending on depth and distance along plume (Holm et al. 1995)	
sulfonamides	large class	antibiotics	Grinsted (DEN) landfill leachates: 0.04-6.47 mg/L directly beneath and declining depending on depth and distance along plume (Holm et al. 1995)	
triclosan	2,4,4'-trichloro-2-hydroxy-diphenyl ether MW 289.55 $C_{12}H_7C_{13}O_2$	antiseptic	0.05-0.15 µg/L in water (Okumura and Nishikawa 1996). Antibacterial widely used for 30 years in a vast array of consumer products. Its usage as a preservative and disinfectant continues to grow, for example, incorporated at <1% in Colgate's "Total" toothpaste. Triclosan's use in commercial products span footwear (in hosiery and insoles of shoes called "odor-eaters"), hospital handwasp, acne creams (e.g., Clearasil), and rather recently as a slow release product called Microban, which is incorporated in a wide variety of plastic products (from children's toys to kitchen utensils, such as cutting boards).	