Ashley E. Suchomel and Helen M. Goeden - Minnesota Department of Health St. Paul, MN

SCREENING AND PRIORITIZATION OF PHARMACEUTICALS IN WATER FOR MONITORING AND ASSESSMENT

Active pharmaceutical ingredients (APIs) are increasingly detected in surface and ground water in MN and throughout the rest of the world. APIs are generally detected in parts per trillion (ppt) to low parts per billion (ppb) concentrations. Unlike many other chemicals, APIs are formulated for maximal potency directed toward specific biological targets. The biological effect, even if therapeutic to some, may have unintended consequences in the non-target population. Evaluating the potential risks of pharmaceuticals is limited by a lack of health-based drinking water criteria. The goal of the Minnesota Department of Health's pharmaceutical risk assessment project is to develop a rapid screening methodology to assess potential risks.

The top 200 most-prescribed pharmaceuticals in the United States for the years 2011 and 2012 were examined. Publicly available information contained within the FDA approved drug label was used to determine the lowest therapeutic dose (LTD), treated as a LOAEL, and potential factors of concern, identified as Factor 1 (F1) etc., for each API, to develop a conservative toxicity benchmark dose (mg/kg-d).

F1: Carcinogen UF 1 or 10
-genotoxic carcinogens excluded
F2: Intraspecies Variability UF 10
F3: LOAEL UF 1, 3, or 10
F4: Duration UF 3 or 10
F5: Database UF 1 or 3
F6: Endocrine Activity UF 1, 3, or 10

$$\textbf{Toxicity Benchmark (mg/kg-d)} = \frac{\text{Lowest Therapeutic Dose (LTD)}}{\text{F2 x F3 x F4 x F5 x (Highest Value of F1 and F6)}}$$

Repetitious and excluded APIs were removed from the initial list for analysis.

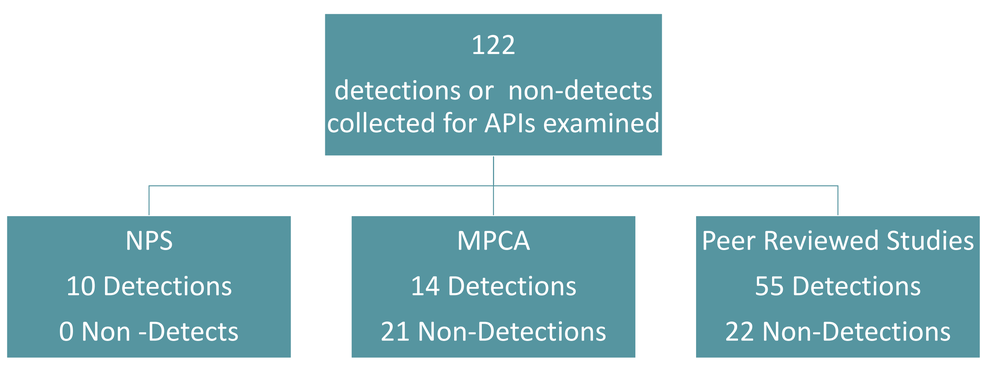
An API was excluded if the primary route of administration was non-oral, it is supplied only as an over-the-counter drug, it is a nutritional supplement, or if it was determined to be a genotoxic carcinogen. Out of the original 200 identified pharmaceuticals, 90 unique APIs were applicable for this screening.

Water concentration values that are protective of highly exposed and vulnerable populations were calculated based on the toxicity benchmark doses and infant water intake rates.

$$\textbf{Screening Water Value} = \frac{\text{Toxicity Benchmark (mg/kg-d) x } 0.8^{a} \text{ x 1000 ug/mg}}{0.289\text{L/kg-d}}$$

[a] Relative Source Contribution Factor (RSC) – set as 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 (US EPA 2000).

Occurrence data was collected for the screened APIs to give context to the derived water values. Occurrence data of APIs in water were collected from National Park Service (NPS) and Minnesota Pollution Control Agency (MPCA) reports, as well as peer reviewed published studies. The reviewed data sources contained occurrence information for 208 unique APIs, 36 of which were contained within our dataset based on the top prescriptions in the United States. For these 36 APIs, 122 (of a total of 876) occurrence data points were applicable to this analysis.



Are pharmaceuticals present in water at concentrations necessary to pose potential harm to the general population?

The toxicity benchmarks and the screening water values ranged across 6 orders of magnitude.

The toxicity benchmarks ranged from 8.3 $x10^{-8}$ to 5.2 $x10^{-2}$ mg/kg-d.
The screening water values ranged from 2 $x10^{-4}$ to 1.5 $x10^{2}$ ug/L (ppb).

To assess potential risk, a screening risk ratio was calculated for each API. This calculated ratio is dependent on the occurrence and detection data found for each API, which may not represent the concentrations everywhere.

$$\textbf{Screening Risk Ratio} = \frac{\text{Detected Occurence Value}}{\text{Screening Water Value}}$$

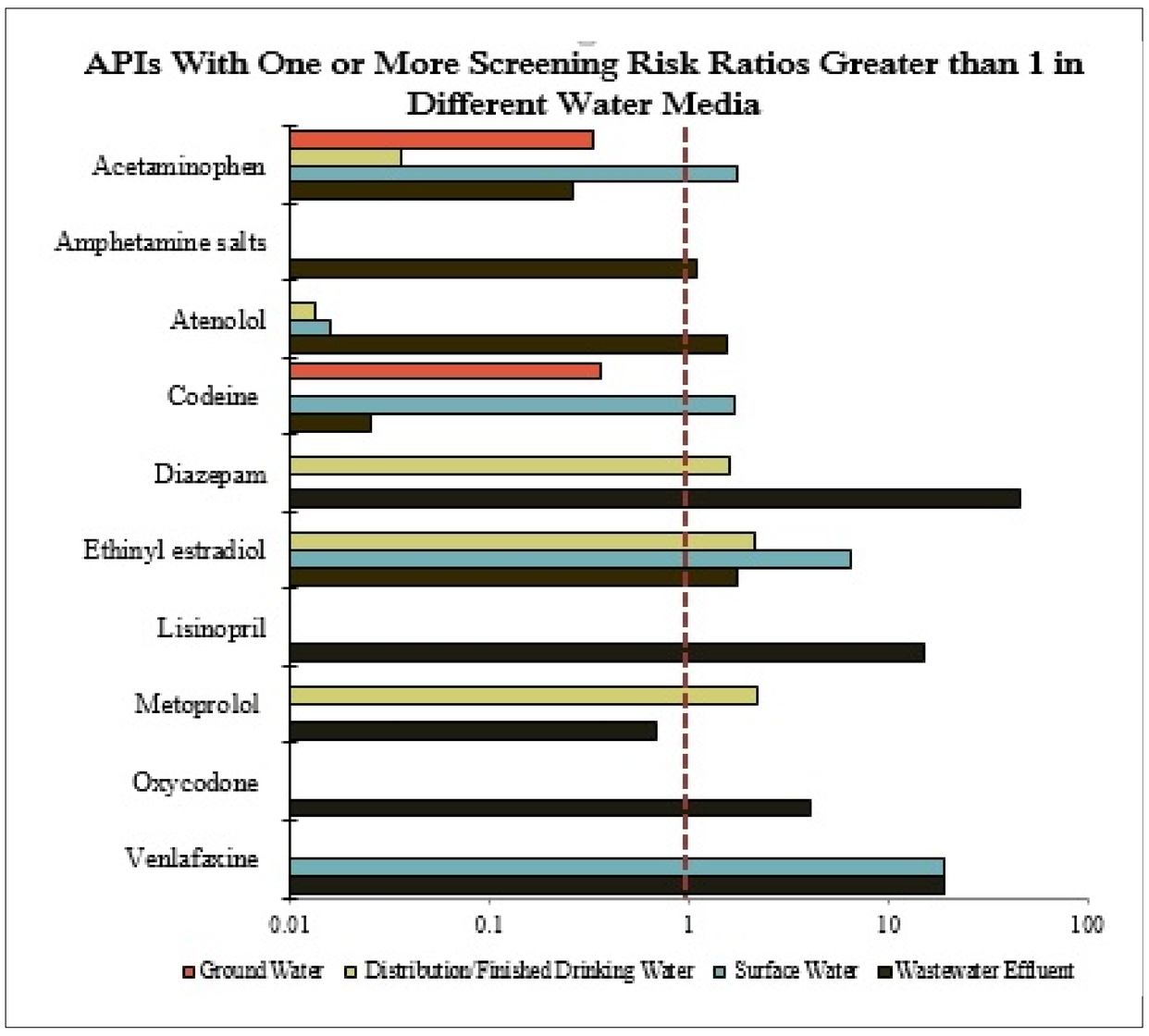
If a screening risk ratio is > 1, there is potential risk , and if the screening risk ratio is ≤ 1, there is no potential risk .

The screening risk ratios were calculated separately for each type of water media occurrence value. Wastewater effluent, surface water, ground water, and finished drinking water ratios were all calculated for each API if occurrence data was available.

The screening risk ratios ranged from 6.5x10^{-4} to 46, spanning nearly 5 orders of magnitude across all water media. The lowest ratios were from surface water media and the highest from wastewater effluent media.

Detection data in the peer-reviewed literature allowed for the calculation of a screening risk ratios for a limited number of APIs: 31 ratios for wastewater effluent, 9 ratios for surface water, 13 ratios for finished drinking water, and 5 ratios for ground water. Minnesota specific data from MPCA or NPS reports resulted in the calculation of surface water ratios for 20 APIs.

Screening risk ratios could be calculated for only 36 (40%) of the 90 unique APIs evaluated.



Of the screening risk ratios calculated for 36 APIs, 10 had a ratio in one or more water media that exceeded 1, indicating that these 10 APIs should be examined more thoroughly as they may pose potential harm to the general population. However, screening risk ratios could be calculated for only 40% of the most prescribed pharmaceuticals in the United States. Potential risks posed by the remaining 60% could not be evaluated due to the lack of occurrence data.

This initial assessment used calculations resulting in conservative and protective in toxicity benchmark values, water values, and screening risk ratios to provide risk context to the available occurrence data, prioritize pharmaceutical monitoring efforts, inform detection limits for analytical methods, and identify pharmaceuticals that should be more thoroughly evaluated. Next steps will include analysis of less commonly prescribed APIs that are found in the occurrence literature and on commonly used laboratory analyte lists. A full report outlining methods, data, and results will be available in the near future.

Visit www.health.state.mn.us/cec for more information and to signup to be notified when the report becomes available.