In Vitro Distribution Model Evaluation

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There is a **dearth of data** on intracellular concentrations

A modified Armitage et al. (2014) mathematical model **overpredicts** intracellular concentrations compared to experimental values

The model accurately captures **trends** in intracellular concentration for each chemical

INTRODUCTION

- Next generation risk 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
- *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

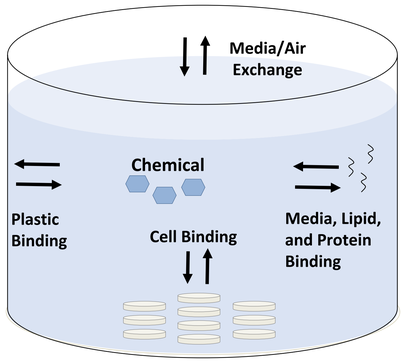

Fig. 1: *In vitro* distribution diagram.

- *In vitro* disposition modeling determines the bioavailable chemical concentration that causes the observed effects
- Hypothesis: A modified Armitage et al. (2014) model will accurately predict intracellular concentrations

METHODS

1. Literature review to find papers that reported experimentally derived intracellular concentrations in *in vitro* tests
   - References provided on GitHub site via QR code
2. Information regarding experimental conditions was then input to the Armitage et al. (2014) *in vitro* disposition model as implemented within R package "httk"

United States Environmental Protection Agency

Scan for a copy of this poster and references:

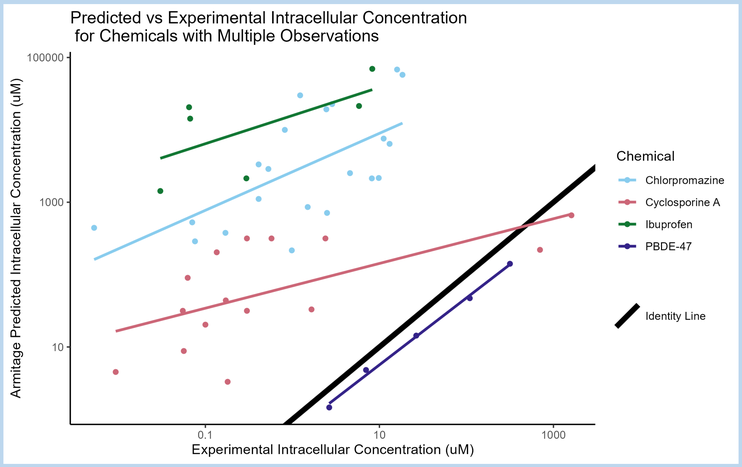

Fig. 3: Linear model trendline for the predicted and experimental intracellular concentrations for each chemical. Thick black line represents x=y, i.e. the trendline if the predicted and experimental values were perfectly correlated.

We are investigating the *in vitro* distribution mathematical model described in:
Armitage, James M., Frank Wania, and Jon A. Arnot. "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *Environmental Science & Technology* 48.16 (2014): 9770-9779.

RESULTS

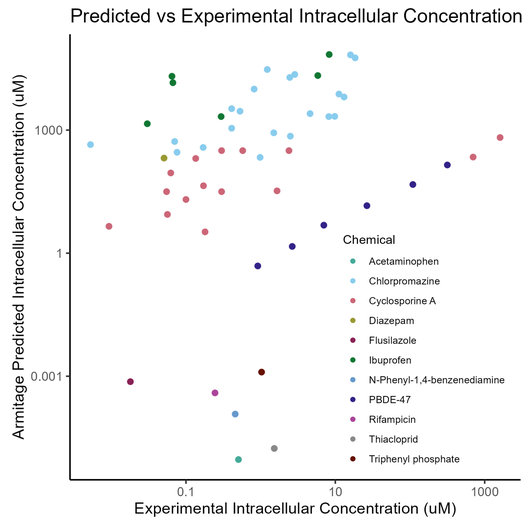

Fig. 2: The predicted and experimental intracellular concentrations for each chemical.

Table 1: The root mean square log 10 error (RMSLE) and R^2 for each chemical with multiple observations (in Fig. 3) and the four chemicals together ("Overall").

Chemical	RMSLE	R^2
Chlorpromazine	3.445	0.431
Cyclosporine A	2.306	0.561
Ibuprofen	4.537	0.718
PBDE-47	0.290	0.999
Overall	3.104	0.009

DISCUSSION

- There is a gap in the data regarding intracellular concentration measurements (Fig. 2)
- The Armitage model overpredicts the intracellular concentration by up to 12,800%
- The RMSLE is large which shows that the model is a poor fit (Table 1)
- However, the predictions correlate with the measured experimental values within individual chemicals (Fig. 3, Table 1)
- Other models relying on these predictions could be underpredicting the bioactive dose from *in vitro* to *in vivo* extrapolation
  - Ramifications in risk assessment and decision making

FUTURE DIRECTIONS

- Develop a specific assay to generate data for *in vitro* distribution models
- Optimize the Armitage model to account for inaccuracies
- Test other *in vitro* distribution models (e.g., Kramer model)
- Develop more models to predict *in vitro* distribution