Pharmaceuticals & Personal Care Products (PPCPs) in the Environment: Agents of Subtle Change?

[based on Daughton & Ternes, 1999]

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BACKGROUND

The Issue: Ecosystem change is brought about by human activities primarily via three routes — habitat disruption/fragmentation, alteration of community structure, and chemical pollution. The scope of the former two is highly delineated 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. A class of potential pollutants receiving very little attention includes pharmaceuticals and active ingredients in personal care products (PPCPs), which are continually introduced to the environment via a number of routes. While their immediate biological actions on non-target species (esp. in aquatic habitats) 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 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). Introduction to the marketplace of new pharmaceuticals is adding exponentially to the large array of chemical classes, each with distinct modes of biochemical action (many 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 mode of action could be significant.

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. This occurs 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. Disposal via 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 1980's have other PPCPs been identified in surface and ground waters — even drinking water. The low concentrations of individual PPCPs (possibly exceeding 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 multiple pounds (or kilograms) per day.

Ubiquitous, persistent, and bioaccumulative: Many PPCPs and their metabolites are ubiquitous and display persistence in, and bioaccumulation (e.g., 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).

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 they accumulate in fin and shellfish lipids) — to name only a few of the representatives from numerous classes.

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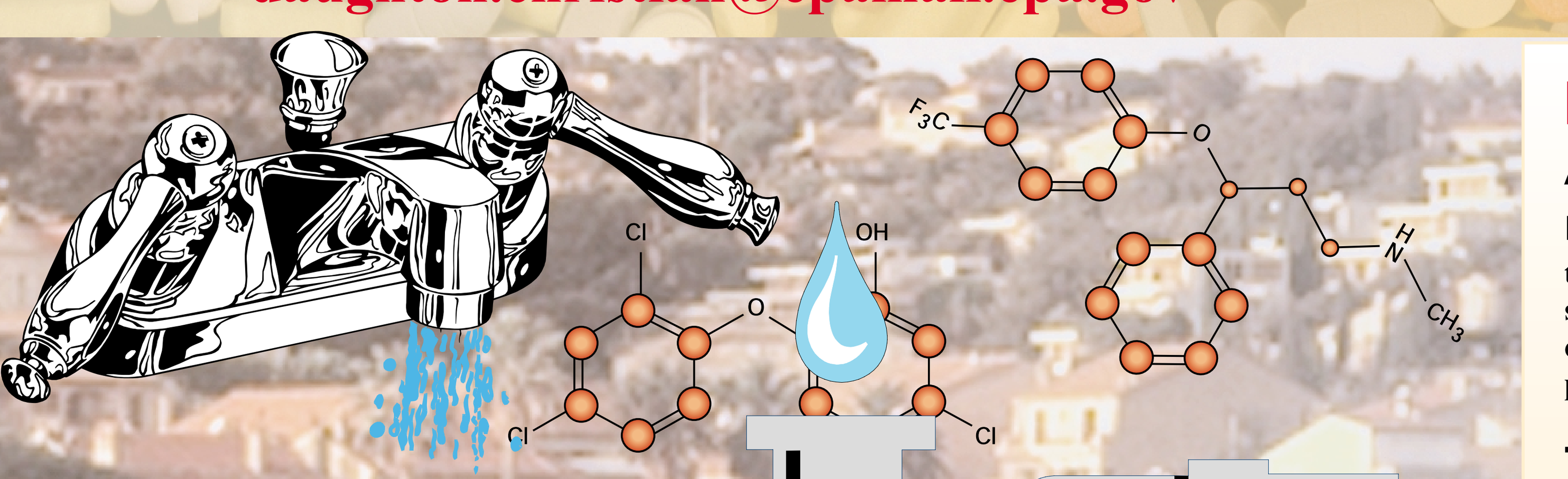

EFFECTS

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 humans, 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 their 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.

Perhaps 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 imperceptible effects that can accumulate over time to yield truly profound changes that seem to arise from nowhere. These subtle effects can masquerade as seemingly normal deviation.

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.

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. Antineoplastics and SSRIs are just two of many drug classes that harbor the ability to effect long-term effects.

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. Perhaps the toxicological significance of these non-specific transporters is in maintaining a "first line of defense" from exposure to multiple xenobiotics in aquatic species. This "extrusion pump" protein system facilitates the removal (and prevents the entrance of) many toxic substances from aquatic organisms. Unfortunately, these transporters can be inhibited — by substances loosely referred to as "chemosensitizers". An 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 the toxicants cannot be readily removed from the exposed organism, exposure time is thereby lengthened by intracellular accumulation. Little is known about which xenobiotics can act as "chemosensitizers" in the aquatic environment, or their frequency of occurrence in the environment.

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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 future for 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 concern. 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) may need to be made for PPCPs.

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-[isopropoxyethoxymethylphenoxy]-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. 1996)	
carbamazepine	5Hdibenz[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 metabolite 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. effluen: 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) 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 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.	gyrase inhibitors (needed for DNA replication); excreted mainly as parent compound; strongly sorbs to soil
fluoxetine (Prozac)	*N*-methyl-2(*p*-trifluoromethylphenoxy)-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 -(trifluromethyl)-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), Galaxolidefi (148-736 ng/g), and Tonalidefi (194-770 ng/g); Celestolidefi 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 concentration). Also found in all the 31 water samples were musk ketone (2-10 ng/L), Galaxolidefi (36-152 ng/L), and Tonalidefi (24-88 ng/L); Celestolidefi 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; Galaxolidefi and Tonalidefi 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 Galaxolidefi, Tonalidefi, and Celestolidefi 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). M ller et al. (1996) identified in the Swiss river Glatt Galaxolidefi, Tonalidefi, and Celestolidefi 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-pentamethylindane 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 $C_{13}H_{18}N_2O_4$			
Galaxolidefi (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.		Galoxolide
Tonalidefi (AHTN) (a polycyclic musk)	7-acetyl-1,1,3,4,4,6-hexamethyltetraline MW 244.38 $C_{17}H_{24}O$			
Celestolidefi (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; 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.	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, repectively; 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. Behecti et al. 1998 tested the acute toxicity of four reduced analogs of musk xylene on Daphnia magna. The p-amino-dinitro compound exhibited the most toxicity of the four, with EC50 values averaging 0.25 µg/L (0.25 ppb).
naproxen	e.g., Naprosyn; (+)-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-(isopropyl)-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)	
sulfanoamides	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 handsoap, 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).	

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