Pharmaceuticals in the Water: A comprehensive approach to prioritization for monitoring, analysis, and evaluation of the potential risk to human health

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Background

The use of pharmaceuticals has grown rapidly and continues to grow. Pharmaceuticals are increasingly detected in drinking water sources throughout the world. The levels that have been detected are generally in the low parts per billion (ppb) to parts per trillion (ppt) range, leading to questions of the possible toxicological consequences at these low levels. However, these occurrences may pose a concern because active pharmaceutical ingredients (APIs) are formulated for maximal potency directed toward specific biological targets.

Objectives

- To create a rapid screening process for orally administered prescription pharmaceuticals
- Use results to prioritize monitoring, analysis, and further evaluation of pharmaceuticals

Table 1. Decision Tree Framework

Information Considered	UF or AF data applies to and possible values a
• FDA Pregnancy Category • Use for life-threatening conditions • Does the LTD only apply to adults; not tested in children or high level of concern for dosing in children • LTD linked to Serious Side-effects • Black Box Warnings	UF1: LOAEL – NOAEL • (1, 3, or 10)
• Database Concerns (lack of suitable studies to evaluate key concerns)	UF2 : Database • (3 or 10)
• Variability among humans; Applied to all APIs	UF3: Intraspecies (10)
• Duration of Use (some short-term use drugs may not have adequate long-term studies)	AF1: Duration • (3 or 10)
• Non-genotoxic carcinogen *the adjustment factor for carcinogenicity is currently still being further examined . Whether or not non-genotoxic carcinogens should be evaluated using this process at all is being evaluated.) • Non-Human Species Specific Cancer • Localized cancer not relevant to oral dosing	AF2: Carcinogen • (1 or 10)
• Endocrine Activity	AF3: Endocrine Activity • (1, 3, or 10)

Methodology of Screening Process

The most-prescribed (2011 and 2012 data) APIs used in the U.S were analyzed. The FDA approved label was used as the source of the lowest therapeutic dose (LTD) and all other toxicity related information. A decision tree framework (Table 1) was developed to guide the evaluation of the drug label. The framework was developed using uncertainty factors (UF) from traditional risk assessment and from reports focused on the addition of adjustment factors (AF).

Conservative water screening values were calculated (Table 2) for 87 unique APIs using a toxicity value based on the LTD. The highest available occurrence data for surface, waste effluent, ground, and finished drinking water were gathered and compared to the calculated drinking water screening values to yield a risk ratio. Non-detects were not considered or used in assessment. This ratio was used to prioritize the APIs based on potential to cause harm to human health as well as to prioritize future water monitoring.

Table 2. Calculations used for assessment

$$\text{Screening Toxicity Benchmark (mg/kg} - \text{d)} = \frac{\text{LTD (mg/kg} - \text{d)}}{\text{UF1} * \text{UF2} * \text{UF3} * \text{AF1} * (\text{AF2 or AF3})^{a}}$$

$$\text{Screening Water Value (ng/L)} = \frac{\text{Screening Tox. Benchmark} * 0.8^{b} * 1\text{x}10 - 6 \text{ ng/mg}}{0.289 \text{ L/kg} - \text{dc}}$$

$$\text{Screening Risk Ratio} = \frac{\text{Highest Detection Value (ng/L)}^{d}}{\text{Screening Water Value (ng/L)}}$$

[a]Only one (AF) of the potential carcinogenicity AF and the endocrine AF should be use in the calculation. Choose the highest value of the two (e.g. if AF2=10 and AF3=3, choose 10)

[b]Relative Source Contribution Factor (RSC) – set at 0.2 for APIs that are also available as OTC as well as in combination prescription pharmaceuticals. Otherwise, a default ceiling value of 0.8 was used based on EPA Decision Tree for RSC Selection

[c]Infant Water Intake Rate was used for conservative calculations

[d]Occurrence data was collected from the published, peer-reviewed literature, Minnesota Pollution Control Agency (MPCA) Reports, National Park Service (NPS) Monitoring Reports, and US Geological Survey (USGS) Reports .

Table 3. APIs with One or More Risk Ratios Above 1

API	Wastewater Effluent	Surface Water	Ground Water	Finished Drinking Water
17α-Ethinylestradiol	**1.7**			**2.2**
Acetaminophen	0.26	**1.8**	0.33	0.04
Amphetamine	**1.1**	0.15		
Atenolol	**1.6**	0.85	0.01	0.01
Codeine	0.20	**1.7**	0.37	
Diazepam	**47**		**2.5**	**1.7**
Escitalopram	**28**			
Glyburide	0.47	**1.7**	0.31	
Lisinopril	15			
Lorazepam		**9.0**	0.69	
Metoprolol	0.70	**7.7**	0.03	**2.23**
Risperidone	**3.1**			0.40
Temazepam	**12**	**2.9**	1.1	0.12
Venlafaxine	**20**	**3.4**	0.32	
Zolpidem	**7.1**	**1.0**		

Results of Initial Screening

Fifty-four APIs (62%) had an identified detection in one or more water media useable for this assessment. Again, this excludes non-detects as they were not considered as detections.

- 53% (46/87) have identified detections in wastewater effluent
- 51% (44/87) have identified detections in surface water
- 26% (23/87) have identified detections in groundwater
- 17% (15/87) have identified detections in finished drinking water

Fifteen APIs (17%) had one or more risk ratios exceeding 1 (Table 3).

- 10% (9/87) had risk ratios exceeding 1 in wastewater effluent
- 9% (8/87) had risk ratios exceeding 1 in surface water
- 2% (2/87) had risk ratios exceeding 1 in ground water
- 3% (3/87) had risk ratios exceeding 1 in finished drinking water

Twenty-six APIs (30%) are not currently being monitored for by US Environmental Protection Agency, US National Parks Service, US Geological Survey, or the Minnesota Pollution Control Agency.

- 55% (48/87) are currently monitored for by EPA
- 44% (38/87) are currently monitored for by USGS
- 46% (40/87) are currently monitored for by MPCA

Table 4. APIs Not Currently Monitored by an Agency and No Identified Detections

API	Range of Screening Water Value (ng/L)	API	Range of Screening Water Value (ng/L)
Levothyroxine	≤ 10	Meloxicam	> 500-1,000
Olanzapine	> 10-50	Celecoxib	> 1,000 -5,000
Drospirenone	> 10-50	Memantine	> 1,000 -5,000
Rosuvastatin	> 50-100	Olmesartan	> 1,000 -5,000
Nebivolol	> 50-100	Lisdexamfetamine	> 1,000 -5,000
Lovastatin	> 100-500	Losartan	> 5,000-10,000
Cyclobenzaprine	> 100-500	Allopurinol	> 5,000-10,000
Tadalafil	> 100-500	Clavulante	> 5,000-10,000
Pravastatin	> 100-500	Amoxicillin	> 10,000-50,000
Alendronate	> 500-1,000	Cephalexin	> 10,000-50,000
Carvedilol	> 500-1,000		

Conclusions

These APIs, particularly those with the lower screening water values, should be prioritized for analytical method development depending, in part, upon predicted environmental fate considerations which have not yet been assessed.

This project evaluated the most-prescribed APIs in the US to create an un-biased data set of what might be in the environment and pose a risk. As a results of the screening,

- a list of APIs that should be more thoroughly evaluated for human health-based concerns was formed from the APIs with risk ratios in water media greater than 1 (Table 3).
- A list of APIs that should be more thoroughly evaluated for environmental fate and possible analytical method development, formed from those APIs not currently being monitored (Table 4).

Next steps of this project include further examination of environmental fate concerns, bioavailability concerns, and evaluating how to fill in the gaps of monitoring and occurrence data.