Use of QSAR-based PBPK models for Regulatory Exposure Assessments

Michael Bartels, Ph.D.

ToxMetrics.com LLC

Outline

- PBPK modeling needs for chemical registrations
- Evaluation of GastroPlus™ for prediction of physical-chemical and pharmacokinetic parameters
- Case Study #1- PBPK modeling of TCVP dermal penetration
- Case Study #2- Dermal and Inhalation absorption modeling for modified MDI substances

PBPK models for Regulatory Exposure Assessments

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

A variety of modeling approaches used during product development and registrations

Modeling software criteria:

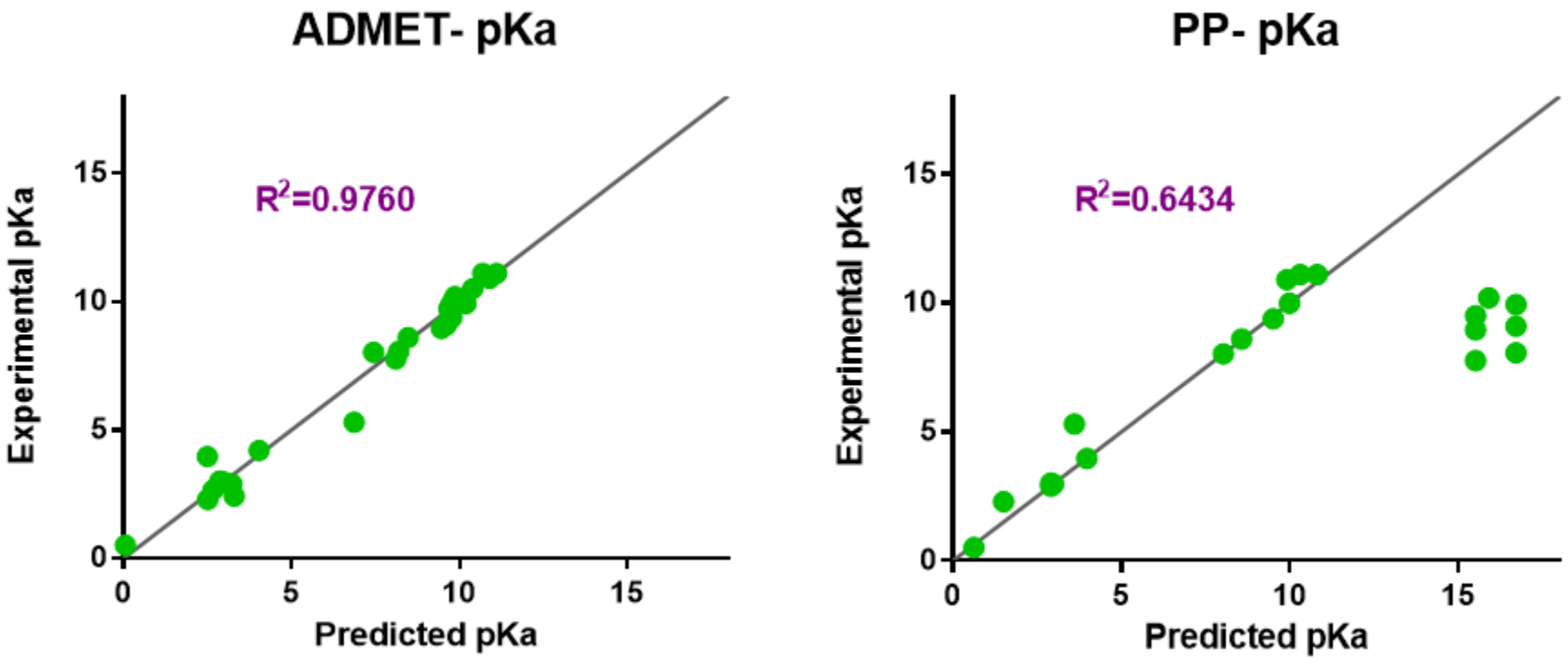
- Support for multiple exposure routes and regimens
  - Oral, Dermal and Inhalation (critical for Chemical Risk Assessments)
  - Acute, steady-state
- Incorporates critical QSARs for:
  - Absorption rates and amounts
  - Metabolic clearance and metabolite structure prediction
  - Plasma protein binding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

Selected: GastroPlus™ from Simulations Plus

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, Dermal, Inhalation exposure routes
    - » Inhalation modeling for both volatile and non-volatile compounds
    - » 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

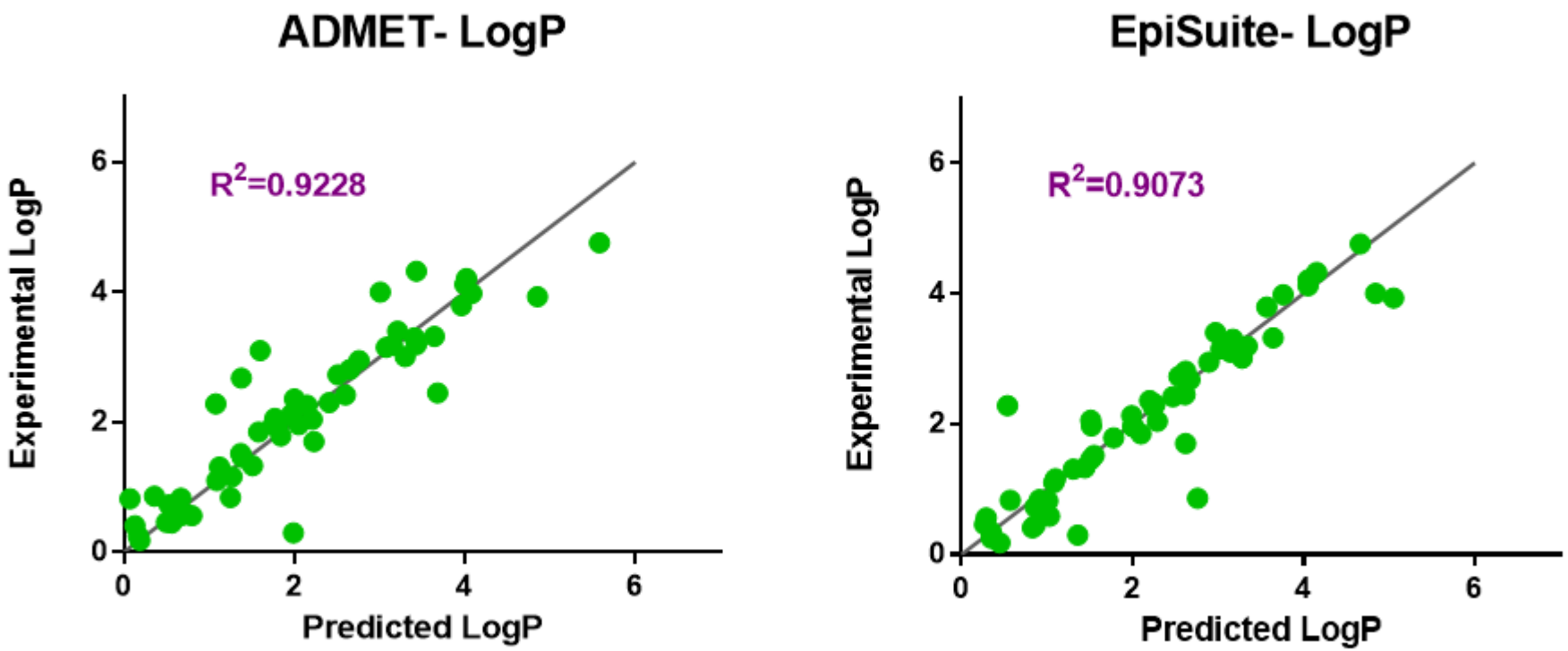
Experimental vs. Predicted pKa Values



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*

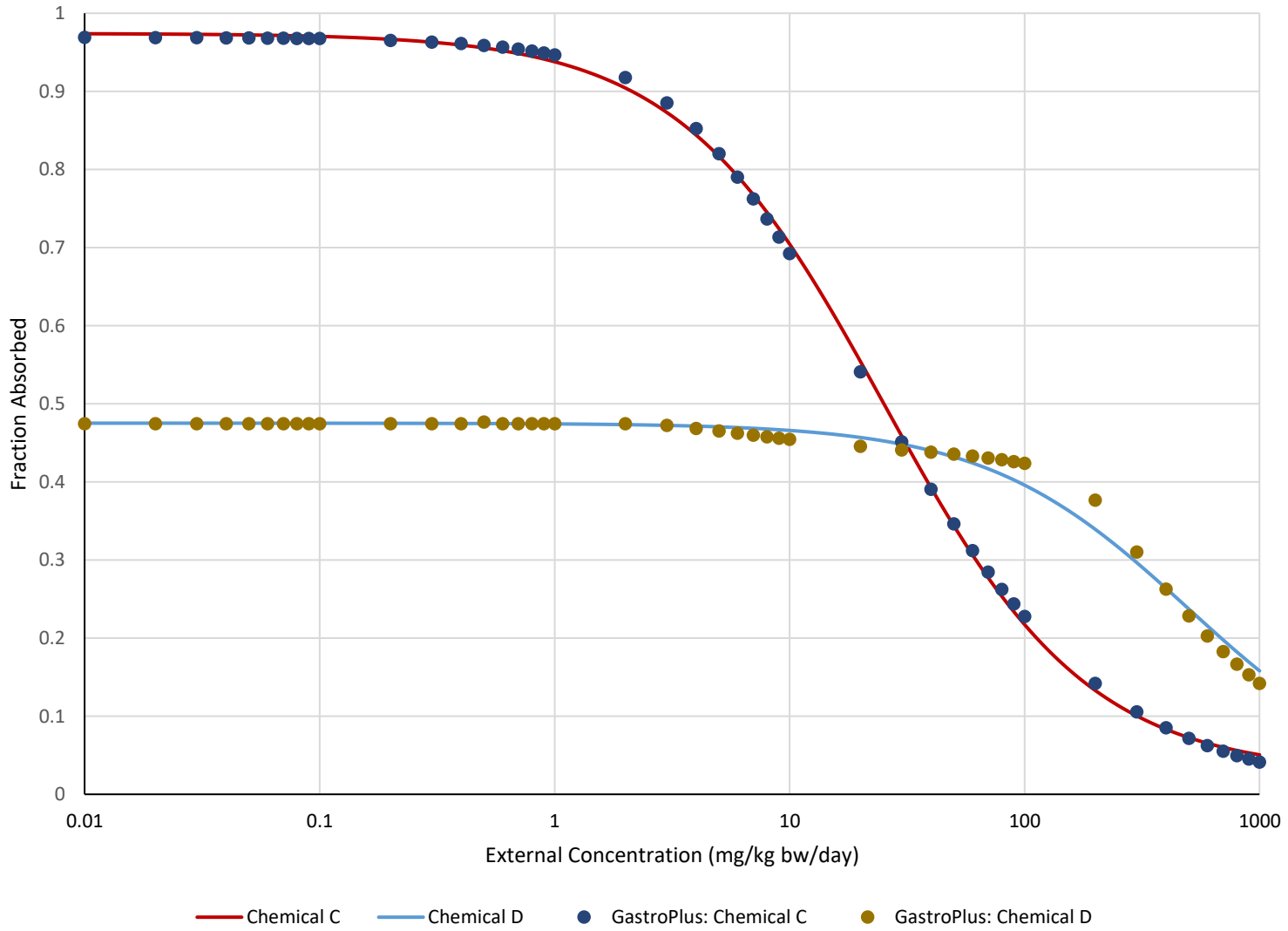
Accuracy of Steady-State Systemic Exposure predictions

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 Fub (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*

Prediction of Saturable Oral Absorption in Rat

- Comparison between compartmental GI tract model (GastroPlus) and algebraic fit-to-data approach (Dolton 2017)



Hoer et al. 2022

Case Study #1 with Tetrachlorvinphos

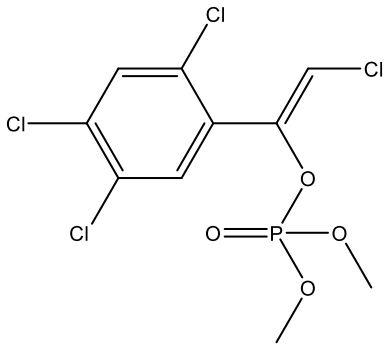
PBPK models for Regulatory Exposure Assessments

Risk Assessments for chemicals are often based on dermal toxicity studies conducted in rats/mice

These assessments may be conservative, due to known higher permeability of rat skin vs. human skin

- Differences in permeability are consistent with species variations in skin thickness:

To refine the risk assessment for the animal health product trichlorvinphos (TCVP), species differences in dermal penetration were assessed via *in silico* modeling as well as *in vitro* and *in vivo* assays



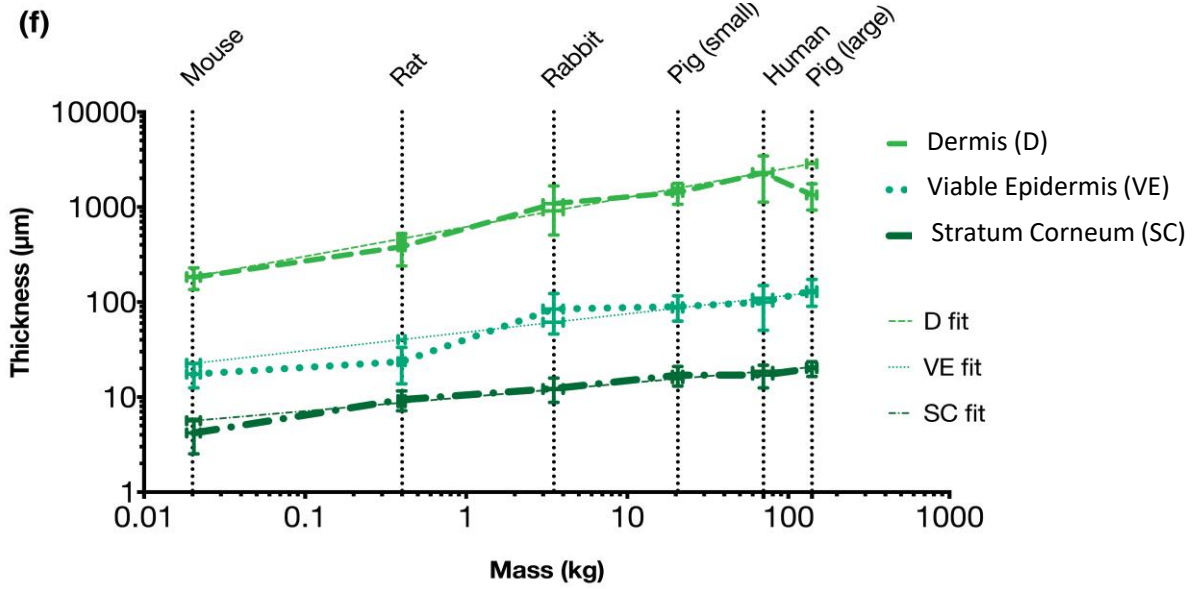
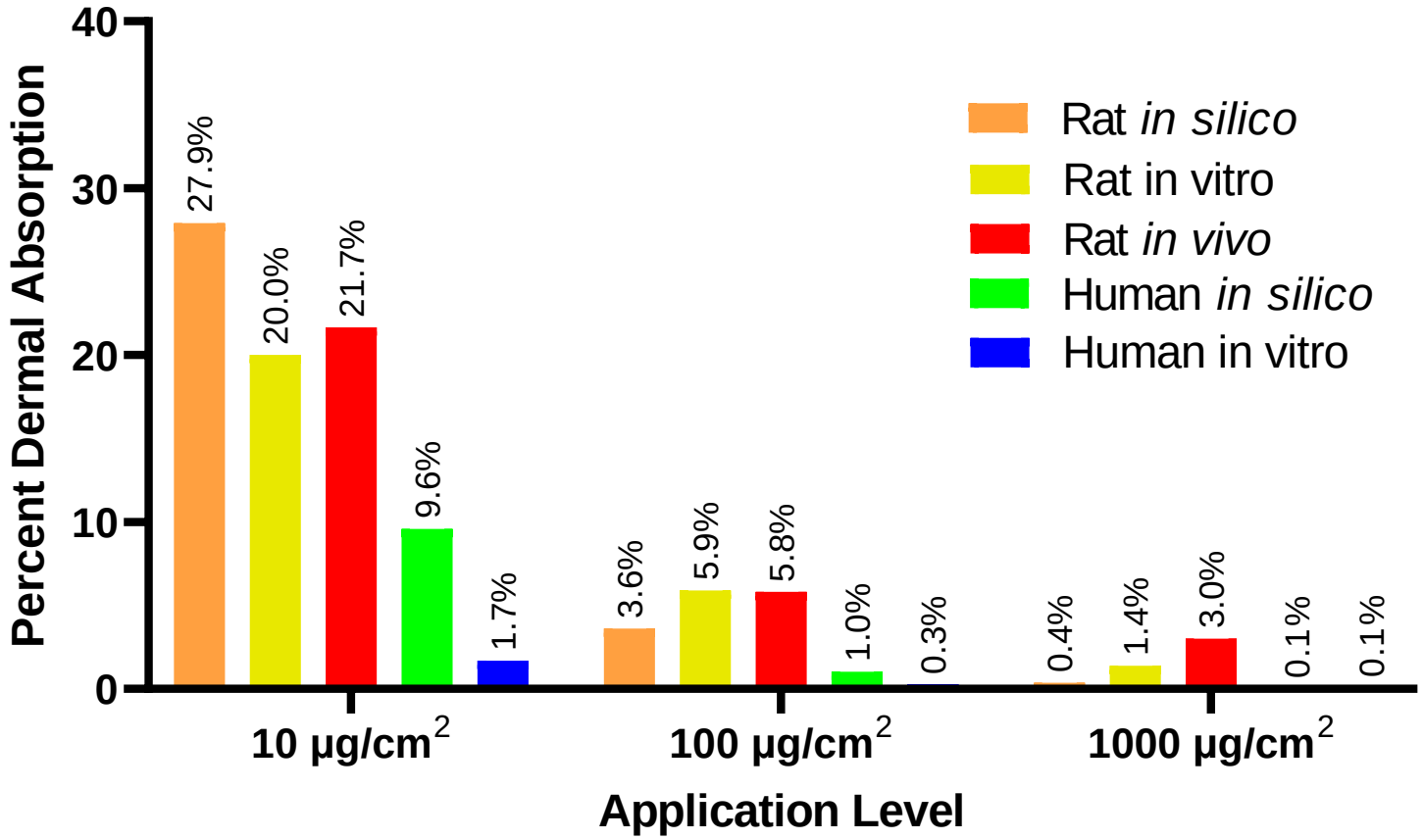


Figure from Wei et al. 2017, used under the Creative Commons CC-BY license)

Prediction of Dermal Absorption:

- Species and dose-dependent differences for TCVP
- Correlation of saturable absorption in rat seen between *in silico, in vitro* and *in vivo* data
- Lower absorption seen in human, both *in vitro* and via *in silico* modeling.

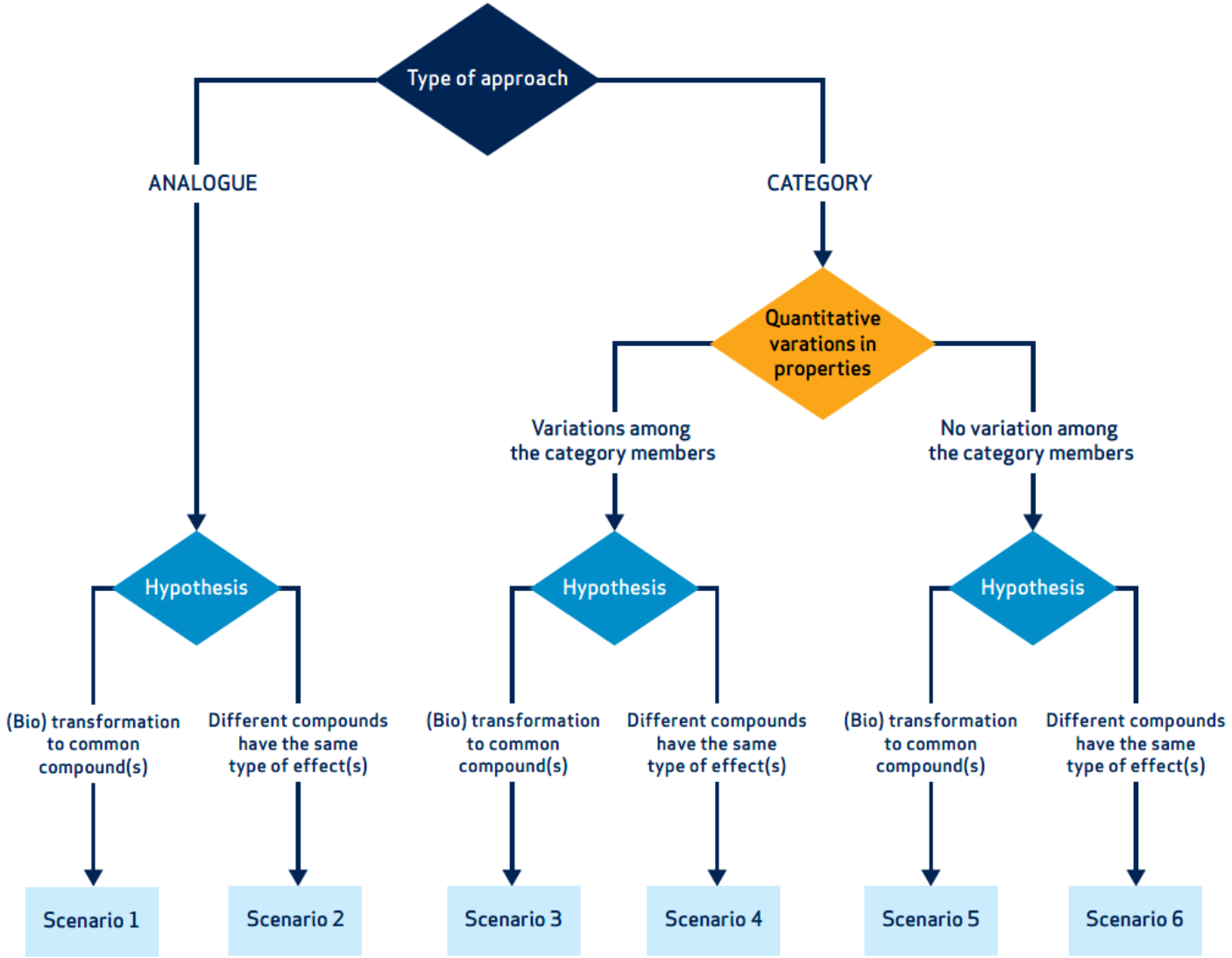


Reifenrath et al., In Preparation

Case Study #2 with Modified Methylene diphenyl diisocyante (MDI) Substances

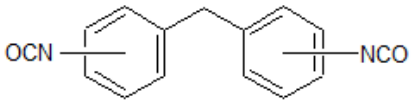
Read Across Assessment Framework (EU ECHA 2017)

- *"'Read-across and grouping', or 'read-across', is one of the most commonly used alternative approaches for data gap filling in registrations submitted under the REACH Regulation. Read-across involves the use of relevant information from analogous substance(s) (the 'source' information) to predict properties for the 'target' substance(s) under consideration."*
- Advantages:
  - Supports use of predictive approaches in the field of chemical registrations
  - Minimizes the use of animals in safety testing
  - Allows for evaluation of individual constituents in mixtures



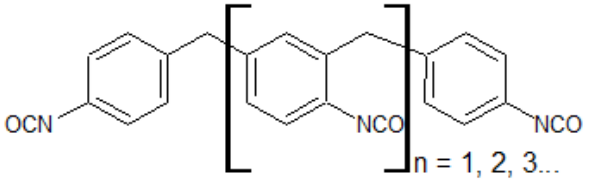
Read Across Assessment for 39 Modified MDI Substances

MDI Monomers (2,2'-; 2,4'-; 4,4'-isomers)



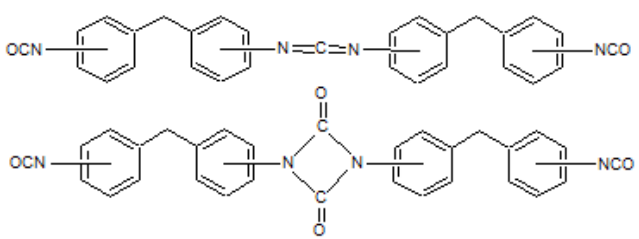
Substances 1-3

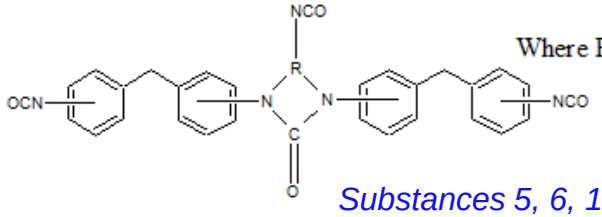
MDI Homologues



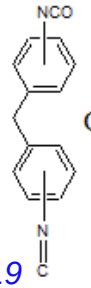
Substances 4, 7

MDI Condensation Products





Where R =



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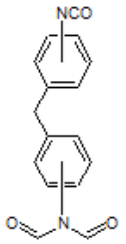
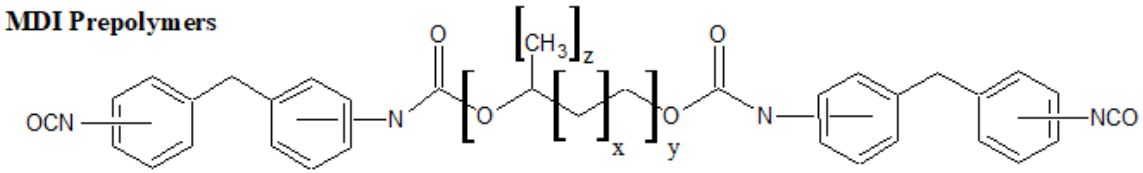
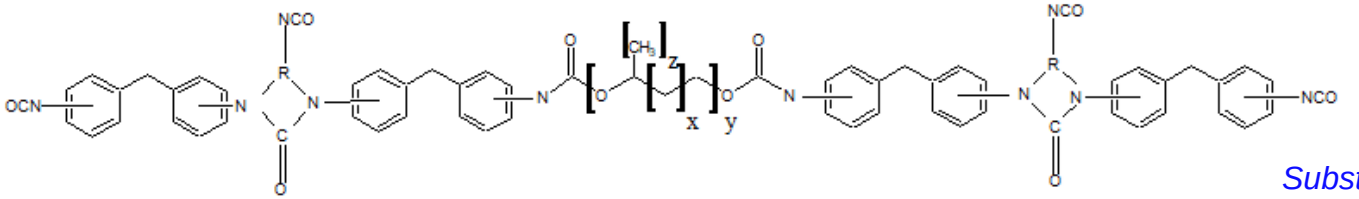


Substances 5, 6, 18, 19

MDI Prepolymers



Where the diol species are represented by:,
x =1, y = 1, z = 1: 1,3-butanediol (BD)
x =0, y = 1, z =1; 1,2-propanediol (PG)
x = 0, y =2, z = 1; Dipropyleneglycol (DPG)
x = 0, y =3, z = 1; Tripropyleneglyol (TPG)
x = 0, y =2, z = 0; Diethyleneglycol (DEG)



Substances 8-17, 20-39

MWT 250

All substances quite lipophilic and contain at least two reactive isocyanate moieties

MWT up to 2172

Read Across Assessment for 39 Modified MDI Substances

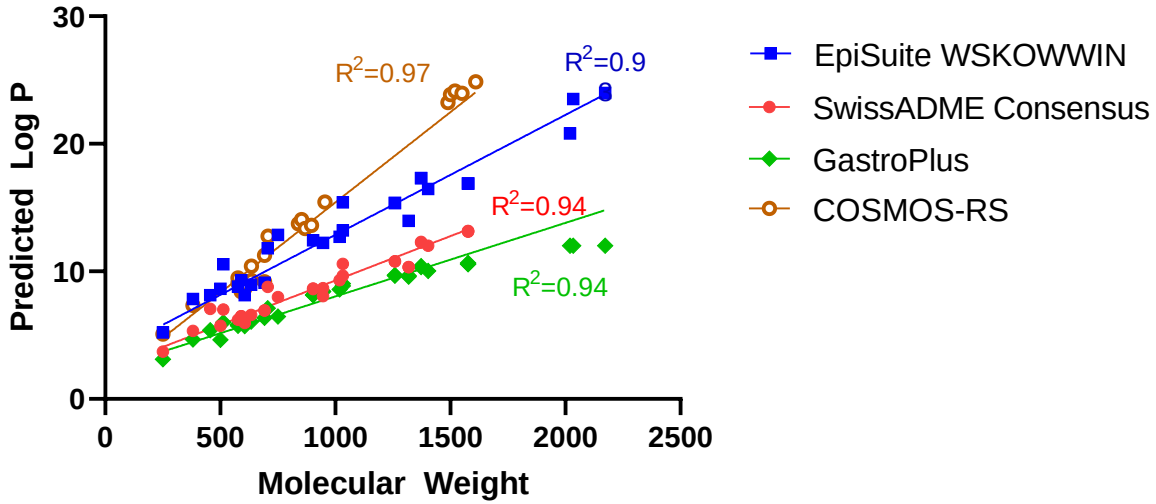
Assessment includes evaluation of the relative absorption of 39 substances via dermal and inhalation exposure routes

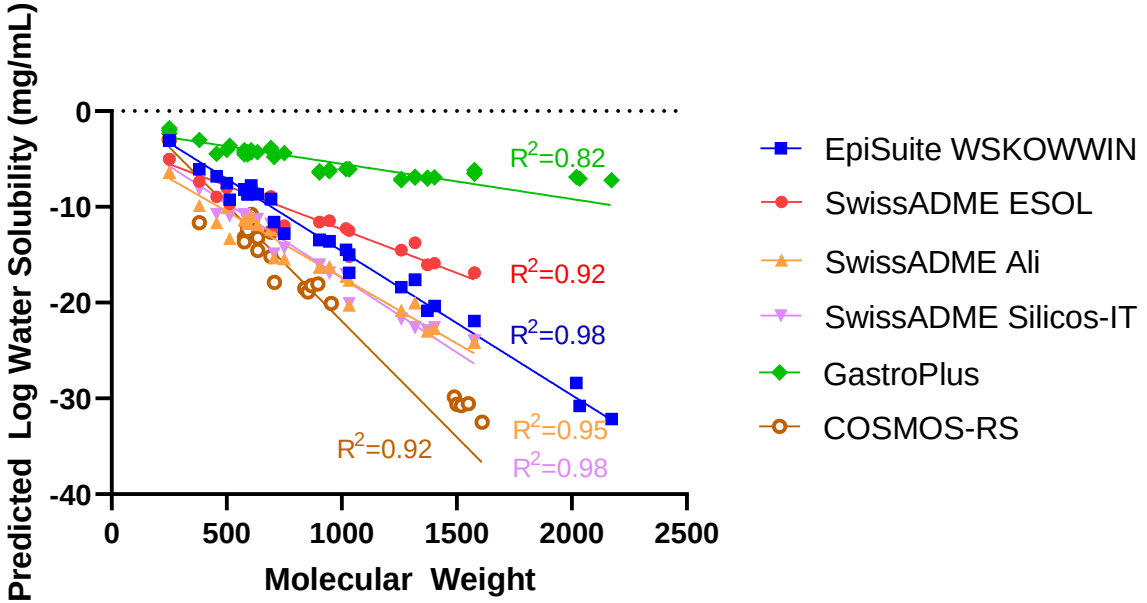
- Gastro Plus-based PBPK modeling therefore conducted via the dermal and inhalation routes to investigate potential relationships in the molecular, physical-chemical, and pharmacokinetic properties within this class of substances
  - Dermal model includes:
    - Presystemic metabolism in epidermis/dermis
    - Solubility- and vehicle-limited dermal uptake and absorption
  - Inhalation model includes:
    - Solubility-and particle-size limited absorption into pulmonary tissues
    - Presystemic metabolism in portal-of-entry tissues
    - Mucociliary clearance
    - Presystemic chemical degradation in GI tract
    - Solubility-limited oral absorption

Bartels et al., 2022

Read Across Assessment for 39 Modified MDI Substances

Physical-chemical properties required for PBPK parameter derivations were first determined with QSAR-based approaches due to the low water solubility and reactivity of the substances

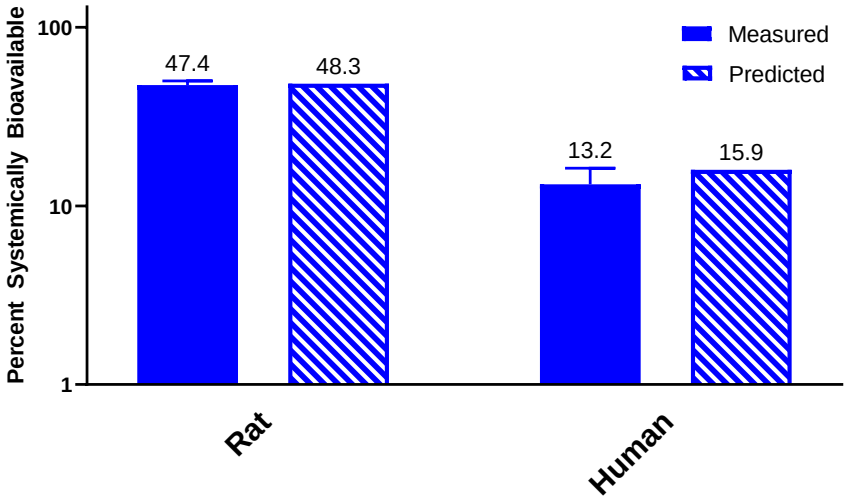




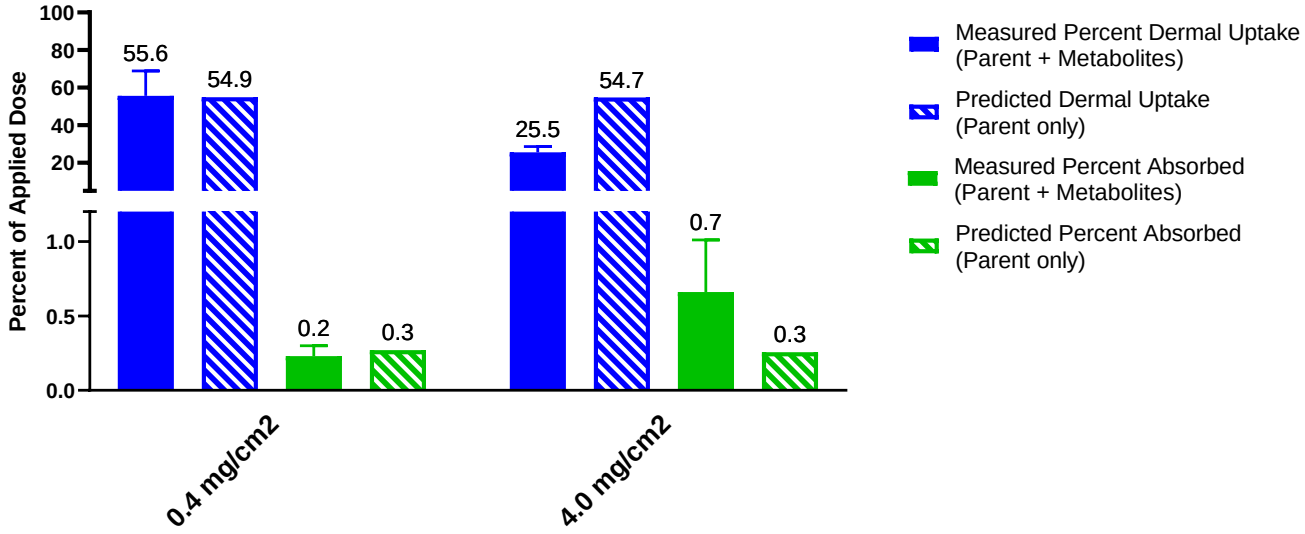
Common trends were found in both Log P and Water Solubility across QSARs - *in silico* predictions derived with GastroPlus therefore used in PBPK models

Read Across Assessment for 39 Modified MDI Substances

Evaluation of dermal absorption for Testosterone (*in vivo* data from Bartek 1972)



Optimization of dermal absorption predictions for 4,4'-MDI in rat (*in vivo* data from Leibold 1999)

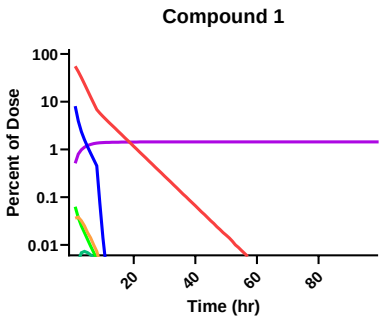


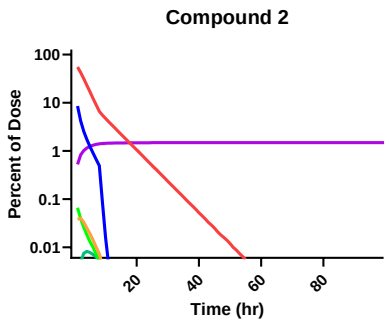
Comparable *in silico* predictions of dermal uptake and/or absorption vs. *in vivo data*

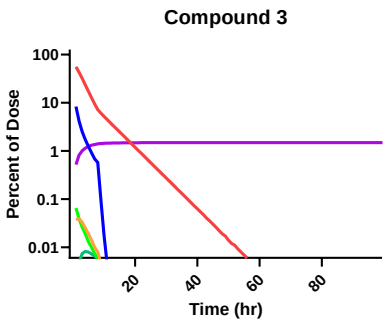
PBPK models for Regulatory Exposure Assessments

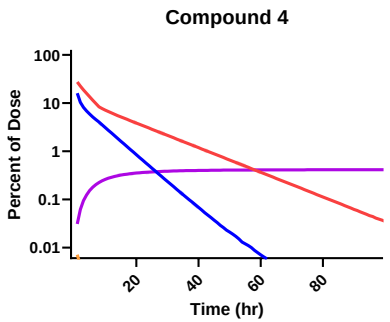
Dermal penetration of selected MDI substances through compartments of human skin

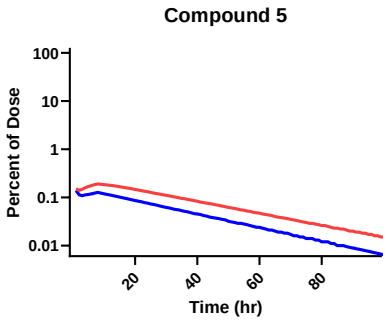
Magnitude and time-course correlated with molecular size

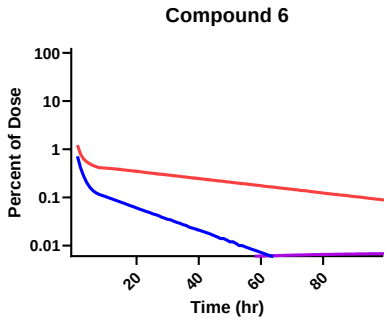


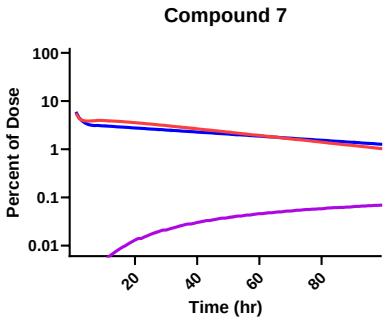


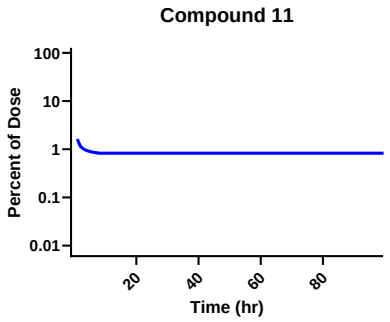


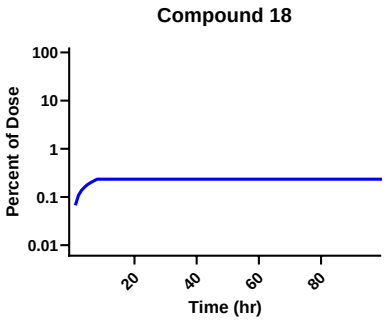


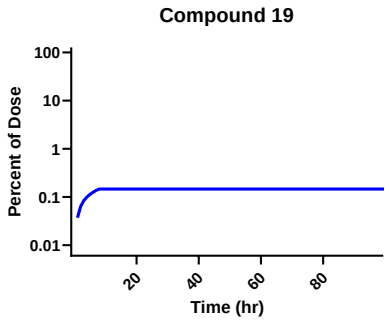




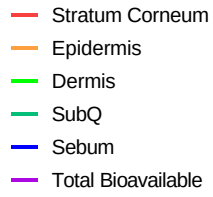






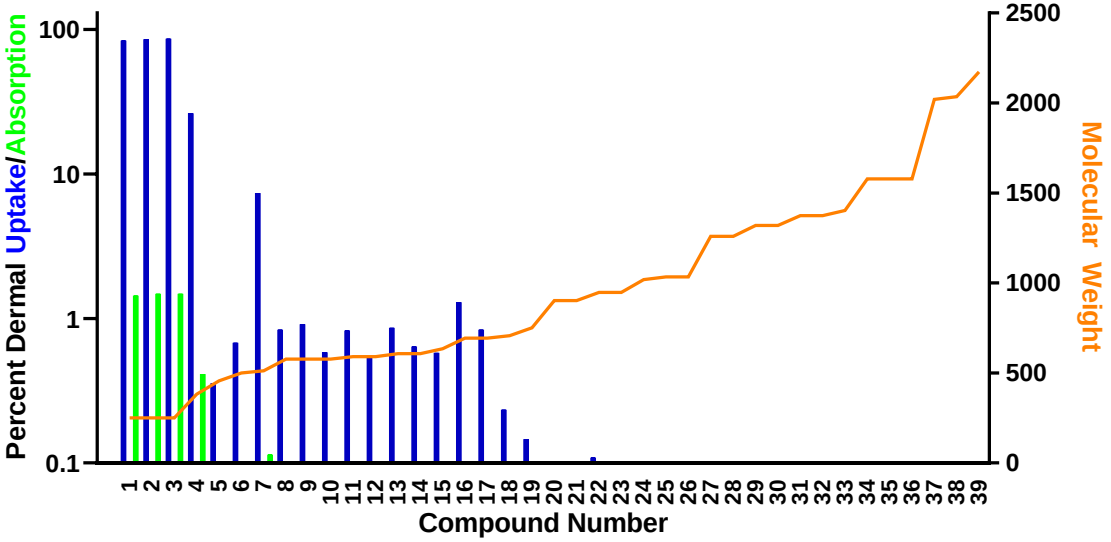


Compound	Chemical Name	Molecular Weight
1	4,4'-MDI	250.3
2	2,4'-MDI	250.3
3	2,2'-MDI	250.3
4	3-Ring Oligomer	381.4
5	4,4'-MDI Carbodiimide Dimer	456.5
6	4,4'-MDI Uretidione	500.5
7	4-Ring Oligomer	512.5
11	4,4'-MDI/1,3-BD/2,4'-MDI	590.6
18	Homopolymer - first condensation adduct	706.7
19	PIR - second condensation adduct	750.8

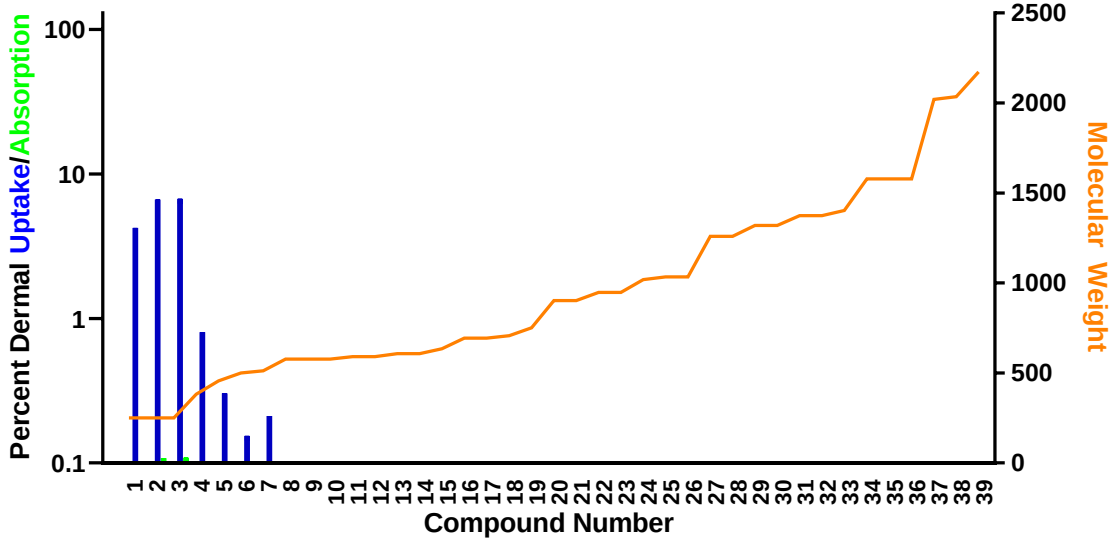


Read Across Assessment for 39 Modified MDI Substances

Test substance in acetone carrier solvent
(8 hr exposure to human skin)



Test substance in octanol carrier solvent
(8 hr exposure to human skin)

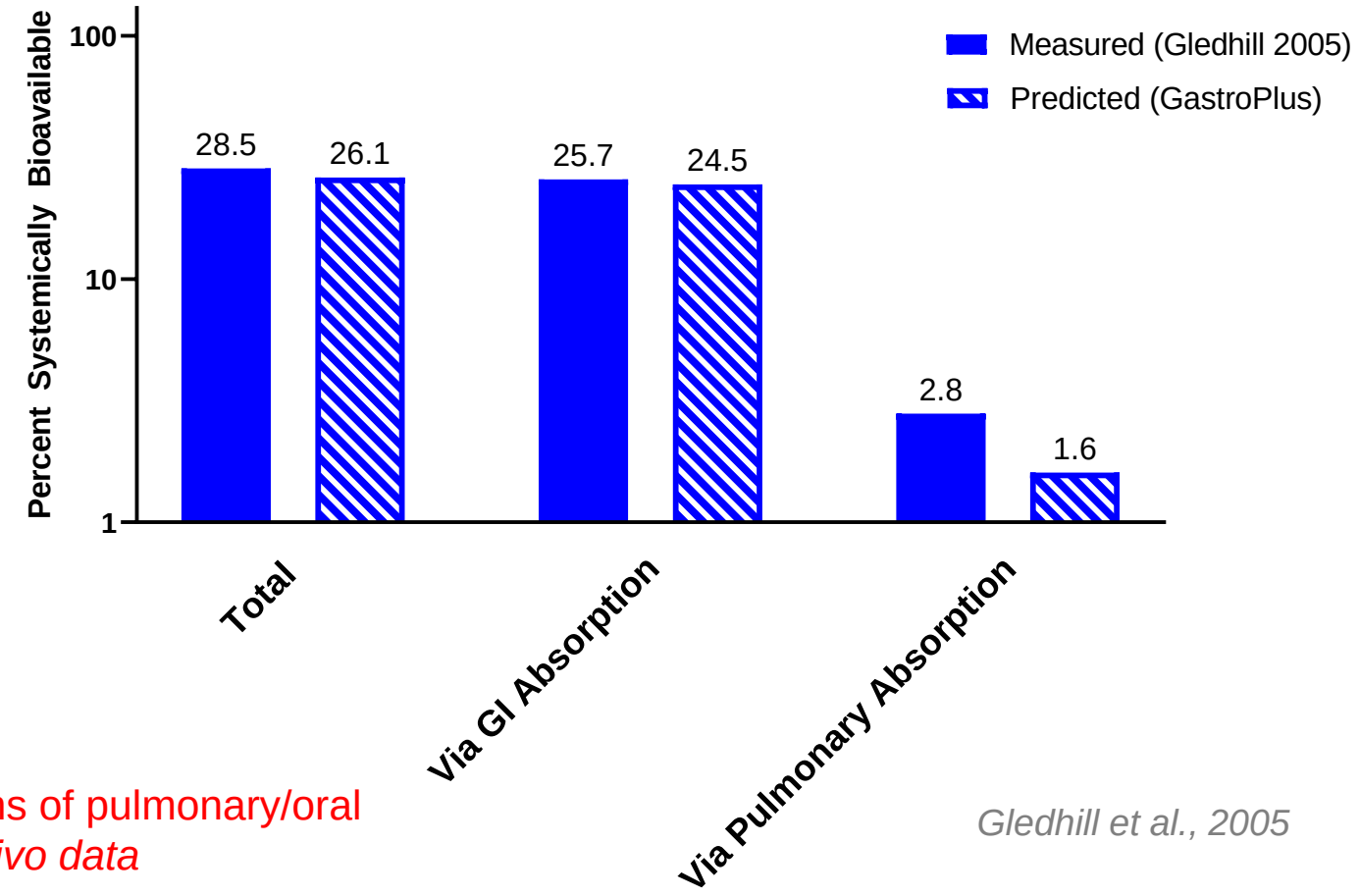


Magnitude of dermal uptake into skin and penetration through skin correlated with molecular size and carrier solvent

Read Across Assessment for 39 Modified MDI Substances

Optimization of pulmonary/oral absorption predictions for 4,4'-MDI in rat following inhalation exposure to ^{14}C-test substance as an aerosol (6 hr x 1.39 µm particle size)

- Empirical uptake of test substance calculated to be 39% via inhalation and 61% via direct oral intake (eg: grooming)
- Absorption of total dose was modeled on interpretation that absorption via pulmonary tissues was 10% of total exposure (with 29% mucociliary clearance)
- Presystemic metabolic clearance in pulmonary tissue and chemical degradation rate in GI tract were optimized to fit *in vivo* data



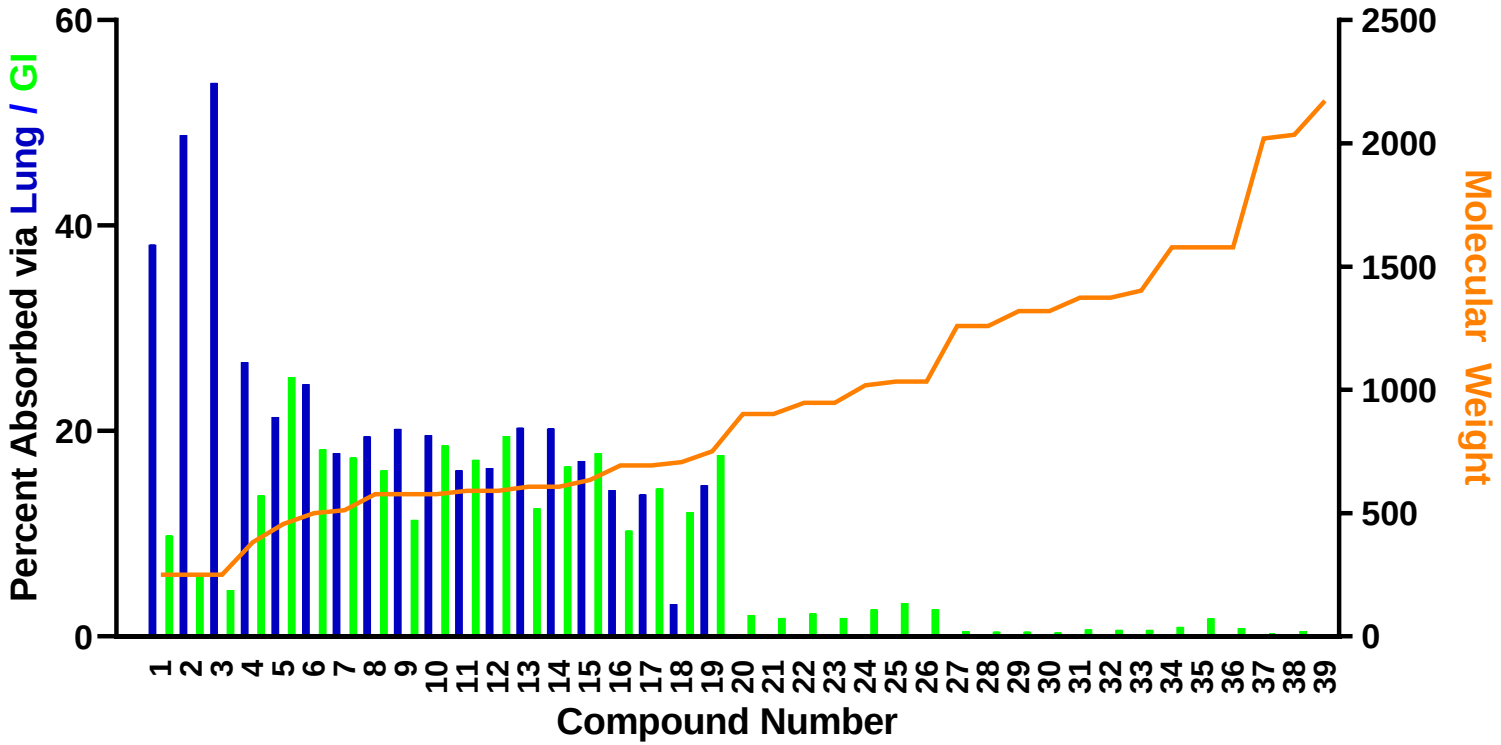
Comparable *in silico* predictions of pulmonary/oral uptake and absorption vs. *in vivo data*

Gledhill et al., 2005

Read Across Assessment for 39 Modified MDI Substances

Predicted pulmonary / Oral Absorption of parent MDI substances in human:

- 6 hr inhalation exposure to 0.01 ppm in air (2.5 µm particle size)
- Metabolic clearance in pulmonary tissues scaled from fitted parameter in rat to species differences in total lung surface area
- Chemical degradation rate in human GI tract assumed equal to rat
- Both metabolic clearance and chemical degradation rates assume to be constant for all 39 test substances



Magnitude of uptake through pulmonary tissues correlated with molecular size

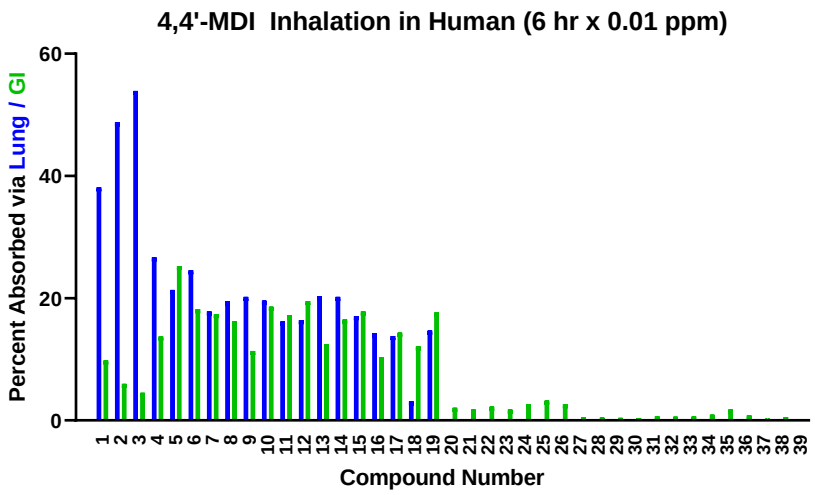
- Highest total absorption is predicted for the three MDI monomers (substances 1-3)

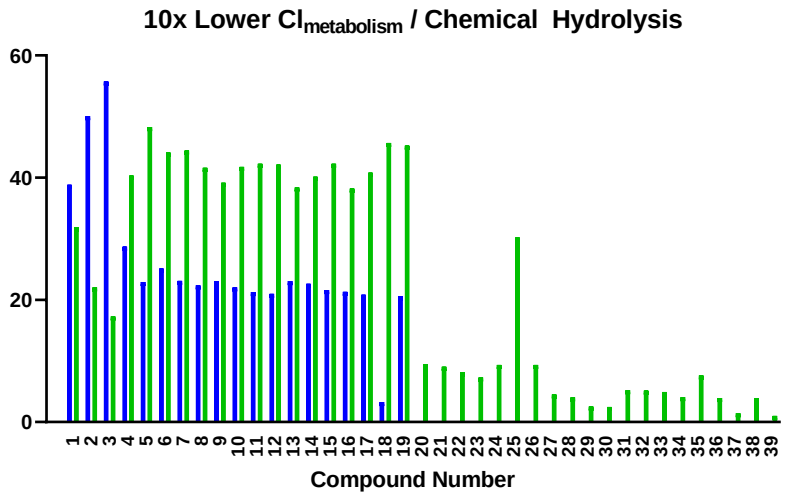
Increased mucociliary clearance predicted for MWT range 380-750

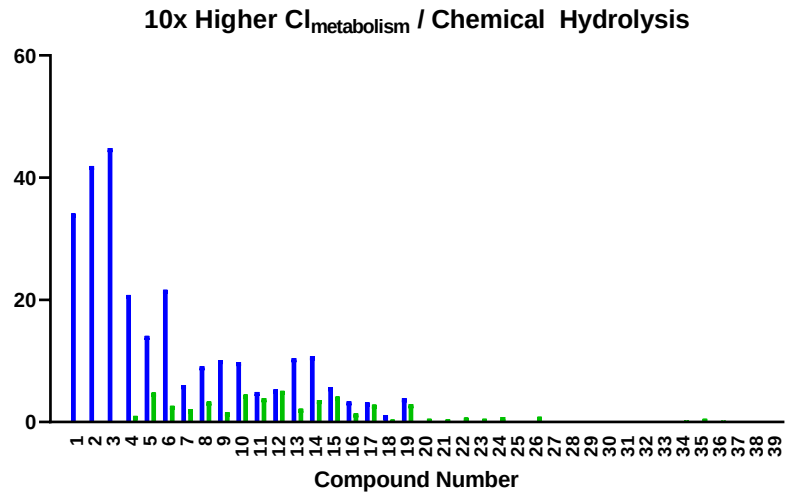
- consistent with lower water solubility and corresponding lower pulmonary uptake than lower MWT MDI monomers

PBPK models for Regulatory Exposure Assessments

Impact of metabolic / chemical clearance on total uptake in human from inhalation exposure







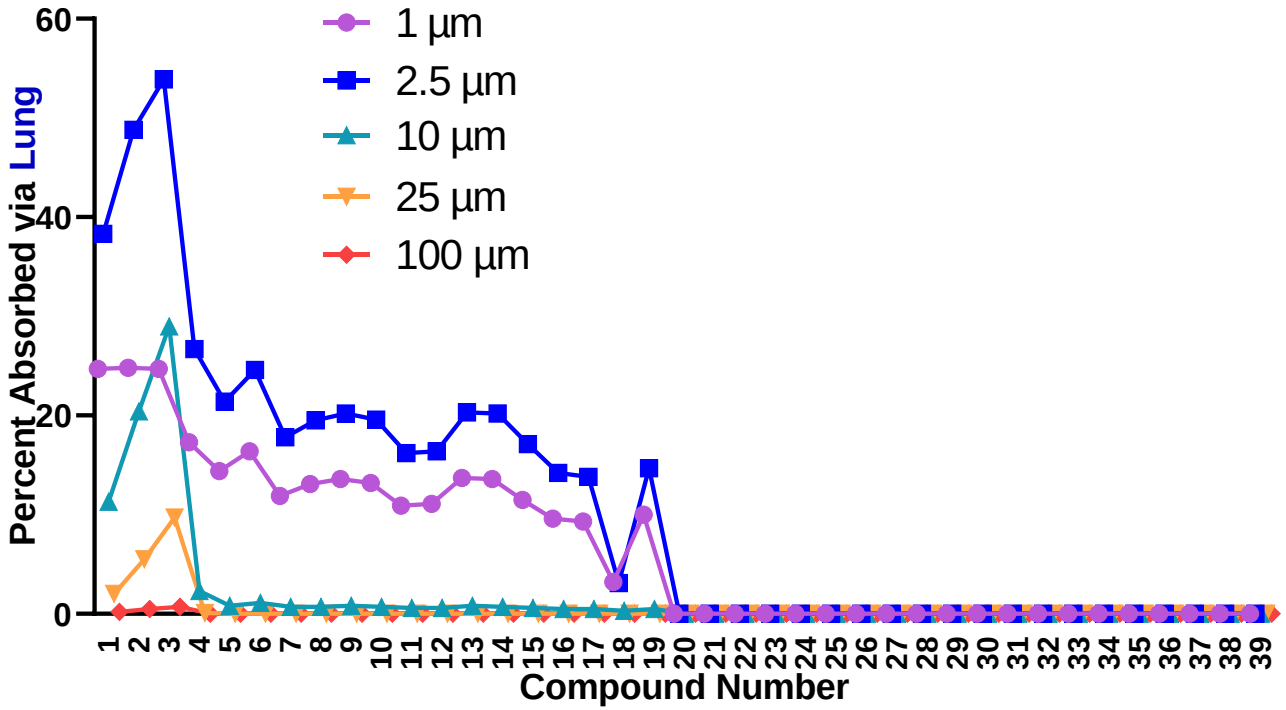
Magnitude of uptake through pulmonary tissues still correlated with molecular size

- 10x reduction in metabolic/chemical clearance predicted to have modest impact on pulmonary absorption
  - however, increased oral absorption predicted for all substances
- 10x increase in metabolic/chemical clearance affords 2-7x reduction in pulmonary absorption
  - also, oral absorption decreases 2-50 fold

Read Across Assessment for 39 Modified MDI Substances

Predicted pulmonary / Oral Absorption of parent MDI substances in human:

- 6 hr inhalation exposure to 0.01 ppm in air
- Test substance particle size varied from 1 to 100 µm
- Test substance deposition based on ICRP66 human respiratory tract dosimetry model



- Magnitude of uptake through pulmonary tissues correlated with molecular size across all particle sizes
- Modeled absorption results with 2.5 µm particle size conservative estimate of pulmonary uptake in human

Summary

- GastroPlus has been shown to provide useful predictions of physical-chemical and metabolic properties, as well as estimates of test substance absorption via the oral, dermal or inhalation exposure routes.
  - Saturable oral and dermal absorption is also supported with GastroPlus in numerous species
- Species differences in modeled dermal absorption of TCVP were compared to empirical data to support refinement in risk assessment
- Dermal and inhalation absorption of MDI substances were modeled to support a Category-based Read Across Assessment
  - Predicted dermal uptake and absorption of low MWT MDI monomers from an acetone vehicle was > 80% and 1-2%, respectively, with lower uptake and absorption predicted for all higher MW analogs
    - Lower absorption and similar MWT trends also predicted from exposures in a more lipophilic vehicle (1-octanol)
  - Modeled inhalation exposures afforded the highest pulmonary absorption for the MDI monomers (38–54%)
    - with 3–27% for the MW range of 381–751 and <0.1% for the higher MW derivatives.
    - Predicted oral uptake, representing mucociliary transport, ranged from 5 to 10% for the MDI monomers, 10–25% for constituents of MW 381–751, and ≤3% for constituents with MW > 900
      - Predictions of appreciable mucociliary transport may also be useful to address data gaps in oral toxicity testing for this category of compounds
  - These *in silico* evaluations should be useful in category-based, worst-case, Read-Across assessments for MDI monomers and modified MDI substances for potential systemic effects

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