Supplemental Material for "Screening for Drinking Water Contaminants of Concern Using an Automated Exposure-Focused Workflow"

Kristin K. Isaacs,[1] Jonathan Taylor Wall,[1] Katie Paul Friedman,[1] Jill A. Franzosa,[1] Helen Goeden,[2] Antony J. Williams,[1] Kathie Dionisio,[1] Jason Lambert,[1] Monica Linnenbrink,[1] Amar Singh,[1] John Wambaugh,[1] Alexander R. Bogdan,[2] and Christopher Greene[2]

[1]*Center for Computational Toxicology and Exposure, Office of Research and Development, U.S. Environmental Protection Agency, 109 TW Alexander Drive, Research Triangle Park, North Carolina, 27711*

[2]*Minnesota Department of Health, 625 Robert St. N, St. Paul, MN 55155*

Corresponding author: Kristin K. Isaacs (Isaacs.kristin@epa.gov)

Supplemental Methods

Other Documents Curated for Implementation in Workflow

Minnesota-specific and other documents used in manual MDH scoring were curated into ORD research databases and integrated into the workflow. These documents include references 1-32 below.

In vitro *Bioactivity Data*

High-throughput screening data from the US EPA ToxCast program were used as *in vitro* bioactivity data (invitrodb version 3.4, released September 2021, DOI: https://doi.org/10.23645/epacomptox.6062503.v6). *In vitro* potency data from level 5 of the ToxCast pipeline, i.e., the 50% active concentrations (AC_{50}, µM), were used. The collection of AC_{50} values for a given chemical were filtered according to logic used previously,[25] to remove potency values from curve fits that (a) were associated with 3 or more caution flags on the fitting or (b) demonstrated low efficacy (within 1.2 times the cut-off) and an AC50 value less than the concentration range screened (fit categories 36 and 45 from the ToxCast pipeline).

Calculation of Administered Equivalent Doses

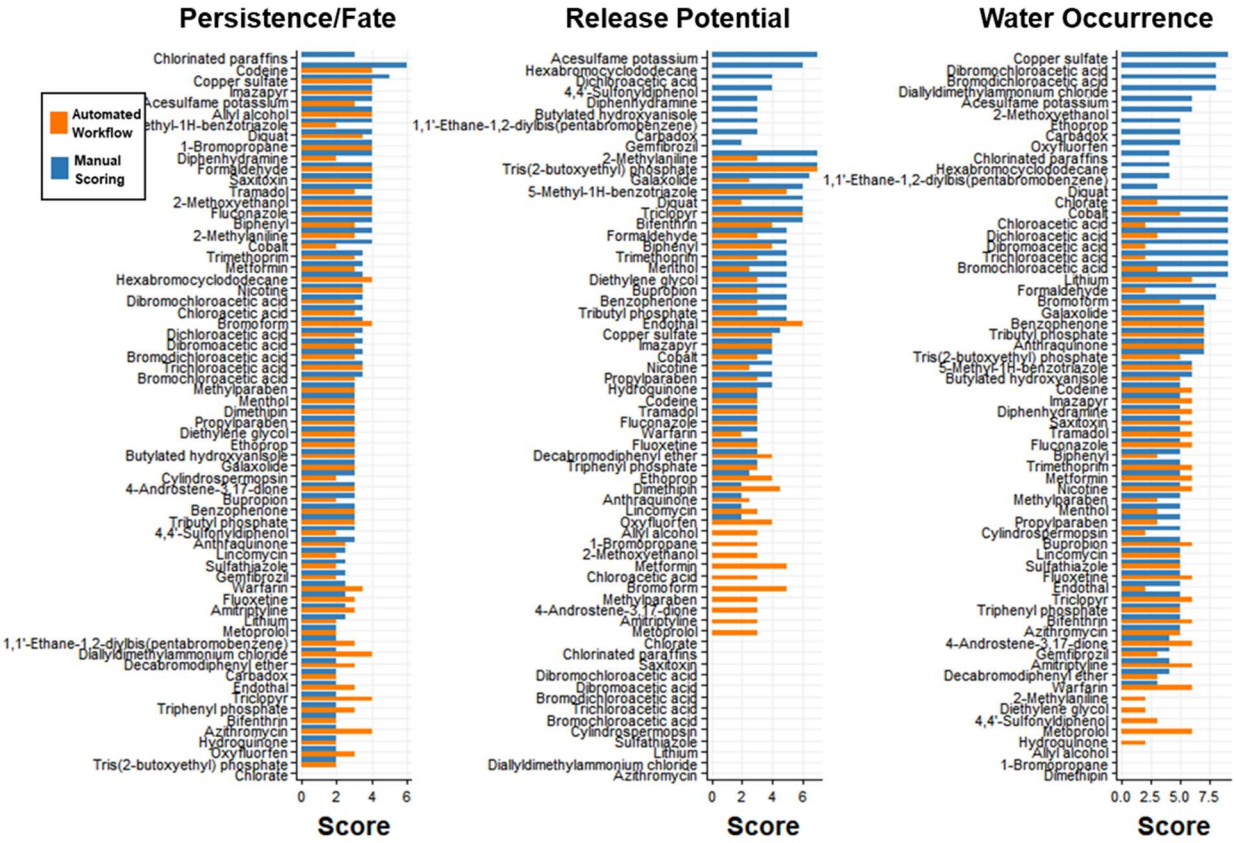
Of the 1867 chemicals on the CEC case study list, 827 chemicals (44%) had sufficient *in vitro* bioactivity data and high-throughput toxicokinetic models and data (R package, httk, version 2.0.5) to estimate administered equivalent doses (AEDs) in mg/kg-day units. The approach used was similar to those of Wetmore et al. (2012, 2015) and Paul-Friedman et al. (2020) as represented by the following equation:

$$AED_{95} = bioactive\ concentration\ (\mu M) * \frac{1\frac{mg}{kg \cdot day}}{Css_{95}\ (\mu M)}$$

where the C_{ss95} is the upper bound estimate of steady-state plasma concentration based on a 3-compartment steady-state model assuming 100% bioavailability. A higher steady-state plasma concentration (C_{ss}) indicates a more sensitive individual (i.e., an individual for whom a lower dose produces the same C_{ss}). AED_{95} thus corresponds to the individual at the 95th percentile of sensitivity (5th percentile of bioactive dose). Monte Carlo simulation was used to vary the following toxicokinetic parameters to simulate population variability: first-order hepatic metabolic clearance, plasma protein binding, liver blood flow, and the rate of clearance via the kidney (Pearce et al. 2017, Wetmore et al. 2012). Specifically, AED_{95} values were calculated using the calc_mc_oral_equiv() function in the httk R package, with the 95th percentile for C_{ss}, restrictive clearance, the 3 compartment steady-state model, and output units of mg/kg/day.

AED_{95} values were calculated for all AC_{50} values (post-filtering the ToxCast data, as described above).

Supplemental Figure



Supplemental Figure S1. Comparison of persistence/fate, release potential, and water occurrence scores for 82 chemicals previously assessed by Minnesota Department of Health.

References

1. Glassmeyer ST, Furlong ET, Kolpin DW, Batt AL, Benson R, Boone JS, Conerly O, Donohue MJ, King DN, Kostich MS, Mash HE, Pfaller SL, Schenck KM, Simmons JE, Varughese EA, Vesper SJ, Villegas EN, Wilson VS. Nationwide reconnaissance of contaminants of emerging concern in source and treated drinking waters of the United States. Sci Total Environ. 2017 Mar 1;581-582:909-922. doi: 10.1016/j.scitotenv.2016.12.004. Epub 2016 Dec 24. PMID: 28024752; PMCID: PMC7017586.
2. Minnesota Department of Agriculture and Minnesota Department of Health. 2015 Reconnaissance Study of Pesticide Compounds in Community Public Water Supply Wells. 2016.
3. Minnesota Department of Agriculture. Minnesota National Lakes Assessment: Pesticides in Minnesota Lakes. MAU-14-102. 2014.
4. Minnesota Department of Agriculture. Minnesota 2012 Water Quality Monitoring Report. 2013.
5. Minnesota Department of Agriculture. Minnesota 2013 Water Quality Monitoring Report. 2014.
6. Minnesota Department of Agriculture. Minnesota 2014 Water Quality Monitoring Report. 2015.
7. Minnesota Department of Agriculture. Minnesota 2015 Water Quality Monitoring Report. 2016.

8. Minnesota Department of Agriculture. Minnesota 2016 Water Quality Monitoring Report. 2017.
9. Minnesota Department of Agriculture. Minnesota 2017 Water Quality Monitoring Report. 2018.
10. Minnesota Department of Agriculture. Minnesota 2018 Water Quality Monitoring Report. 2019.
11. Minnesota Pollution Control Agency. Endocrine Disrupting Compounds-A Report to the Minnesota Legislature. 2008.
12. Minnesota Pollution Control Agency. Statewide Endocrine Disrupting Compound Monitoring Study. 2010.
13. Minnesota Pollution Control Agency. Wastewater Treatment Plant Endocrine Disrupting Compound Monitoring Study. 2010.
14. Minnesota Pollution Control Agency. Wastewater Treatment Plant Endocrine Disrupting Chemical Monitoring Study. 2011.
15. Minnesota Pollution Control Agency. Endocrine Active Compound Monitoring in Minnesota Lakes, 2009-2011: Lake Habitat and Land Use. 2012.
16. Minnesota Pollution Control Agency. Endocrine Active Chemicals and Other Contaminants of Emerging Concern in Minnesota's Groundwater, 2009-2010. 2012.
17. Minnesota Pollution Control Agency. The Condition of Minnesota's Groundwater, 2007 – 2011. 2013.
18. Minnesota Pollution Control Agency. Pharmaceuticals and Endocrine Active Chemicals in Minnesota Lakes. 2013.
19. Minnesota Pollution Control Agency. Pharmaceuticals and Personal Care Products in Minnesota's Rivers and Streams: 2010. 2013.
20. Minnesota Pollution Control Agency. Pharmaceuticals and Chemicals of Concern in Rivers: Occurrence and Biological Effects 2017.
21. US EPA. Region 8. Analytical Results. Project: National Park Service - Pesticides 2013 / 1304004. 2013.
22. National Park Service. Screening For Contaminants of Emerging Concern in Surface Waters of the Great Lakes Network Parks 2013–2014. NPS/GLKN/NRDS—2015/786. 2015.
23. Elliott SM, VanderMeulen DD. A regional assessment of chemicals of concern in surface waters of four Midwestern United States national parks. Sci Total Environ. 2017 Feb 1;579:1726-1735. doi: 10.1016/j.scitotenv.2016.11.114. Epub 2016 Dec 6. PMID: 27932214.
24. US EPA. Occurrence Data from the Unregulated Contaminant Monitoring Rule. UCMR 1. https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule.
25. US EPA. Occurrence Data from the Unregulated Contaminant Monitoring Rule. UCMR 2. https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule..
26. US EPA. Occurrence Data from the Unregulated Contaminant Monitoring Rule. UCMR 3. https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule.
27. US EPA. Occurrence Data from the Unregulated Contaminant Monitoring Rule. UCMR 4. https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule.
28. US Geological Survey. Water-Quality Assessment of the Cambrian-Ordovician Aquifer System in the Northern Midwest, United States. Scientific Investigations Report 2011–5229. 2012.
29. US Geological Survey. Pesticide Trends in Major Rivers of the United States, 1992–2010. Scientific Investigations Report 2014–5135. 2014.
30. US Geological Survey. Anthropogenic Organic Compounds in Source Water of Select Community Water Systems in the United States, 2002–10. Scientific Investigations Report 2014–5139. 2014.
31. US Geological Survey. An Overview Comparing Results from Two Decades of Monitoring for Pesticides in the Nation's Streams and Rivers, 1992–2001 and 2002–2011. Scientific Investigations Report 2014–5154. 2014.
32. US Geological Survey. Pharmaceutical Compounds in Shallow Groundwater in Non-Agricultural Areas of Minnesota—Study Design, Methods, and Data, 2013. Data Series 878. 2014.

33. Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K et al Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment. Toxicol Sci 2012; 125: 157-174.
34. Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW et al Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. Toxicol Sci 2015; 148: 121-136.
35. Paul Friedman K, Gagne M, Loo LH, Karamertzanis P, Netzeva T, Sobanski T et al Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization. Toxicol Sci 2020; 173: 202-225.
36. Pearce RG, Setzer RW, Strope CL, Sipes NS, Wambaugh JF httk: R Package for High-Throughput Toxicokinetics. J Stat Softw 2017; 79