Toxicokinetics in Risk Assessment: From Predictive Evaluations to Regulatory Testing

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The Dow Chemical Company

Outline

- Product Development and Registration Timeline
  - Empirical and Predictive Toxicokinetics
- GastroPlus Validations
- High-Throughput applications of GastroPlus for IVIVE

Product Development Timeline

Toxicokinetic activities

In silico Toxicokinetic modeling

Probe AME *in vivo* study (4 species)

In vitro Comparative metabolism study (EU)

ADME study (OECD 417)

In vivo Toxicokinetics Endpoint

Preliminary PBPK model (interspecies)

High-end PBPK models (interspecies & multiple routes)

In silico High throughput PBPK models (IVIVE)

Product Development Timeline

High-end PBPK models (interspecies & multiple routes)

In silico Toxicokinetic modeling

Opportunity: Standardize modeling approaches

Preliminary PBPK model (interspecies)

In silico High throughput PBPK models (IVIVE)

Toxicokinetic Model Requirements

Modeling software criteria:

- Support for multiple exposure routes and regimens
  - Oral, Inhalation, Dermal (critical for relevant Risk Assessments)
  - Acute, steady-state
- Incorporates critical QSARs for:
  - Absorption rates and amounts
  - Metabolic clearance
  - Plasma protein binding
  - Tissue distribution
- Based on Compartmental PK or PBPK designs
- Provides model predictions of parent compound and metabolite(s)
- Supports various species and lifestages
- Minimal to no coding required
  - Best option for regulatory buy-in
- Batch modeling feature

Selected: GastroPlus™ from Simulations Plus

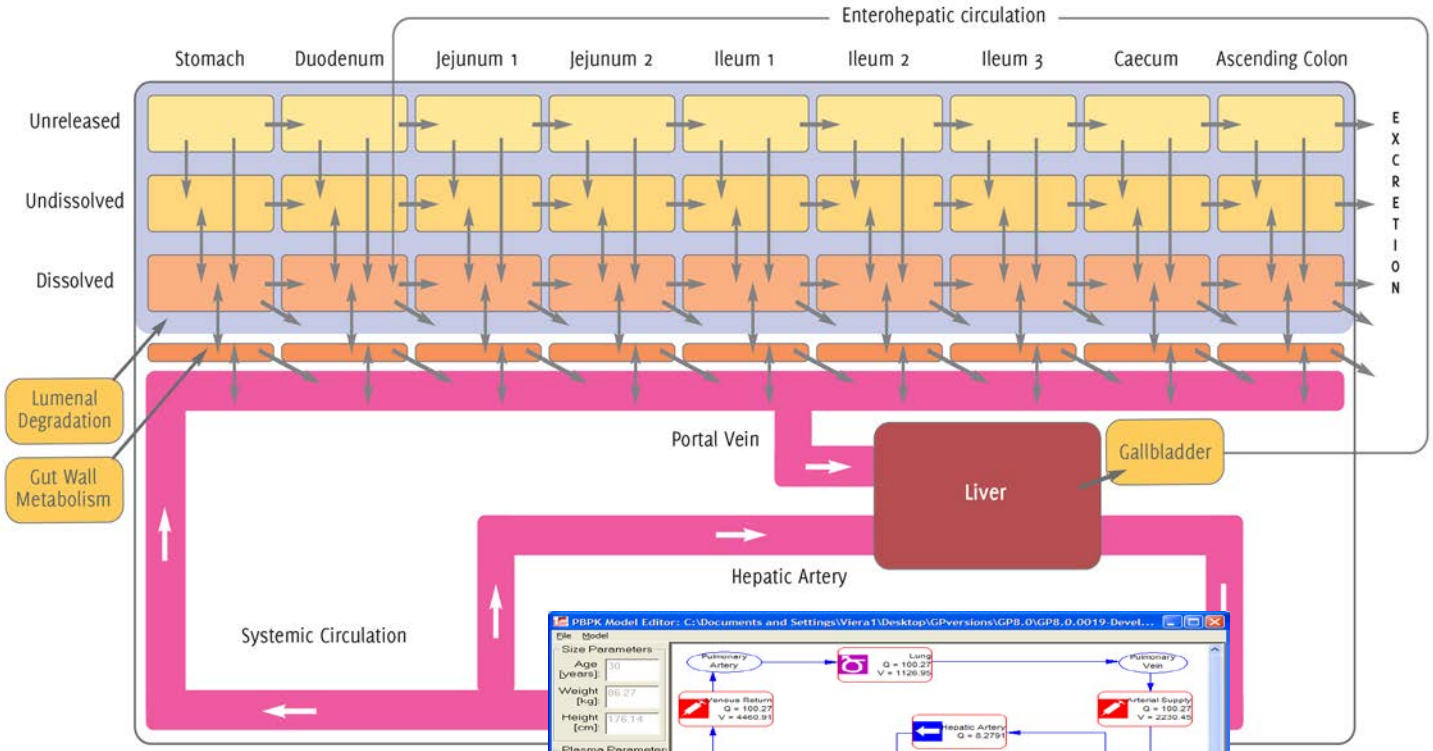
Toxicokinetic Model Requirements

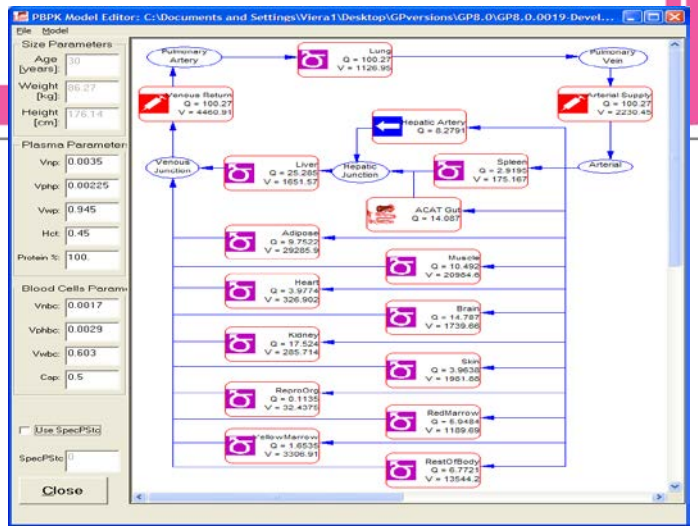
Modeling software criteria:

- GastroPlus validated primarily with pharmaceutical compounds delivered via the oral route
- Needed to validate QSAR and PK / PBPK predictions for:
  - Broad range of chemistries for non-pharmaceuticals
  - Oral, Inhalation, Dermal exposure routes
    - Inhalation modeling for non-volatile compounds only
    - Multiple dermal formulation types
- Multi-step validation plan
  - Accuracy of physical-chemical property predictions
    - pKa, LogP
  - Accuracy of pharmacokinetic parameter predictions
    - Metabolic clearance, plasma protein binding, Fa%, F%
  - Accuracy of systemic exposure predictions
    - Cmax, AUC

GastroPlus Model Design

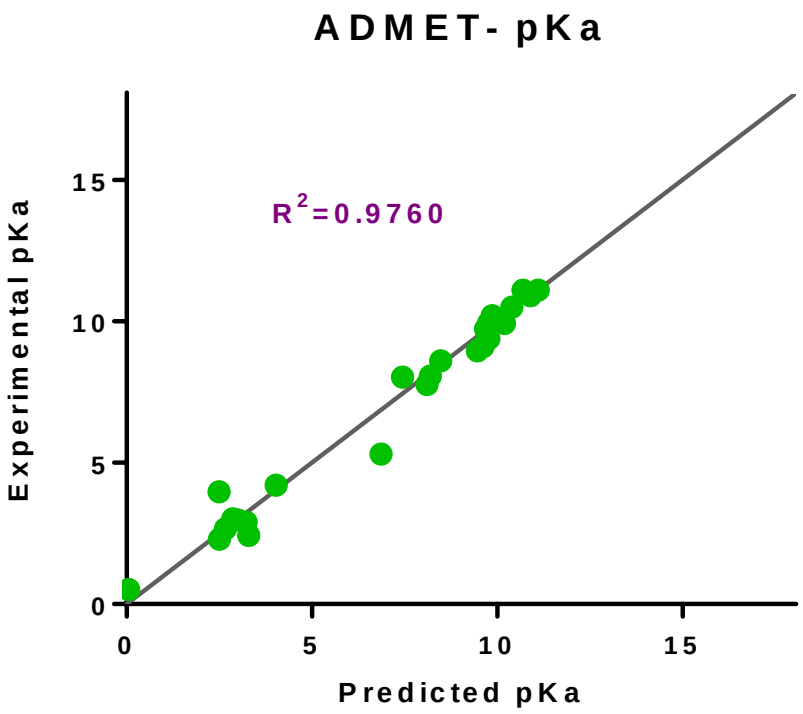
Advanced Compartmental Absorption and Transit Model (ACAT™)

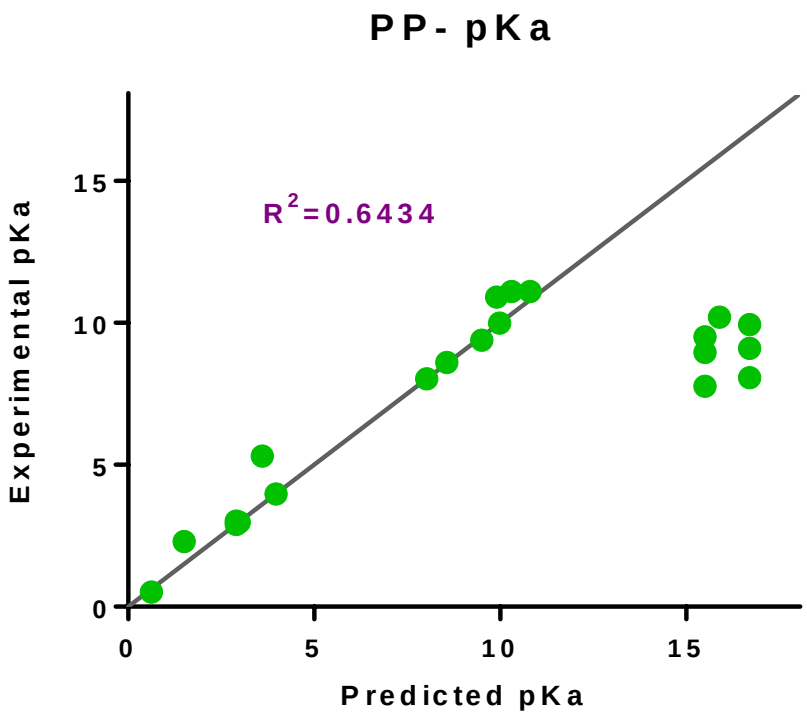




- *Accommodates multiple formulation types*
- *Contains species-specific portal of entry physiologies*

Experimental vs. Predicted pKa Values

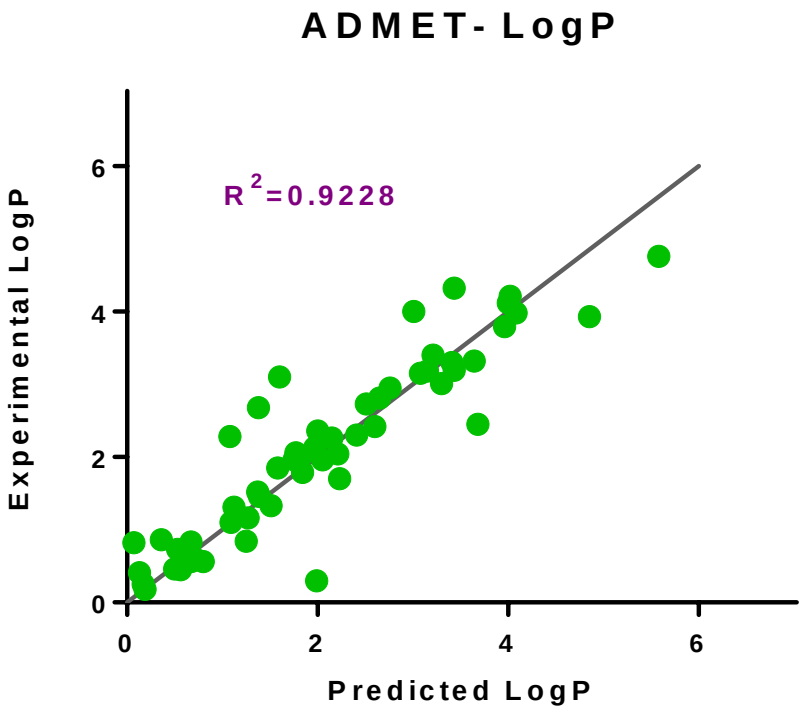


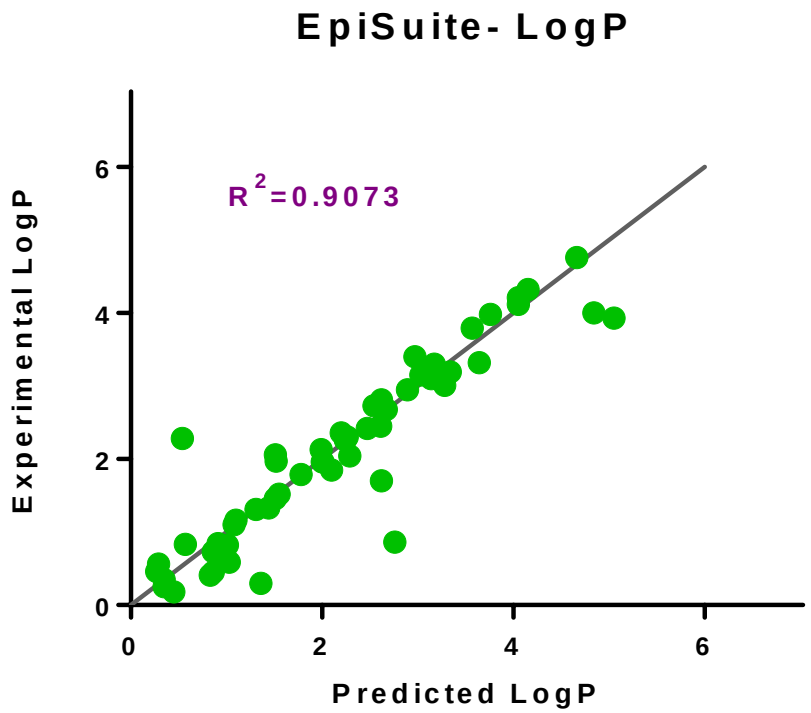


from ADMET Predictor model of GastroPlus™ (ADMET) or Pipeline Pilot™ (PP)

The predicted pKa values from ADMET correlated well with the literature data and were better than those predicted by PP

Experimental vs. Predicted LogP Values





from ADMET Predictor model of GastroPlus™ (ADMET) or US EPA EpiSuite

The predicted LogP values from ADMET correlated well with the literature data and were comparable to those predicted by EpiSuite

Accuracy of PK parameter predictions

Cl_{int}		Fraction Unbound in Plasma	
Fold difference from empirical data	Percent of the total compounds *	Percent (%) difference from empirical data	Percent of the total compounds **
1 to 3	38%	1 to 10	61%
3 to 10	29%	10 to 30	26%
10 to 100	29%	> 30	13%
> 100	7%		
* n=463		** n=441	
Empirical data for Clint and Fup via personal communication (J. Wambaugh, 2015)			

Metabolic clearance and Fup predictions by GastroPlus are quite acceptable:

- *67% of predicted Clint values within 10x of empirical data*
- *87% of predicted Fup values within 30% of empirical data*

Accuracy of Steady-State Systemic Exposure predictions

Comparison of GastroPlus Prediction Results with Published IVIVE Modeling Results (oral route)

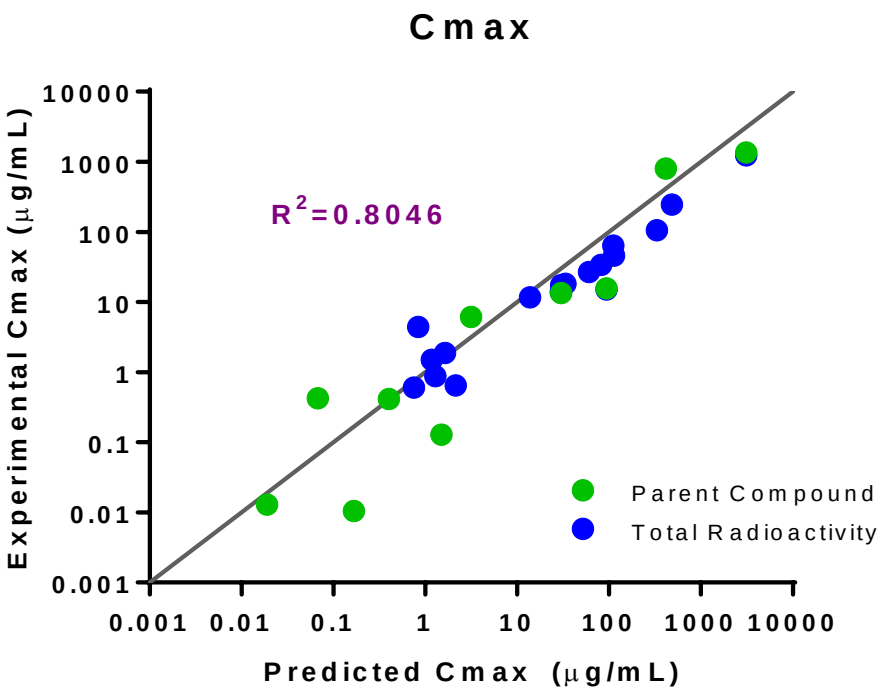
Chemical Name	Reference PK or PBPK derived (Css µM) *	Restrictive hepatic clearance (Css µM) *	GastroPlus Predicted (Css µM)	GastroPlus Predicted with Empirical Clint* and Fup* (Css µM)
2.4-D	9.05-90.05	43.27	64.56	57.95
Cacodylic acid	1.8	3.06	9.53	7.37
Carbaryl	0.03	0.07	1.13	0.47
Fenitrothion	0.03	17.92	0.84	15.7
Lindane	0.46	13.21	7.96	6.68
Parathion	0.17	24.64	1.66	17.28
Perfluorooctane sulfonic acid	19,990	153.23	143.68	155.42
Perfluorooctanoic acid	20,120	53.16	89.57	61.34
Picloram	0.27	57.63	39.27	67.96
Thiabendazole	0.45	13.76	11.76	15.8
Triclosan	2 to 10	1.56	7.67	1.36
Bisphenol A	<0.13	0.35	2.60	2.49

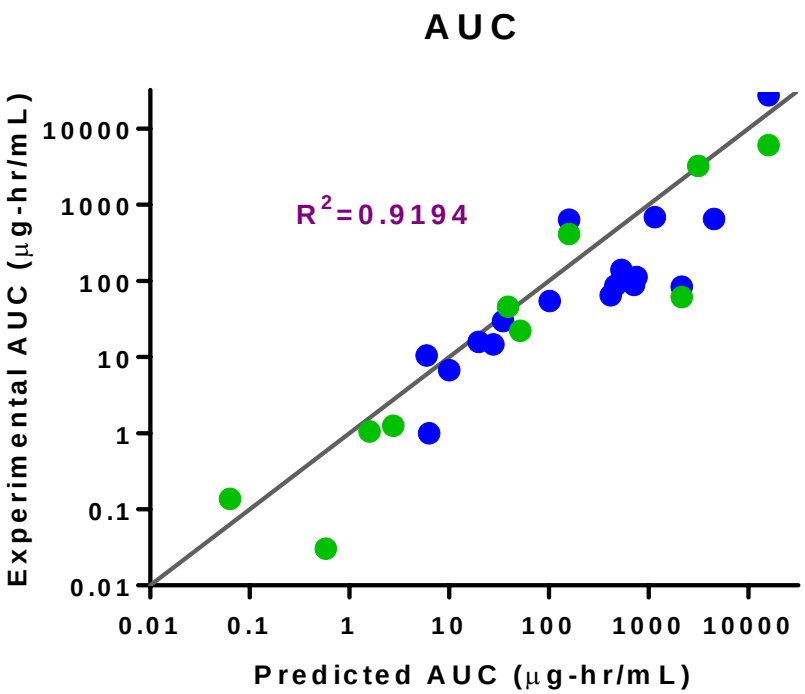
* *Data from Wetmore, et al. 2012 (Toxicol Sci 125(1): 157-174)*

- *Steady state blood level predictions from GastroPlus consistent with those obtained with SimCYP and overall conservative vs. Reference data*
- *Predicted Css values generally improve with inclusion of measured Clint and Fup*

GastroPlus Model Validation

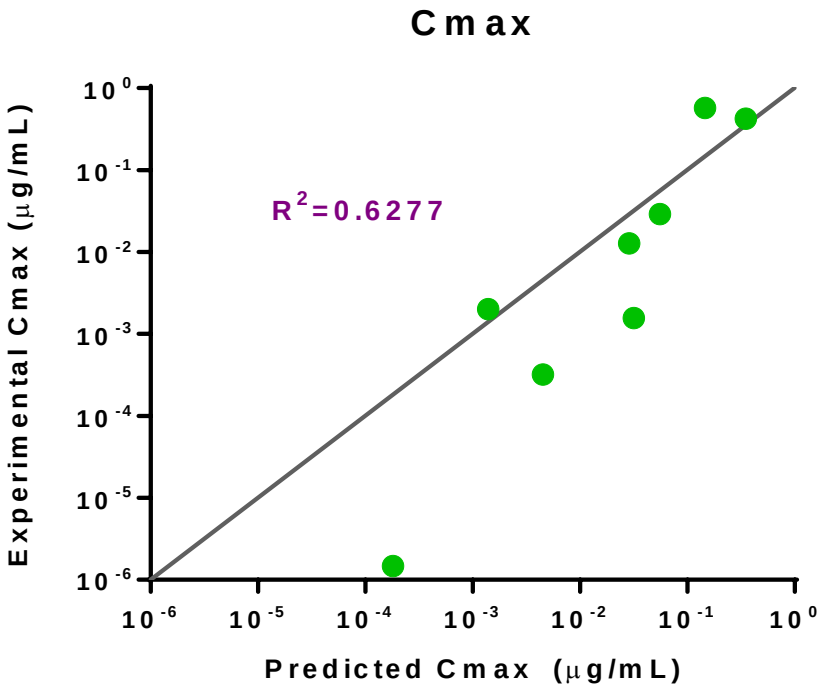
Oral Acute Exposures

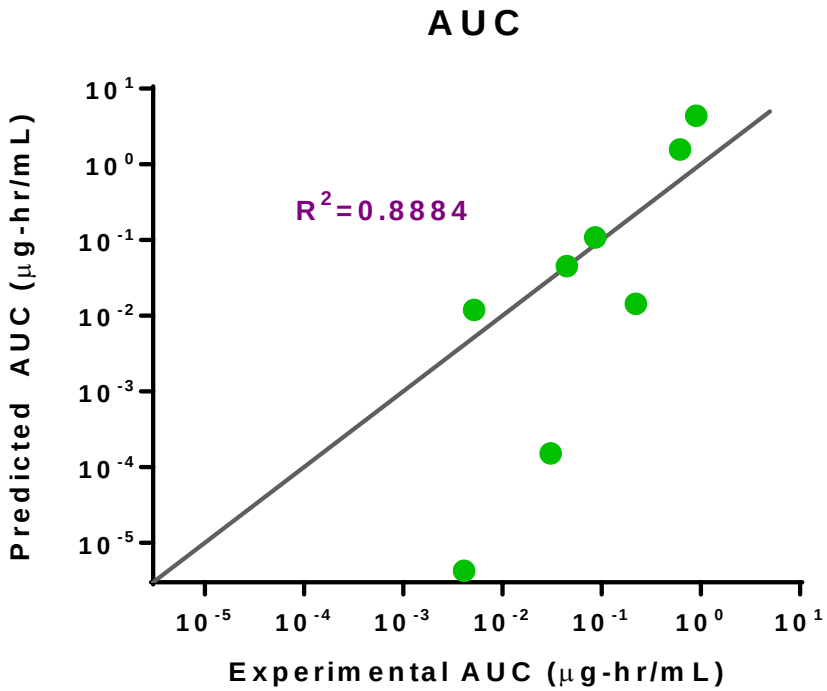




The predicted pharmacokinetic values from GastroPlus correlated well with the literature data
Cmax: 69% within 3-fold, and 88% within 10-fold of experimental data
AUC: 54% within 3-fold, and 85% within 10-fold of experimental data

Inhalation Acute Exposures

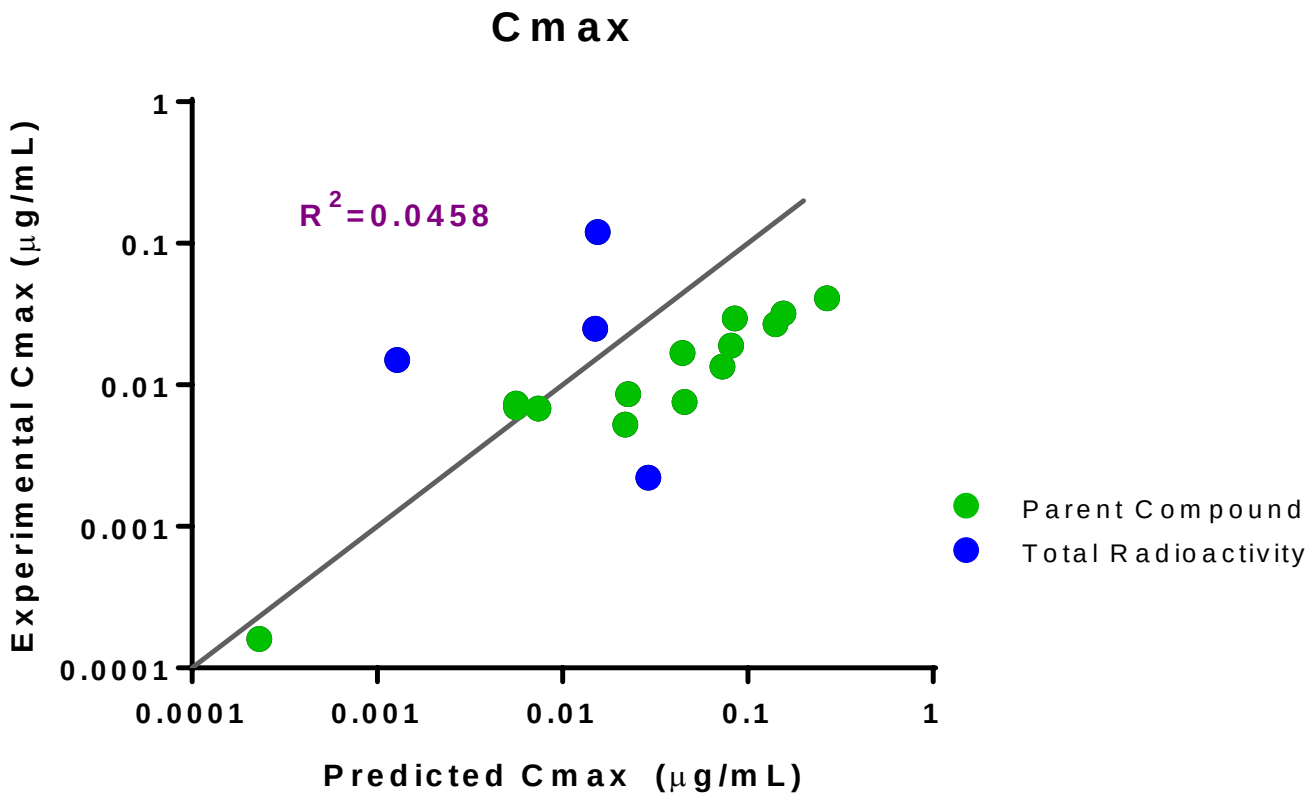




The predicted pharmacokinetic values correlated acceptably with the literature data
Cmax: 50% within 3-fold, and 63% within 10-fold of experimental data
AUC: 50% within 3-fold, and 63% within 10-fold of experimental data
- generally over-predicted (conservative)

GastroPlus Model Validation

Dermal Acute Exposures

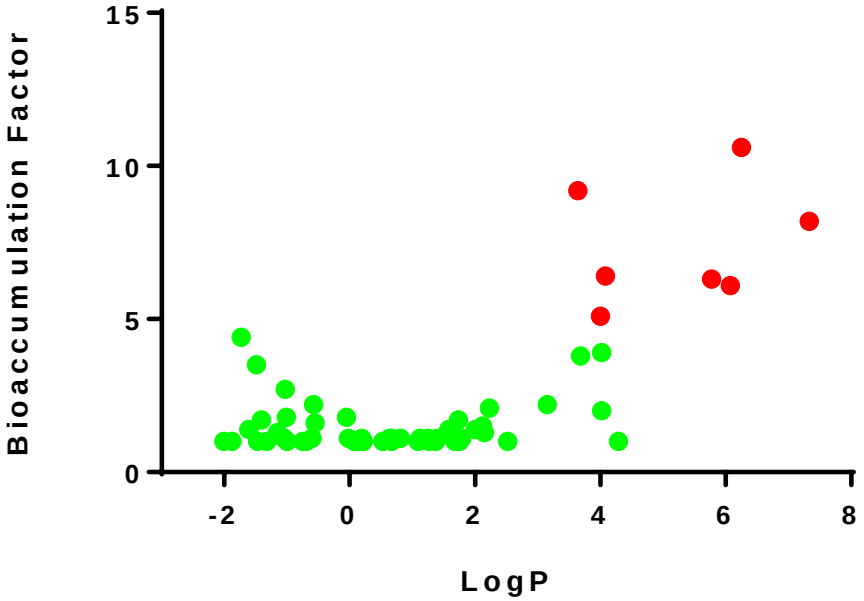


The predicted pharmacokinetic values correlated acceptably with the literature data
Cmax: 44% within 3-fold, and 89% within 10-fold of experimental data
- generally over-predicted (conservative)

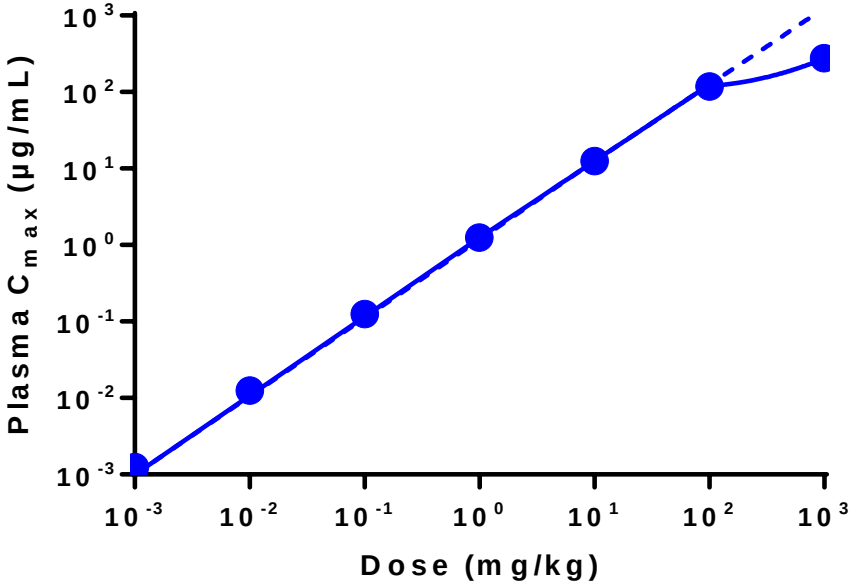
Methods for High Throughput Exposure assessment Tool (HEAT)

- Determine external exposures for Dow products
    - Using formulation data and validated Occupational or Consumer exposure models
- Pre-define predictions of blood levels across a range of external exposures (0.001-1000 mg/kg)
    - Oral, Inhalation and Dermal routes
    - Select most conservative formulation types and exposure conditions for each route

Trends in Systemic Exposure Predictions with GastroPlus

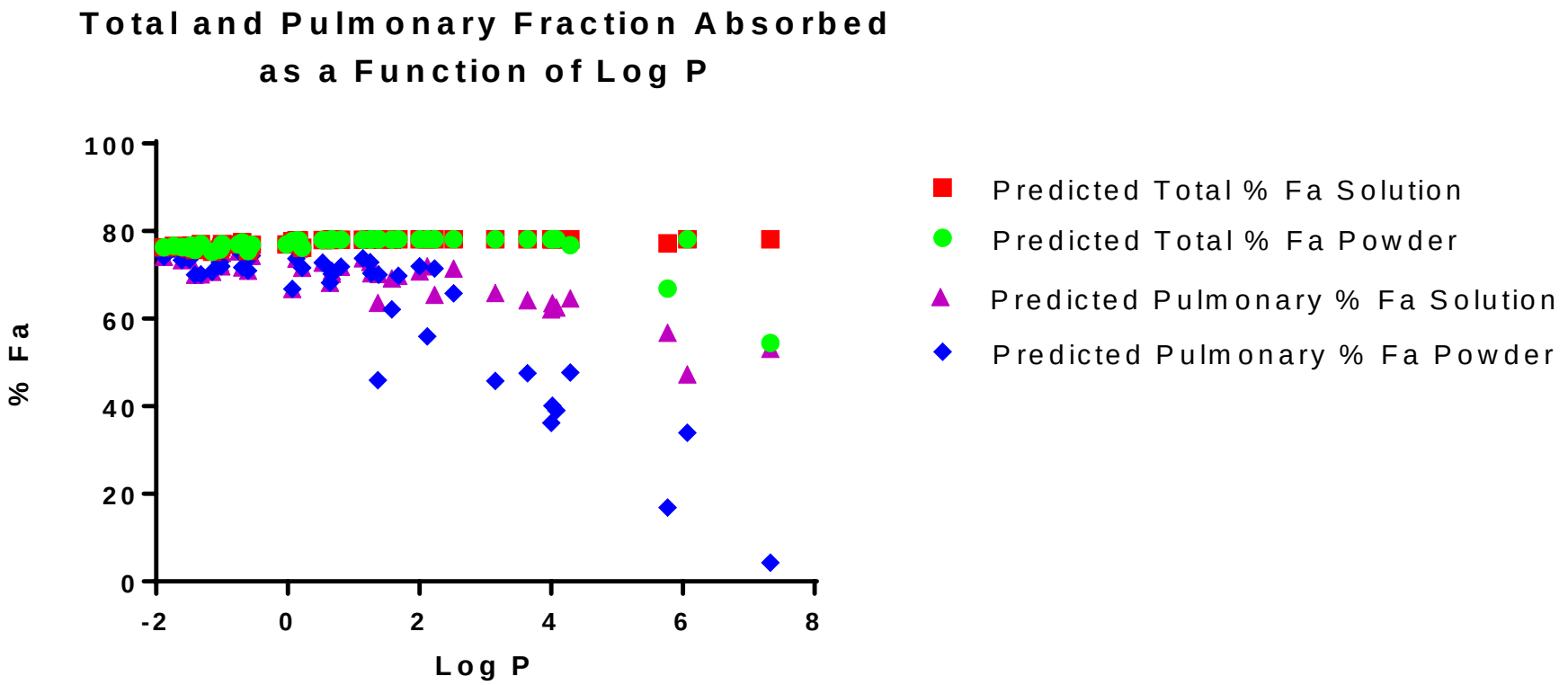


Bioaccumulation after 28 days oral exposure



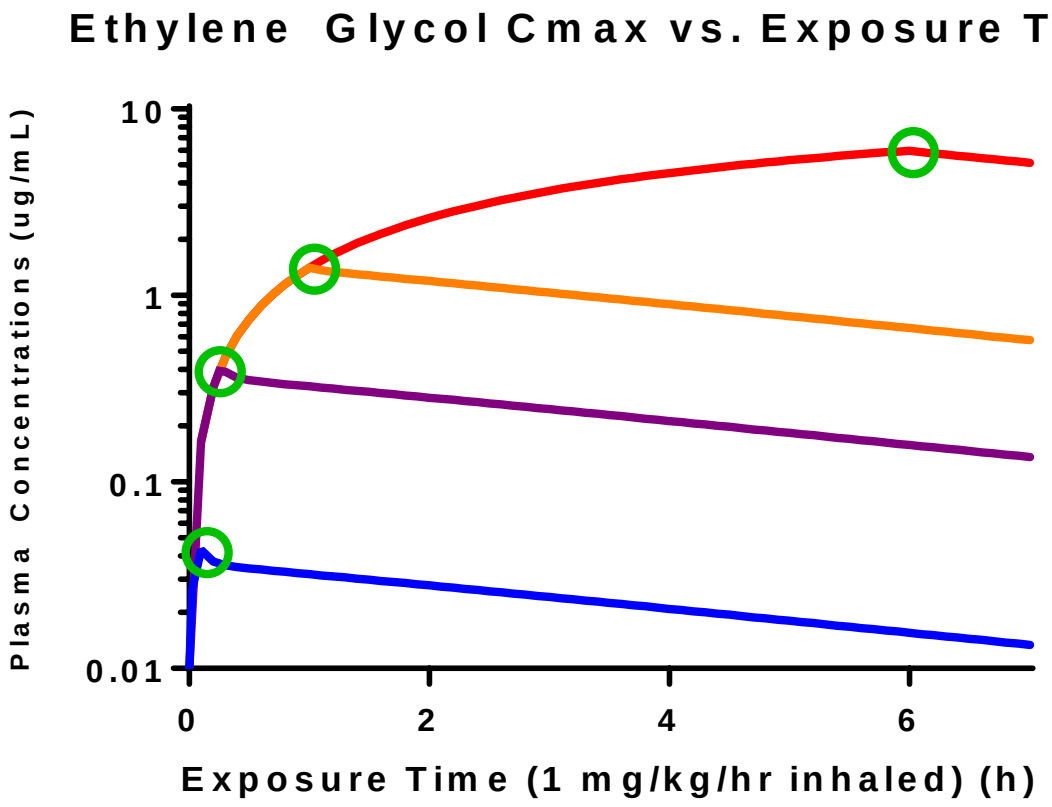
Saturation of oral absorption

Trends in Systemic Exposure Predictions with GastroPlus



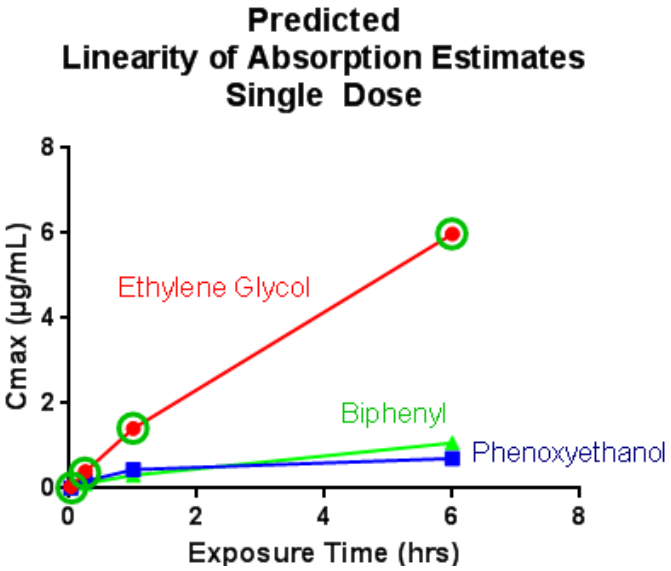
Trends towards lower uptake of inhaled chemicals through pulmonary tissue
- trend enhanced for solid formulations vs. solutions

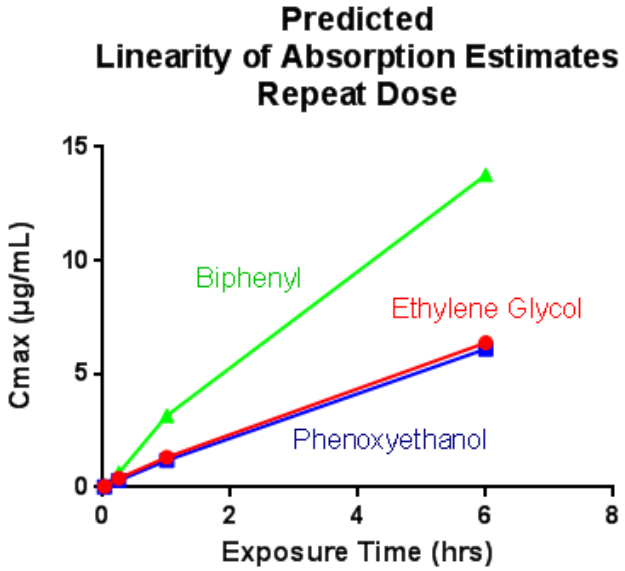
Selection of Optimal Exposure time for *de novo* Inhalation modeling

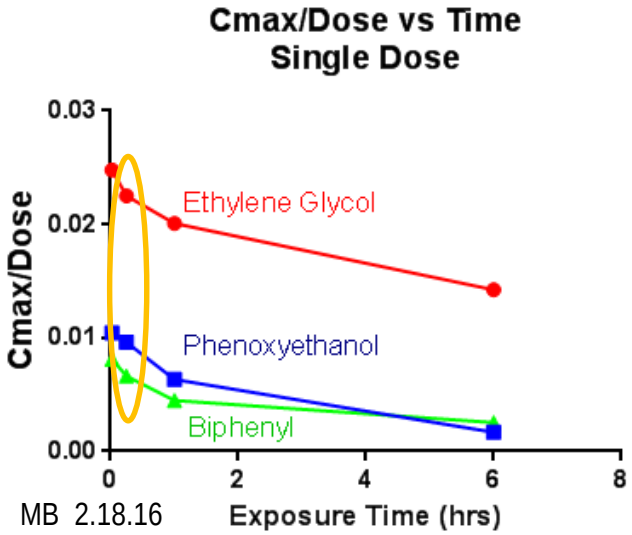


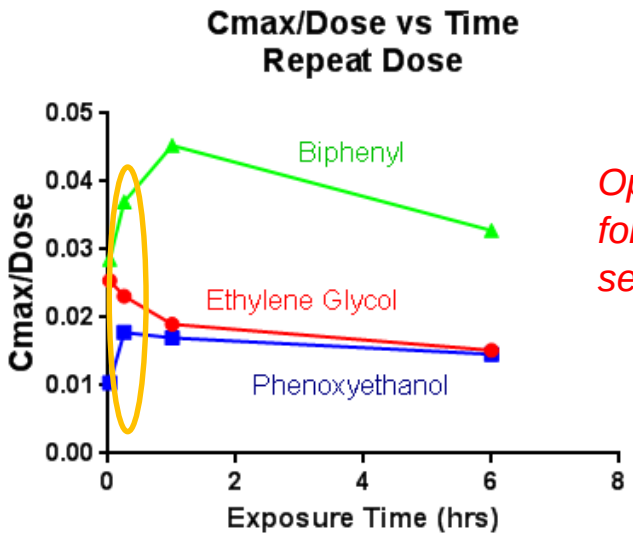
GastroPlus Model Validation

Selection of Optimal Exposure time for *de novo* Inhalation modeling



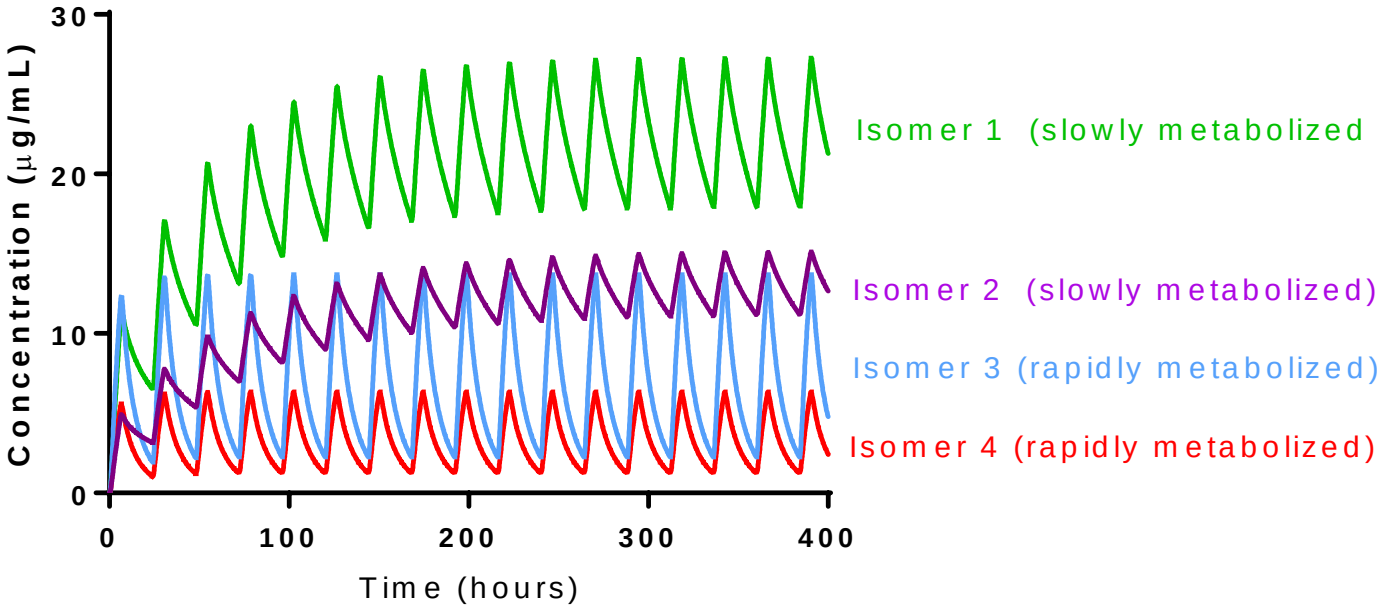






Optimal Exposure time for Inhalation Exposures set to 0.25 hr

Impact of metabolism on systemic bioavailability via inhalation



Time to steady state dependent on metabolic stability of compound:
- isomers with two CYP-metabolizable moieties more rapidly cleared than analogs with one moiety

Conclusions

- GastroPlus has been shown to provide adequate predictions of PhysChem properties, pharmacokinetic parameters and systemic blood levels, compared to literature values and/or other validated QSAR programs
- Predicted systemic blood levels are being generated for a test data set (~ 60 compounds) by the oral, inhalation and dermal exposure routes for the HEAT exposure model
    - Formulation types and exposure scenarios chosen to provide conservative blood level predictions
- Future research work
    - Refine model predictions with empirical Clint and Fup values
        - Note: GastroPlus provides estimates of CYP metabolism only
    - Derive correlations for pulmonary clearance of unmetabolized volatile compounds
- Proper understanding of the benefits and limitations of predictive modeling tools such as GastroPlus™ will allow for optimum implementation of animal alternatives in novel high throughput safety assessment programs.

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