



## SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

# Determination of an Internal Margin of Exposure Between Rodent Oral and Human Dermal Exposure to Phenoxyethanol using Physiologically Based Modeling

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## Conflict of Interest Statement

The presenter is an employee at The Procter & Gamble Company and technologies in this presentation may be used in the safety evaluation of P&G products.



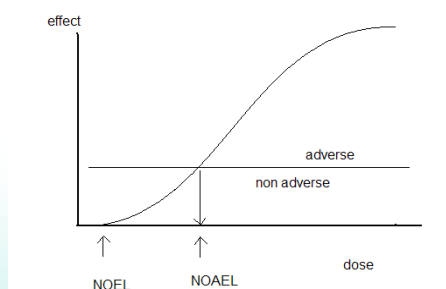
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## Traditional Risk Assessment

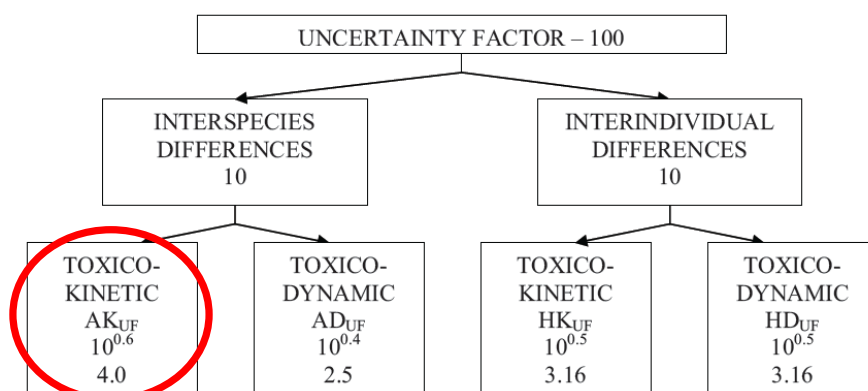
- In simple terms, human risk is determined from hazard data obtained from tox studies and exposure data
- For non-cancer endpoints, safe levels are determined by dividing a threshold (NOAEL) dose by uncertainty factors (UFs) that are assumed to be health protective
- UFs are conservative due to uncharacterized uncertainty in extrapolations between dose level, duration and populations



Dose-response to understand thresholds of toxicity

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## Uncertainty Factors



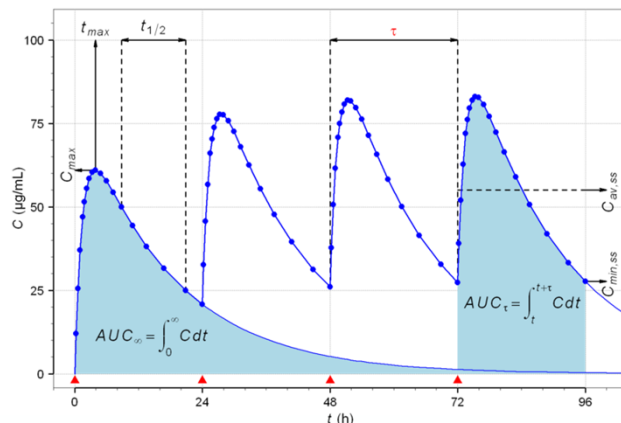
- Default UFs specifically account for differences in toxicokinetics and toxicodynamics
- When animal or human data are available, PK and dosimetry models can be used to refine (and replace) default UFs with chemical-specific adjustment factors



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## Concepts and Principles of ADME



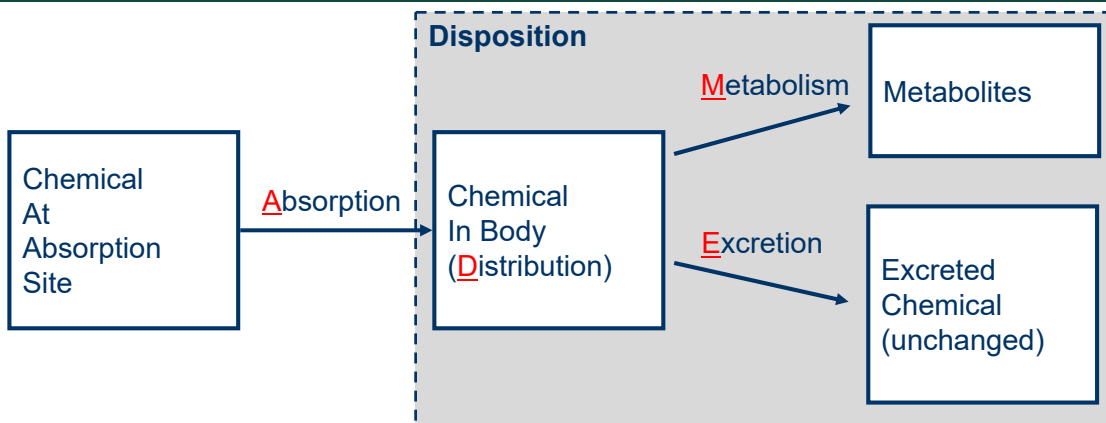
- **Exposure level, frequency and route of entry** are major factors that influence chemical action
- If differences between test species and human can be quantified, uncertainty is reduced



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## Absorption and Disposition Basics



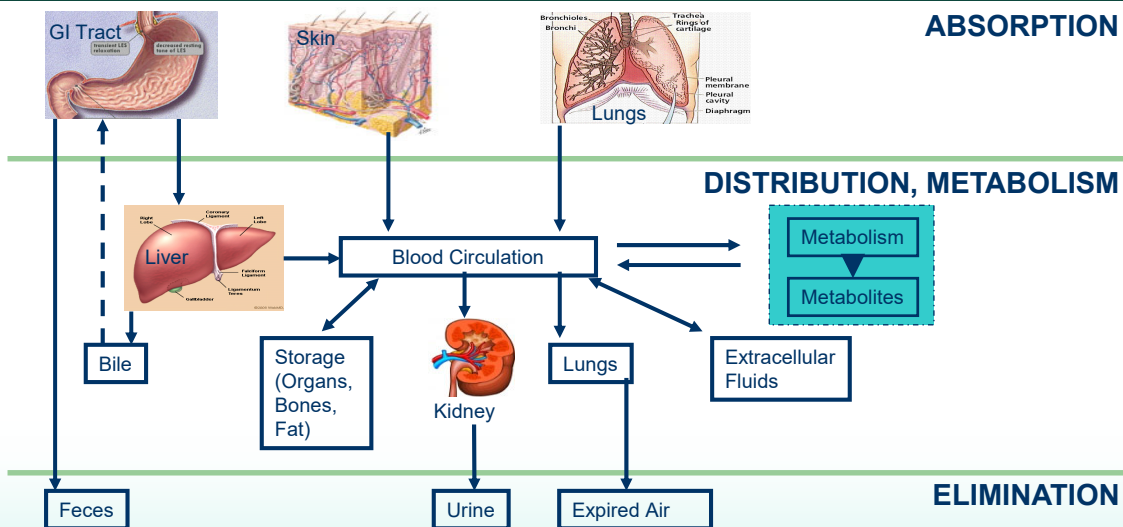
- Pharmacokinetics is the study of what the body does to the chemical as a function of time
- Specifically, it's the study of the kinetic processes of absorption, distribution and elimination



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## Understanding ADME Processes

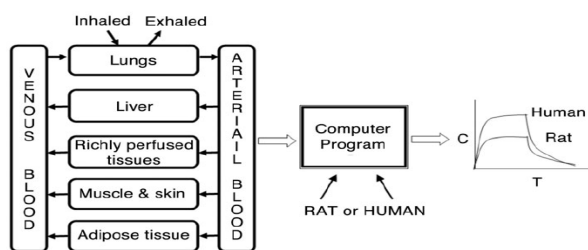


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## Application of Route-, Species- and Age-Specific PBPK Models

- It is now widely accepted that PBPK models can improve our ability to predict internal concentrations of drugs, chemicals or active metabolites and thus improve the scientific basis for human health risk assessments
- Refinement of default TK/TD uncertainty factors
  - **Inter-species differences**
  - Inter-Individual differences
  - Dose route extrapolation
  - Dose level extrapolation



Khalil and Laer (2011). *Journal of Biomedicine and Biotechnology*

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## Risk Characterization of Phenoxyethanol

- At PhE external dosages  $\geq 400$  mg/kg/day, toxic effects include hepatotoxicity, renal toxicity and hemolysis
- Available safety data collected in the mouse, rat and rabbit by different routes show differences in toxicity profiles when viewed based on external dose
  - **NOAEL range:** 80-1875 mg/kg/day
  - **LOAEL range:** 400-3700 mg/kg/day
- Rat NOAEL of 369 mg/kg/day from critical drinking water studies was identified as the appropriate repeat dose POD using Benchmark Dose Modeling, based on liver effects following repeated exposures



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## Objectives

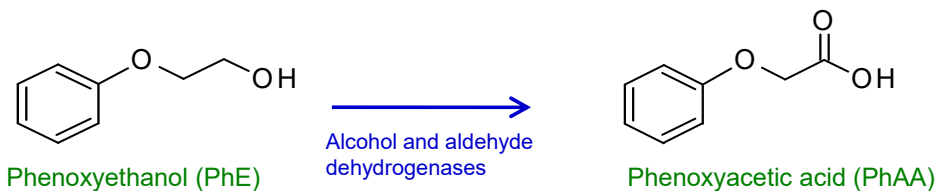
- Use PBPK models to quantify the impact of species-specific differences in metabolism and routes of exposure on induction of both adverse and non-adverse effects, which are inconsistent across studies.
- Use the estimated “internal exposure” to reduce uncertainties in the kinetic differences across species
- Refine and improve human health risk assessments through application of PBPK modeling methods that are approved by globally recognized regulatory bodies



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## ADME of Phenoxyethanol



- ADME of PhE has been well characterized in mammals
- PhE is rapidly metabolized following oral or dermal absorption
- 75-100% of an orally ingested or dermally absorbed dose is excreted in urine as PhAA
- PhAA metabolite is a relevant biomarker of PhE exposure
- Cumulative amount in urine (24 hr) provides a direct measure of daily exposure
- We used a wide range of measured data to develop and evaluate the model



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## Experimental ADME Data for Phenoxyethanol

Species	Metric	Sample matrix	Dose route	Dose level (mg/kg)
Rat	PhE, PhAA	plasma	Oral bolus	152, 456
Rat	<sup>14</sup> C-PhE	tissue, urine	Oral bolus	40, 400
Human	<sup>14</sup> C-PhE	urine	Oral bolus	0.152
Rat, Human skin	<sup>14</sup> C-PhE	Receptor fluid	In vitro skin penetration	0.86–2.9 (Rat) 0.10 (Human)
Rat	<sup>14</sup> C-PhE	urine	Dermal	18.4, 24.4
Human	<sup>14</sup> C-PhE	urine	Dermal	0.9–7
Rat	<sup>14</sup> C-PhE	urine	Dermal	16, 27, 161
Rat	<sup>14</sup> C-PhE	blood	Oral bolus	30, 40, 100, 300, 400
Human	PhAA	urine	Dermal	unspecified
Human, preterm infants (23–27 GA)	PhE, PhAA	urine	Dermal	unspecified

Troutman et al. / *Regulatory Toxicology and Pharmacology* 73 (2015) 530–543

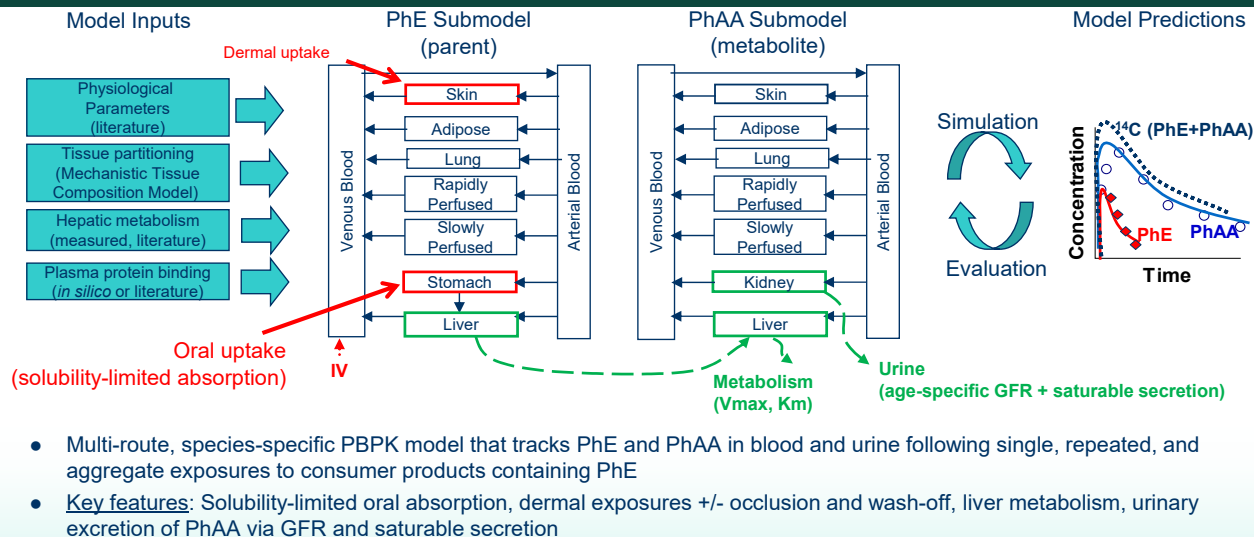
- PBPK model for PhE and PhAA metabolite is based on extensive *in vitro* and *in vivo* ADME datasets collected in rats and humans following exposure by oral and dermal routes.
- Administered doses ranged from 0.1–456 mg/kg PhE.



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## Model Structure

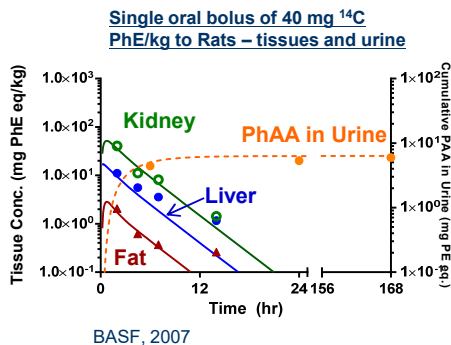
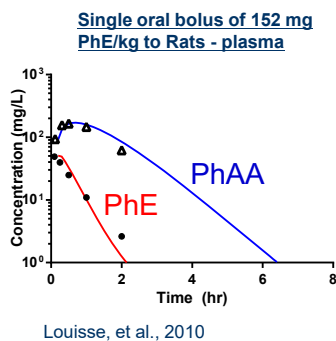


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## Oral Rat Model Development and Performance

Good agreement between measured and model-predicted conc-time profiles in rats following oral exposure



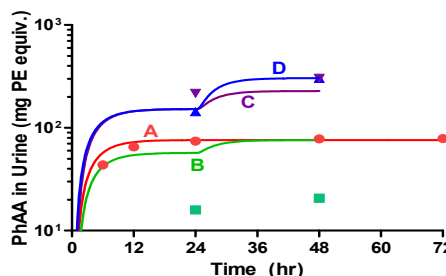
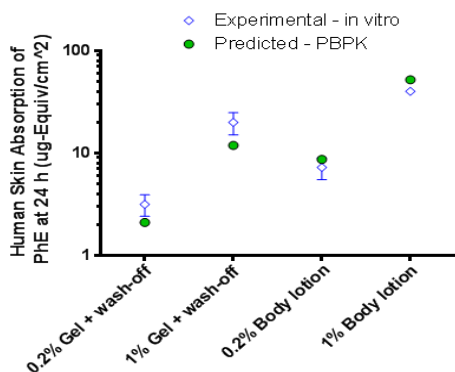
- Symbols represent experimental values
- Solid lines represent predicted concentrations from the PBPK model

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## Dermal Human Model Development and Performance

Good agreement between measured and model-predicted dermal absorption data



- *In vitro* human skin pen of <sup>14</sup>C PhE (Vincent and Marty, 2002)

- Cumulative urinary excretion - single and repeated dermal exposure to humans (Howes, 1991)

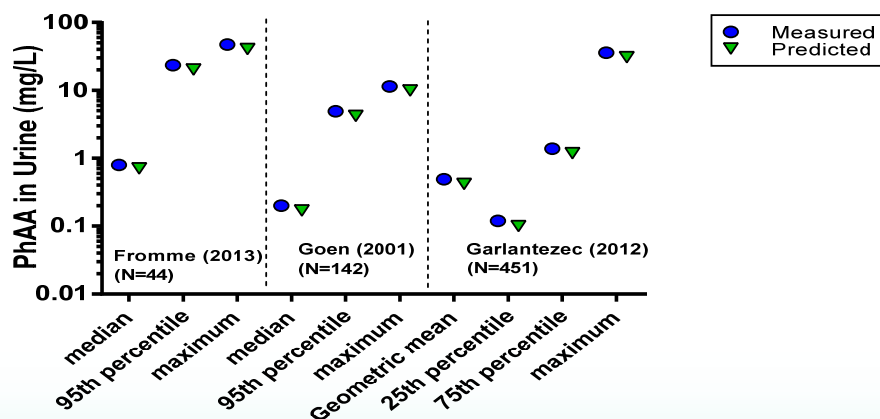


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## Urine Biomonitoring of PhAA Concentration in Adults

Model Verification with Population-based PhAA Urine Data (N=637)



Excellent correlation for urinary PhAA predictions with numerous human biomonitoring datasets

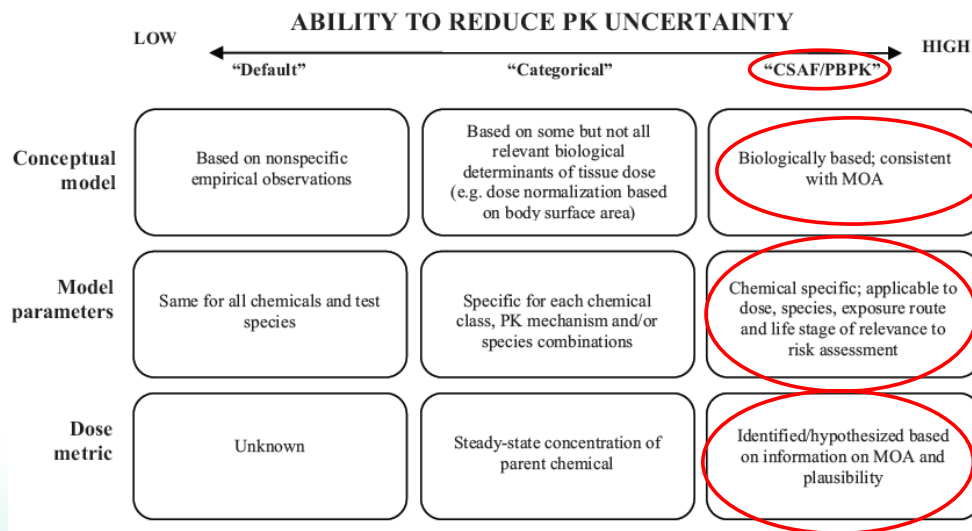


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## Refinement of TK Uncertainty Factors



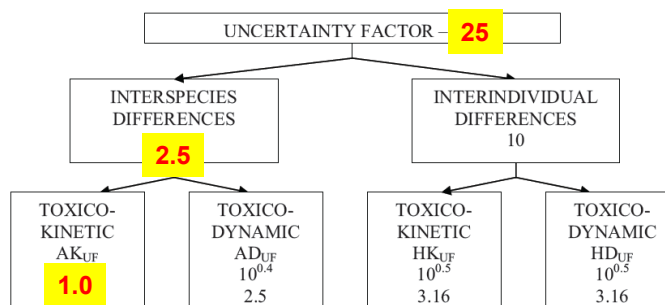
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## Refining Inter-Species Uncertainty Factors

With the application of the PBPK model to describe key kinetic ADME processes in rats and humans:

- The interspecies TK default UF of 4.0 can be reduced to 1.0
- The toxicodynamic portion of the default interspecies UF (2.5) must be applied to complete the interspecies extrapolation and is accepted as adequately protective



- The net result is a refinement of the **total default UF value of 100 to a refined value of 25** (1.0 for TK factor X 2.5 TD factor for inter-species X 10 for inter-individual TK and TD differences)

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## Internal Dose to Humans from Consumer Products/Cosmetic Use: Aggregate Exposures in Adult Humans

- Consumer use data was derived from the SCCS Notes of Guidance 8<sup>th</sup> Revision
- All products were assumed to contain PhE at a maximum of 1% (conservative)
- Wash-off times were set equal to the application frequency (conservative)
- Aggregate steady-state AUC and Cmax values were calculated from the sum of discrete simulation runs for each product exposure scenario

Product	Exposed skin surface area (cm <sup>2</sup> )	Application volume (mL or cm <sup>3</sup> )	PhE dose level (mg/kg/application)	No. of exposures per day	Exposure frequency (hr)
Shower gel	17500 <sup>a</sup>	0.19	0.0279	1	24
Shampoo	1440 <sup>b</sup>	0.11	0.0151	1	24
Hair conditioner	1440 <sup>b</sup>	0.04	0.0067	1	24
Hair styling	1010 <sup>c</sup>	0.40	0.0574	1	24
Liquid foundation	565 <sup>d</sup>	0.51	0.0790	1	24
makeup remover	565 <sup>d</sup>	0.50	0.0833	1	24
Hand wash soap	860 <sup>e</sup>	0.020	0.00333	10	2.4
Body lotion	15670 <sup>f</sup>	3.910	0.616	2	12
Face cream	565 <sup>d</sup>	0.770	0.121	2	12
Hand cream	860 <sup>e</sup>	1.080	0.164	2	12
Deo non-spray	200 <sup>g</sup>	0.750	0.110	2	12
Eye makeup	24 <sup>h</sup>	0.010	0.00165	2	12
Mascara	1.6 <sup>b</sup>	0.013	0.00210	2	12
Lipstick	4.8 <sup>b</sup>	0.030	0.00450	2	12
Eyeliner	3.2 <sup>b</sup>	0.00250	0.000400	2	12
Toothpaste	N/A	N/A	0.011	2	12
Mouthwash	N/A	N/A	0.163	2	12



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## Internal Dosimetry Predictions

Species/ Subpopulation	BW (kg)	Description	External Exposure (mg/kg/day)	AUC (mg*h/L)	
				PhE	PhAA
Rat	0.25	NOAEL (drinking water)	369	61.5	690
Adult Human	60	Aggregate (oral+cosmetics)	2.69	0.608	8.82

- Model simulations were performed for a 13-week rat drinking water study (NOAEL 369 mg/kg/d) and human aggregate product exposure scenarios, as defined in the dossier
- Steady-state AUCs were compared (appropriate dose metric) for both PhE and PhAA
- Exposures for adult human aggregate (oral care+cosmetics) are based on conservative product use assumptions
- Oral care exposure in adults assumed bolus dosing with 100% ingestion of toothpaste and mouthwash
- Removal of unabsorbed PhE from the skin surface was set equal to the re-application frequency rather than the wash off time for normal use procedures



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## Margin of Internal Exposure

Species/ Subpopulation	BW (kg)	Description	External Exposure (mg/kg/day)	AUC (mg*h/L)	
				PhE	PhAA
Rat	0.25	NOAEL (drinking water)	369	61.5	690
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$$\text{Margin of Internal Exposure (MOIE)} = \frac{\text{Internal AUC—Rat}}{\text{Internal AUC—Human}}$$



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## Margin of Exposure

Species/ Subpopulation	BW (kg)	Description	External Exposure (mg/kg/day)	AUC (mg*h/L)	
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$$\text{Margin of Internal Exposure (MOIE)} = \frac{\text{Internal AUC—Rat}}{\text{Internal AUC—Human}}$$

Species/ Subpopulation	BW (kg)	Description	External Exposure (mg/kg/day)	MOE	
				PhE	PhAA
Adult Human	60	Aggregate (oral+cosmetics)	2.69	101	78



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## Summary

- Using a traditional approach, a default total UF of 100 (10 inter-species x 10 intra-species x 1 duration) would be required for extrapolation of the drinking water NOAEL of 369 mg/kg/day to humans, resulting in a **reference dose of 3.69 mg/kg/day** for repeated dose toxicity in humans for PhE.
  - Expected MOE between NOAEL of 369 mg/kg/day and human exposure would be 100
- However, species- and route-specific toxicokinetic information on PhE was evaluated to develop a PBPK model in order to refine the inter-species toxicokinetic factor.
- Using a PBPK approach, a PBPK-refined total UF of 25 can be used for extrapolation of the drinking water NOAEL of 369 mg/kg/day to humans, resulting in a **reference dose of 15 mg/kg/day** for repeated dose toxicity in humans for PhE
  - Refined MOE between NOAEL of 369 mg/kg/day and human exposure would be 25
- Calculated margin of internal exposure (MOIE) for aggregate cosmetic use scenarios in adults was above the PBPK-refined total UF of 25 for normal use of PhE at a concentration up to 1%
- Importantly, the refined chemical-specific UF and MOEs were obtained using conservative PBPK model assumptions as well as exaggerated product composition and use



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