Pharmaceutical Compounds in the Environment

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Introduction:

Low levels of Pharmaceutically Active Compounds (PhACs) have been measured in surface waters, groundwater, drinking water resources, and wastewater effluent throughout the US and Europe (for example, Kolpin et al 2002). These compounds include antibiotics, analgesics, antidepressants, beta-blockers, and hormones and hormone mimics such as estrogen or estradiol. PhACs number in the thousands, with more than 90 PhACs prescribed at rates greater than 10 tons/yr in the US. Because PhACs are designed to target specific metabolic and biological pathways at low levels, there is concern that, after release to the aquatic environment, some compounds may disrupt key processes in sensitive non-target organisms, including certain human populations. Due to the issue's relatively recent emergence and PhACs wide-ranging chemical properties, published data describing the occurrence, fate and transport, and effects of these compounds is sparse, incongruent, and geographically scattered compared to more "established" pollutants such as PCBs, PAHs, and heavy metals. Little is known about the potential human and ecological health risks of PhACs or PhAC-mixtures pose at environmentally relevant concentrations, nor which among the thousands of compounds or compound classes should be prioritized for in-depth toxicological and fate and transport research.

Human PhACs enter aquatic environments primarily through the discharge of treated and untreated wastewater to surface water bodies, or to aquifers from septic systems and groundwater recharge. PhAC use is widely distributed, with 3.6 billion prescriptions dispensed in the US in 2003 and 45 percent of US residents using at least one prescription drug per month (1999-2002) (http://www.cdc.gov/nchs/fastats/drugs.htm). Following consumption of these prescritption drugs, both metabolites and unmetabolized PhACs are excreted in urine and feces. Metabolism rates vary greatly across compounds, from <1% to >95% metabolized before excretion into the waste stream. PhACs undergo additional transformations or physical removal within a wastewater treatment plant (WWTP), but removal efficiency is highly variable across compounds and can be substantially less than 100% . The relatively long environmental half life of many PhACs, once released from WWTPs, results in their accumulation to measurable levels in aquatic ecosystems (Tixier et al, 2003). Another important source of pharmaceutical compounds to the environment is the inappropriate disposal of unused prescriptions.

The ability of individual PhACs or PhAC-mixtures to induce toxic effects in humans and aquatic organisms at environmentally relevant concentrations, and the most appropriate endpoints for assessing toxicity, remain topics of on-going investigation and debate. When detected in natural waters, individual PhACs are generally measured at concentrations less than 1 ppb, while combined PhAC concentrations can exceed 1 ppb (Kolpin et al., 2002). At these levels, studies argue that the potential daily human exposure to PhACs through drinking water is at least three orders of magnitude lower than the daily therapeutic dose, and that exposure at such levels does not pose unacceptable human health risks (Webb et al., 2003). Other studies have arrived at similar conclusions (Christensen 1998, Schulman et al 2002, Schwab 2005, Cooney 2005). However, *in vitro* work suggests that PhACs can induce effects at low concentrations

along non-therapeutic pathways. Pomati et al (2006) exposed human cell lines to a suite of PhACs at environmentally relevant concentrations and found that, among other outcomes, the drug mixture inhibited human embryonic cell growth. The effects of mixtures of pharmaceuticals and the importance of the timing of exposures are still largely uncertain.

The ecological risks posed by PhACs are difficult to characterize because of the myriad interdependent organisms – from microbes to vertebrates – that comprise a healthy ecosystem, and the multiple routes along which toxic compounds can exert effects. The study of human pharmaceutical compounds in the environment are further complicated by the fact that similar drug receptors conserved in many taxa may affect different metabolic processes in different species. For example, serotonin is found not only in humans and other mammals, but also in many other phyla, including invertebrates. In humans, serotonin activity regulates appetite, sleep, sexual arousal, and depression. This role of serotonin is not the same in all organisms. In bivalves, serotonin activity regulates spawning and other reproductive processes. In gastropods, serotonin activity regulates egg-laying, while in protozoans, it regulates cilia regeneration (Lange and Dietrich, 2002). It is therefore possible that common anti-depressant drugs such as Prozac, a selective serotonin reuptake inhibitor, may have unintended consequences for ecological receptors at low concentrations.

Environmental Loadings of Pharmaceutical Compounds and Risk Prioritization

There is currently no objective, widely accepted approach for *a priori* identifying high priority PhACs. It would highly inefficient (an infeasible) to conduct detailed studies for each of the thousands of commonly used PhACs. The measurement of PhACs in environmental media can be expensive, requiring sophisticated laboratory equipment and highly trained laboratory

staff. In addition, many PhACs have never been analyzed for in environmental samples, and therefore have no established methods for their analysis. Unless PhACs are prioritized based on their relative potential to exert adverse outcomes, potentially important PhACs will go understudied because research will be biased toward compounds with well-established analytical methods or high name recognition.

In a study recently competed in our laboratory, we developed and evaluated a quantitative prioritization scheme for PhACs based on their potential "toxic load" (TL) to aquatic environments (Shine et al., 2008). The 'Toxic Load' concept combines estimates of a PhAC's mass loading to the environment and its potential human- or eco-toxicity. We applied this prioritization scheme, using publicly available data, to rank the top 200 generic pharmaceuticals prescribed in the US. Mass loading to the environment (kg/yr) was quantified by estimating the total amount of a PhAC prescribed per year, and subtracting out the fraction metabolized by the human body and/or removed during wastewater treatment. We divided this net environmental loading by a toxicological threshold to calculate the TL. Therefore, compounds with very high loadings, or where the toxicity thresholds is very low will have high values of TL. We calculated 9 sets of TLs using nine different toxicity endpoints that ranged from human data, rat and mouse data, and data for aquatic organisms. These endpoints included (including the source of the data):

1) Adult Initial Dose (Physicians Desk Reference)
2) Human No Observable Effects Level (NOAEL, Calculated using procedure in Layton et al., 1987)
3) Mouse Acute Toxicity (RTECS Database: http://www.cdc.gov/niosh/rtecs/)
4) Mouse Lowest Observed Adverse Effect Level (LOAEL, RTECS Database)
5) Rat Acute Toxicity (RTECS Database)
6) Rat LOAEL (RTECS Database)

7) Algae EC50 (ECOSAR Module of EPI Suite Software, http://www.epa.gov/oppt/exposure/pubs/episuite.htm)

8. Daphnid 96-Hr LC50 (ECOSAR)

9) Fish 96-Hr LC50 (ECOSAR)

The final results of this analysis are shown in attached Figure 1 and Table 1. Figure 1 shows the importance of normalizing to toxicity when evaluating relative risks. The top panel in Figure 1 shows the gross production of all the compounds we evaluated. Two compounds in are highlighted in particular, guaifenesin (a mucus thinner) and methotrexate (an antimetabolite used in chemotherapy). While guaifenesin is one of the top pharmaceuticals produced in this country, once we control for metabolism in reducing loading to the environment (the middle panel) and normalize the environmental loading to toxicity, it becomes one of the lowest priority compounds in the analysis. Methotrexate, on the other hand, while having only modest gross production, is poorly metabolized by the body and has low removal by sewage treatment, leading to relatively higher environmental loadings. Furthermore, because methotrexate can be quite toxic at low levels, it has a relatively higher 'toxicity loading' to the environment.

Table 1 summarizes the top ten pharmaceuticals with respect to their risk-based loadings to the environment. In addition to an overall Risk Priority Score that combines all nine endpoints together, we also have individual rankings for the Human-based endpoints, the Mouse/Rat endpoints, and the Aquatic endpoints. The interesting aspect of these results is that the top 2 compounds identified in this analysis, furosemide and tramadol, have rarely been studied in the environment. Indeed, many of the compounds highlighted by this exercise have not been extensively studied. This highlights the need to prioritize which human pharmaceuticals may be of concern, including environmental transport and fate, an issue not accounted for in this study.

There are four additional issues not touched on by this research. They are: (1) veterinary pharmaceuticals, (2) endocrine disruption as a toxcicological end-point, (3) the effects of anti-biotics in the environment, and (4) personal care products. With respect to veterinary pharamaceuticals , they are used widely in both terrestrial and aquatic farming. There may be locations where local water supplies are compromised by the presence of pharmaceutical compounds migrating from these operations. The second issue is anti-biotics. The above analysis did not avoid antibiotics, but did not seek them out. Studies are beginning to show increased incidence of anti-biotic resistance genes in natural bacteria in areas receiving inputs of anthropogenic waste effluent (Lachmayr, 2007). It is unclear what this means with respect to the prevalence of anti-biotic resistance at large, however. With respect to endocrine disruption, the above analysis looked a nine standard toxicological endpoints. Although the observed (or modeled) toxicity may be due to endocrine disruption, this analysis did not attempt to examine the chronic effects of inappropriate endocrine signaling of pharmaceutical compounds in non-target receptors. Finally, there are vast quantities of chemical compounds used in personal care products that we can see in environmental samples. These include compounds such as platicizers, sun-screen agents, and polycyclic musk compounds. What are the risks posed by these particular compounds? These are all further areas where we will need more information to truly assess the risks of pharmaceutical compounds and personal care products in the environment.

In summary, it should not be surprising that we can detect measurable levels of pharmaceutical compounds in natural waters. As a society we use large quantities of pharmaceutical compounds from which we derive many health benefits. We also have very sophisticated analytical equipment that can measure trace quantities of these compounds.

Because these compounds are ubiquitous, it is impossible to completely limit our exposure to pharmaceuticals, either through drinking water ingestion or via other environmental exposures. Instead, we must understand the risks posed by the presence of these compounds in the environment, risks posed to both human and ecological receptors. In addition, we can't possibly regulate the many hundreds of pharmaceutical compounds currently in use. Instead, we must prioritize which compounds may be of concern, and examine the nature of the risks, particularly when compared to other risks in drinking water such as microbial pathogens and disinfection by-products.

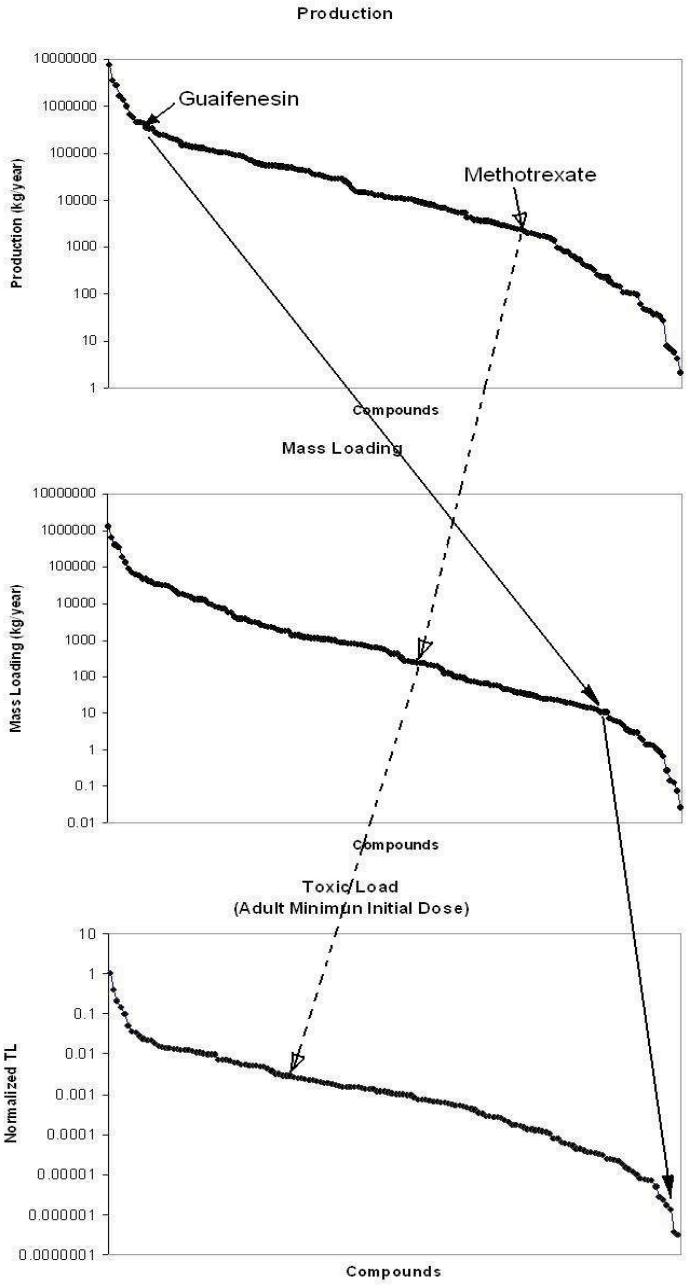

Figure1. Demonstration of the importance of toxicity normalization when prioritizing the risks of pharmaceuticals released to the environment. The top panel ranks all of the compounds studies with respect to gross production. The middle panel shows loading to the environment after accounting for metabolism and removal via sewage treatment. The bottom panel shows the environmental loadings normalized to a toxic threshold (in this case, Adult Initial Dose). The rankings for 2 compounds, guaifenesin and methotrexate, are highlighted to show how rankings (and prioritization) can change when considering removal processes and risk-based thresholds.

Rank	All Endpoints Combined (N=9)			Human Endpoints Only (N=2)			Mouse/Rat Endpoints Only (N=4)			Aquatic Endpoints Only (N=3)		
	Compound	n	Priority Score	Compound	n	Priority Score	Compound	n	Priority Score	Compound	n	Priority Score
1	Furosemide	9	1.81	Hydrochlorothiazide	2	2.37	Furosemide	4	2.25	Tramadol HCl	3	1.73
2	Tramadol HCl	5	1.60	Furosemide	2	2.21	Metformin HCl	2	1.90	Quinine Sulfate	3	1.72
3	Amoxicillin Trihydrate	9	1.41	Amoxicillin Trihydrate	2	1.94	Codeine Phosphate	2	1.59	Hydroxychloroquine Sulfate	3	1.52
4	Codeine Phosphate	7	1.40	Lisinopril	1	1.93	Acetaminophen	4	1.58	Verapamil HCl	3	1.48
5	Atenolol	8	1.36	Atenolol	2	1.75	Phenazopyridine HCl	1	1.47	Amiodarone HCl	3	1.32
6	Cephalexin	7	1.20	Famotidine	1	1.55	Tramadol HCl	1	1.43	Amoxicillin Trihydrate	3	1.30
7	Ranitidine HCl	8	1.19	Nadolol	2	1.49	Atenolol	3	1.38	Codeine Phosphate	3	1.29
8	Metformin HCl	6	1.18	Cephalexin	1	1.41	Ranitidine HCl	3	1.37	Hydroxyzine	3	1.25
9	Hydroxychloroquine Sulfate	6	1.18	Tramadol HCl	1	1.38	Cephalexin	3	1.36	Trimethoprim Sulfate	3	1.24
10	Acetaminophen	9	1.15	Ranitidine HCl	2	1.38	Methocarbamol	2	1.32	Erythromycin	3	1.16

Table 1. Risk-Based Priority Scores for human pharmaceuticals released to the US environment. Data are shown for all 9 endpoints combined, or grouped by the 2 human-based endpoints, the 4 mouse/rat endpoints, or the 3 aquatic endpoints. The priority scores are based on a combination of gross production, net release to the environment, and the particular toxicity of a compound to a particular receptor.

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