Evaluating an *In Vitro* Distribution Model

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Introduction

- New approach methods (NAMs)-based assessment aims to use non-animal models to establish toxicity reference values
- *In vitro* to *in vivo* extrapolation (IVIVE) is needed to translate observed cellular responses to whole organisms
- Currently, most IVIVE models rely on nominal chemical concentrations as proxy for free concentration within the system
- *In vitro* disposition describes the way that a given chemical partitions within the *in vitro* system
    - i.e., the difference between the amount of chemical placed in the test system and the actual amount available to cause bioactivity

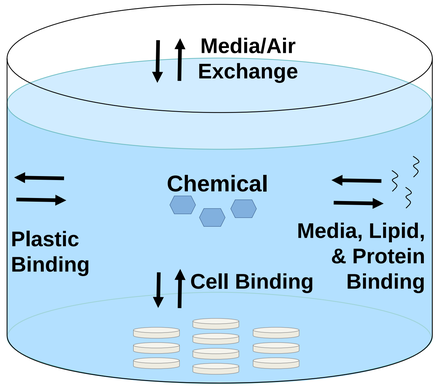

Figure 1: *In vitro* distribution diagram.

Methods

1. Literature review for papers reporting experimentally derived intracellular concentrations from *in vitro assays*
    - References provided via QR code
2. Information regarding experimental conditions was then input to a modified Armitage et al. (2014) *in vitro* disposition model which includes ionization to match the 2021 version as implemented within the R package "httk"

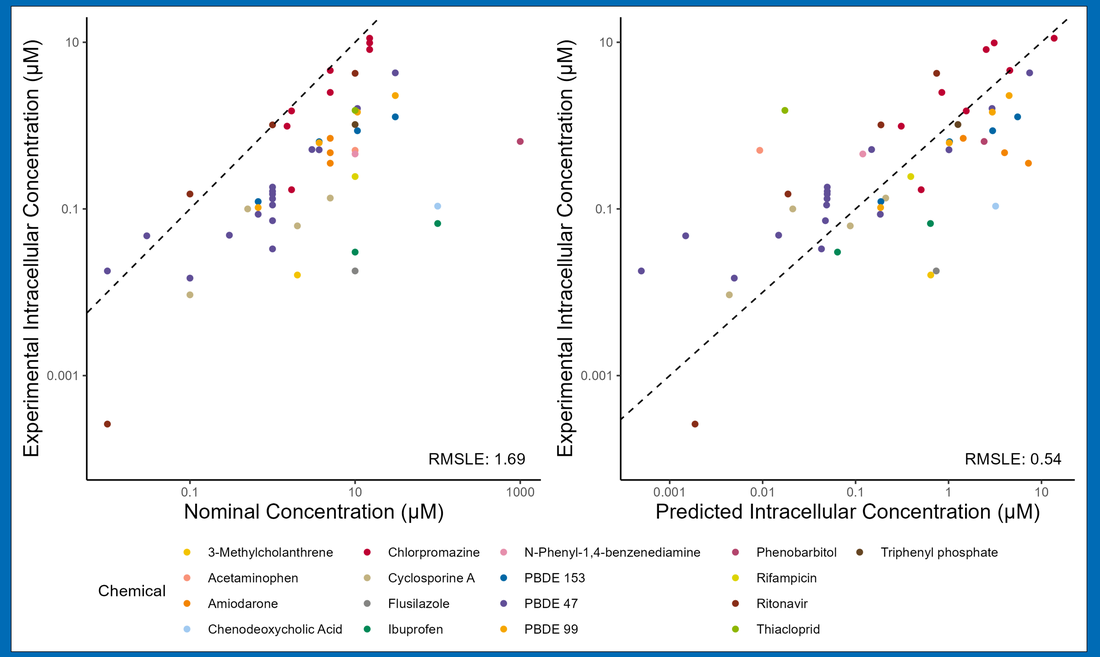

Figure 2: Comparing experimental intracellular concentration with the nominal concentration and the Armitage model's predicted intracellular concentration. Dashed line shows unity.

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Results

- The *in vitro* distribution model has a lower root mean square log error (RMSLE) than the nominal concentration
    - RMSE reduced from 137.58 to 2.01
- The nominal concentration has a larger spread compared to the intracellular concentrations predicted by the Armitage model
- Nominal concentration is 1 log10 μM larger than the experimental intracellular concentration on average

Discussion

- IVIVE models currently using the Armitage *in vitro* distribution model are predicting the intracellular concentrations more accurately than those relying on the nominal concentration
    - The model reduces error by a factor of 68
- The average nominal concentration is larger than the experimental intracellular concentration
    - This method does not account for chemical partitioning/distribution which reduces the free concentration
- Lack of experimental data is the main factor in determining the accuracy of the Armitage model
    - 17 chemicals/5 assays analyzed

Future Directions

- Standardize using intracellular concentrations instead of nominal as good practice in IVIVE
- Generate more data, especially for charged and volatile chemicals

We are investigating the *in vitro* distribution mathematical model described in: Armitage, J. M., Wania, F., & Arnot, J.A., "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *ES&T* (2014)

Disclaimer:
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