Modeling *in vitro* distribution improves accuracy of bioavailable dose estimation

Meredith N. Scherer[1,2], Katie Paul Friedman[2], John F. Wambaugh[2]
[1]Oak Ridge Institute of Science and Education, Oak Ridge, TN
[2]Center for Computational Toxicology and Exposure, U.S. EPA Office of Research and Development

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Meredith Scherer | scherer.meredith@epa.gov | ORCID: 0000-0002-9785-7363

Introduction

- New approach methods (NAMs)-based risk assessment uses *in vitro* to *in vivo* extrapolation (IVIVE) to translate observed cellular responses to whole organism effects
- IVIVE is affected by *in vitro* distribution: chemical partitioning within the system such that the nominal effect concentration is different from the bioavailable effective dose
- The aim of this project is to adjust large quantities of NAM data to account for *in vitro* distribution; therefore, we are examining the accuracy of an *in vitro* distribution model in the context of a high throughput approach

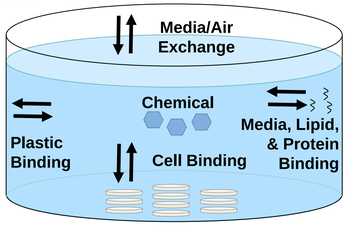

Figure 1: *In vitro* distribution diagram.

Methods

1. Literature Review

Experimentally derived intracellular concentrations from *in vitro* assays (References provided via QR code)

2. Model Implementation

Experimental conditions were input to a modified Armitage et al. (2014) *in vitro* disposition model which includes ionization and plastic binding as implemented within the R package *httk*

Results

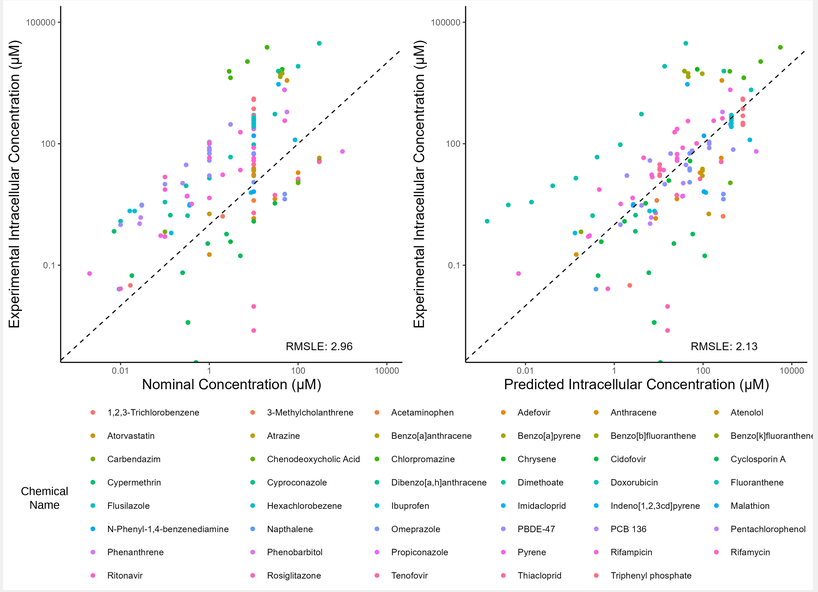

Figure 2: Comparing experimental intracellular concentration with the nominal concentration and the Armitage model's predicted intracellular concentration. Dashed line shows unity.

IOC Type	Nominal RMSLE	Predicted RMSLE
Acid	1.52	1.27
Base	5.20	3.55
Neutral	2.68	1.96

Table 1. Root mean squared log error (RMSLE) for intracellular concentrations compared to nominal concentrations and intracellular concentrations predicted by the Armitage model.

View poster and references:

Results

- Armitage model predictions of bioavailable concentrations are more accurate than using the nominal concentration as a proxy for the bioavailable concentration (Figure 2)
  - The error is reduced from 1000 times to 100 times
- Among the ionization states, basic chemicals show the greatest improvement when predicted using the Armitage model (Table 1)

Discussion

- This research suggests that the Armitage chemical distribution model is a more accurate method for predicting bioavailable concentrations for high throughput applications including next generation risk assessments using IVIVE
- Lack of experimental data is the main factor in determining the accuracy of these models
  - 13 papers containing 47 chemicals total

Future Directions

- Continue updating the *httk in vitro* distribution model to include lysosomal sequestration and ion trapping
- Standardize modeling bioavailable concentration instead of using nominal as proxy as good practice in IVIVE
- Generate more data, especially for charged and volatile chemicals

Disclaimer

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