Ensuring Safety for Early Life Exposures: Adequacy of Current Methods and Opportunities to Advance the Science

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Conflict of Interest Statement

Susan Felter is employed by the Procter & Gamble Company, which manufactures and sells consumer products that are used by infants and children

Outline

- Basis for Differential Susceptibility
  - Exposure (qualitative/quantitative differences)
  - Differential sensitivity based on immaturity
- Safety assessments: Are current methods adequate?
- Opportunities to refine assessments
  - PBPK modeling to address lifestage differences
- Case Study: Phenoxyethanol

Terminology*: Sensitivity, Susceptibility, Vulnerability

- **Sensitivity:** Differences in response resulting from toxicokinetic and/or toxicodynamic differences. Can arise from factors such as lifestage, genetics, gender, disease status, etc.

- **Susceptibility:** Differences in risk resulting from variation in both toxicity response (sensitivity) and exposure

- **Vulnerability:** Differences in risk resulting from the combination of both intrinsic differences in susceptibility and extrinsic social stress factors (e.g., socioeconomic status, violence, access to health care)

* From US EPA's ExpoBox: https://www.epa.gov/expobox/exposure-assessment-tools-lifestages-and-populations-highly-exposed-or-other-susceptible

Differential Exposure

- NAS (1993) "Pesticides in the Diets of Infants/Children": Differences in diet (*exposure)* are generally more important than age-related differences in sensitivity.

    - Children may be *more or less* sensitive than adults

    - Quantitative differences in sensitivity between children and adults are usually < 10-fold

- Similar conclusions reached by the EU Scientific Committee on Food (SCF, 1998)

Potential Susceptibility: Higher Exposure?

- Well-known that infants and young children have a higher exposure to food/water/air than adults.

- Consumer products (dermal exposure):

  - Infants have higher Skin Surface Area-to-Body Weight ratio

    - 2.3 fold at birth,
    - 1.8 fold at 6 months
    - 1.6 fold at 12 months,
    - 1.5 fold at 5 years   [Renwick 1998]

  - This is not relevant for an assessment where the exposure assessment is done specifically for the infant/child population

Exposure Assessments for Personal Care Products (PCPs)

- Consider habits & practices for target age(s), and associated physiological parameters, e.g.: body weight, surface area

  - Infants are growing and maturing quickly so values for these parameters need to be conservative yet pragmatic

- Characteristics that might impact dermal absorption (first part of PK [ADME])–often considered in context of exposure assessment

Barrier Properties of Infant Skin

- By the time of delivery at term, the stratum corneum is histologically mature

- Weisberger et al., 2003: Intact skin in healthy term and near-term infants exhibits barrier function comparable to older children and adults. Based on:
  - Measurements of transepidermal water loss (TEWL)
  - Carbon dioxide emission rates
  - Drug absorption

- Fluhr et al., 2011: Despite different methodologies used, there is general agreement that basal TEWL values in nonstressed skin in infants is similar to that in healthy adults.

Local (Site-of-Contact) Effects

- Safety assessments (in units of ug/cm^2 skin) are conducted for sensitization based on appropriate product specific habits and practices and infant/child-specific exposure parameters.

- Confirmation of initial safety assessment for dermal endpoints can be provided by clinical skin irritation/sensitization tests

- Clinical "in use" studies may also be conducted.

Dermal Sensitization: Lower Risk in Early Life

Cassimos et al., 1980

- Reactivity of infants up to 9 mo old to 2, 4-dinitrochlorobenzene (DNCB) is low compared to adults.

- Lower reactivity is likely reflective of a reduced capacity for cell-mediated immunity in neonates.

- [n=284 infants]

Age	Reaction Rate
First 15 days	6.8 %
2-4 wks	25.7 %
2 mo	33.3 %
3 mo	62.9 %
4 mo	76.7 %
5 mo	81.5 %
7 mo	88.5 %
9 mo	91.3 %

Cassimos C, Kanakoudi-Tsakalidis F, Spyroglou K, Ladianos M, Tzaphi R. Skin sensitization to 2,4-dinitrochlorobenzene (DNCB) in the first months of life. *J Clin Lab Immunol* 1980: 3: 111–113.

Systemic Toxicity: Threshold-Based Effects

$$RfD = \frac{NOAEL}{UF}$$

▸ **Key Question:**
Does the traditional 10X UF for intrahuman variability provide sufficient protection for infants and children?

  ▸ 3.2X Toxicokinetics
  ▸ 3.2X Toxicodynamics
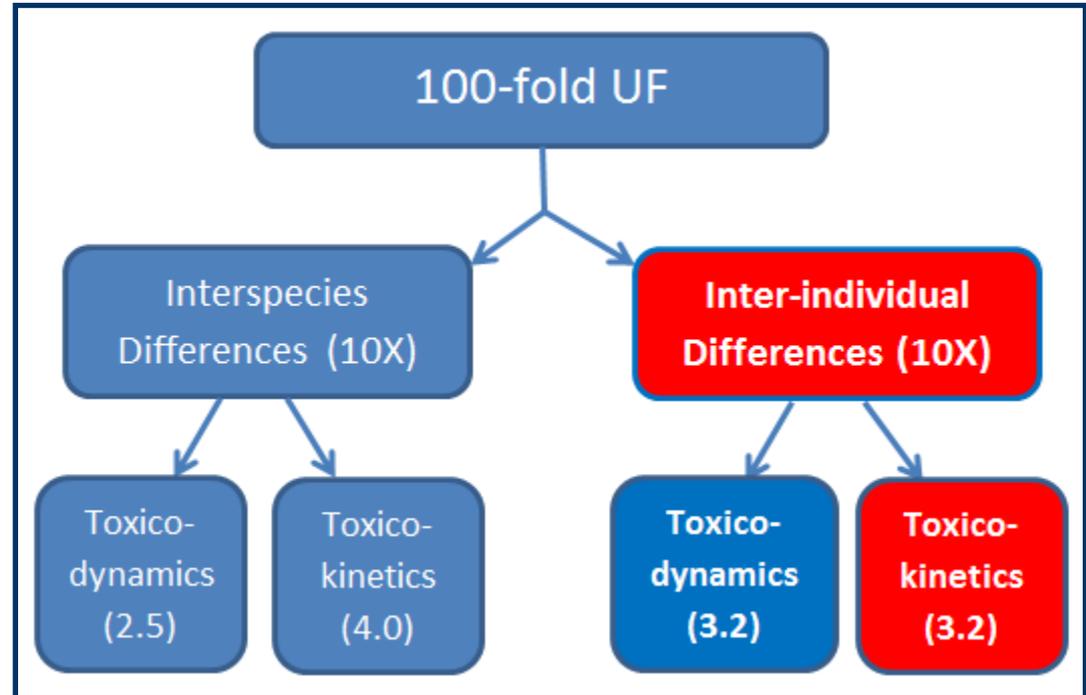
From: IPCS, 1994

Intrahuman Variability: Kinetics
Absorption, Distribution, Metabolism, Excretion

- Absorption
  - Not significantly different for dermal exposures
  - Sometimes included in the exposure assessment

- Distribution
  - Infants have a higher volume of distribution
  - Protein binding often lower (amount and specificity)
  - *These factors can result in increased or decreased sensitivity*

Intrahuman Variability: Kinetics
Absorption, Distribution, Metabolism, Excretion

- Phase I (oxidation, reduction, hydrolysis)

- Phase II (conjugation)

- Lack of maturity of hepatic enzymes can increase or decrease susceptibility. Most relevant for infants < 6 mos

- Caution against over-interpretation of what this means for overall risk, e.g.:

  – Redundant metabolic pathways

  – Hepatic blood flow might be rate-limiting

Hepatic Blood Flow (Nong et al., 2006)

- Metabolism of many chemicals in the liver at environmentally relevant doses is rate-limited by blood flow

Hepatic Blood Flow Normalized to Liver Volume					
Age	Hepatic blood flow (L/min)	Liver volume (L)	Ratio HBF/LV	Body wt (kg)	Ratio HBF/BW
< 1 mo	0.09	0.07	1.28	1.8	0.05
1-12 mo	0.18	0.23	0.78	8	0.023
1-11 yr	0.48	0.61	0.78	20.9	0.023
18+ yr	1.81	1.82	0.99	70.0	0.026

Age-Related Variability in Xenobiotic Metabolism (from Dorne et al., 2005)

- Default 3.2X factor for TK variability found to be quite conservative when considering healthy adult population

- Children/infants: Data on kinetic variability were available for 10 pathways, and in neonates for 5 pathways:

  CYP1A2, CYP3A4, glucuronidation, glycine conjugation, renal excretion.

- Majority of pathway-related UFs for children were below the 3.2X default for intrahuman TK variability, but were higher in neonates.

  – Data from neonates from pharmaceutical studies involving i.v. dosing; data from children and adults from oral exposures

Intrahuman Variability: Kinetics
Absorption, Distribution, Metabolism, Excretion

- Major route of excretion for toxicants is via the kidneys

- Dependent on renal blood flow, which increases in the weeks following birth

- Overall, adult values in kidney function (GFR) reached by ~5 months old

- In older infants and young children, kidney function is often greater than that of adults

Literature Reviews of the Default (3.2X) Intraspecies UF for Toxicokinetics

- "Infants and children do not generally represent a special group from a kinetic viewpoint … and they would be covered adequately by a 3.16-fold factor applied to the mean data for adults."
  - Emphasize that any special consideration of children should focus on the potential for different exposures and the potential for higher sensitivity of developing organs compared with adults

*Renwick (1998). Food Addit. Contam. **15: 17–35.***
*Renwick & Lazarus (1998). Regul. Toxicol. Pharmacol. **27: 3–20.***
*Renwick et al. (2000). Regul. Toxicol. Pharmacol. **31: 286–296.***

Systemic Toxicity: Threshold-Based Effects: Toxicodynamics

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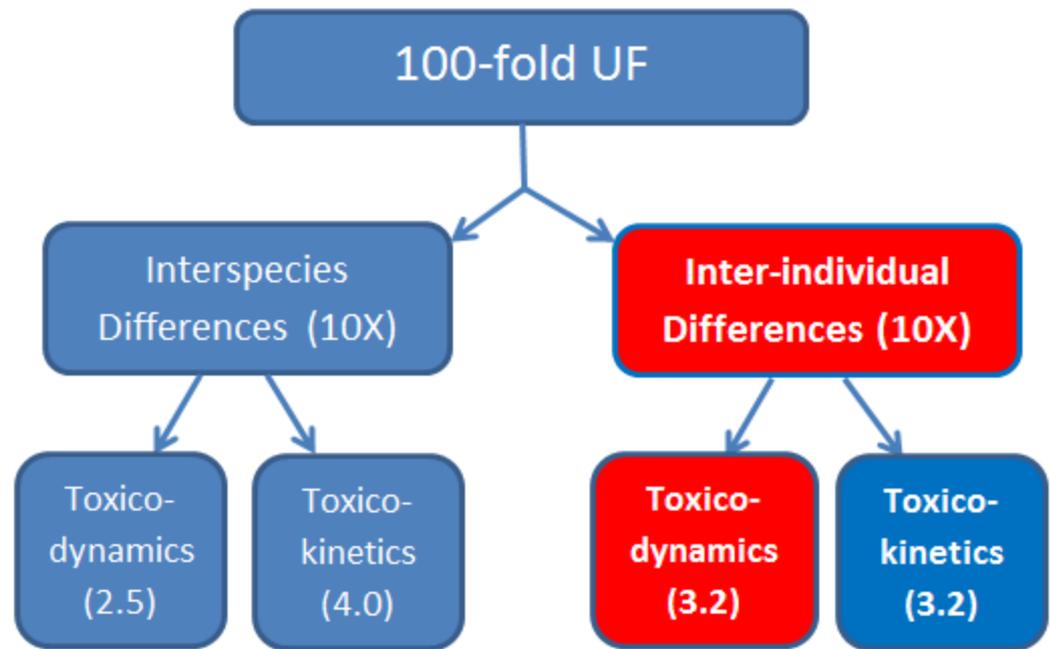
From: IPCS, 1994

Intrahuman Variability: Toxicodynamics

- Less known about differences in toxicodynamics across the human population/lifestages

- For early life exposures, majority of information comes from
  - Developmental toxicity studies (rodent)
  - Multi-generation or reproductive toxicity studies that include early-life exposure (rodent)
  - Pharma data (human)

- Where there are findings in these studies, these will drive the risk assessment

Toxicodynamics

- Main focus is during the first six months when growth and the rate of maturation are highest.

- Potential for permanent adverse consequences to a developing organ?

- Older infants and children can be highly resilient and can often tolerate higher exposures than adults.

- Target organs/effects for which increased sensitivity of infants has been shown most often include:

  - CNS/neurotoxicity

  - Immunotoxicity

  - Endocrine-mediated effects

  - Skeleton/bone

Also represent areas of higher priority for further research

Empirical Data on Sensitivity of Infants/Children Compared to Adults

- Data sources:
  - Data on physiological differences
  - Acute tox (high dose) studies (rodents)
  - Clinical data from pharmaceuticals.

- Immaturity of metabolic/excretory pathways is such that they can be saturated more easily than the same pathway in adults.

- Infants can be more susceptible to relatively high doses that saturate these pathways, but has limited relevance to lower exposures

Differential Sensitivity: Examples*

- Increased sensitivity
  - Chloramphenicol, Quinolones, Lead

- Decreased sensitivity
  - OP-induced delayed neurotoxicity, Aminoglycosides

- Both increased and decreased sensitivity
  - Propylene glycol

- Differential sensitivity based on dose
  - Chlorpyrifos, Type II Pyrethroids

* Described in Felter et al., 2015

Safety Assessments: Are Current Methods Adequate?

- Important to consider potential for differential exposure
- No single conclusion can be drawn regarding the relative sensitivity of infants and children compared to adults
  - Can be similar, higher, lower, quickly changing
- In the absence of specific toxicological data during early-life, current risk assessment methods, including the use of a default 10X UF to account for human heterogeneity, are generally appropriate and protective for all age groups, including infants
  - Less relevant for pharmaceuticals, for which both efficacy and safety must be considered.

Opportunities to Refine Assessments

- Exposure
  - "Worst case" assumptions vs. actual exposure data
  - Probabilistic modeling
  - Dermal penetration?
- Setting an acceptable exposure limit
  - Are (human) data available in early lifestages (may or may not be sensitive)? (e.g., fluoride, nitrate, lead)
  - Are repeat-dose toxicity data available that include early lifestages? (e.g., multi-generational studies, developmental toxicity studies?)
  - Are PK data available? Can a PBPK model be developed?

Case Study: Phenoxyethanol Safety Assessment

- Preservative used in consumer products

- Repeat dose toxicity studies in rats, mice, and rabbits by different routes of exposure (dermal, oral) and with different critical effects

  - Dermal rabbit: hematological effects
  - Oral rat: renal effects

- Significant PK database

  - Oral rat: blood, tissue and urine data
  - Dermal rat: urine data
  - Human: Urine data following oral and dermal exposure, including from premature infants.
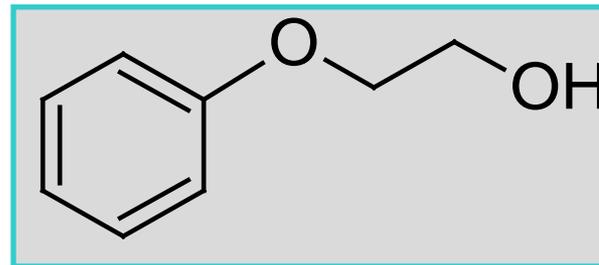
Phenoxyethanol Safety Assessment

- Used as a preservative in consumer products
  - Aggregate exposure estimates: *theoretical; assume used in all products at highest allowable level (1%)*
  - Available for adults and infants

| Subpopulation	Description	External dose mg/kg/day
Rat	NOAEL (drinking water)	369
Adult Human	Aggregate (oral+cosmetics)	2.69
Infant/children	Part 1 (Daily Baby Care)	1.71
Infant/children	Part 2a (Leave-on/nappy)	2.64
Infant/children	Part 2b (wipes/nappy)	2.00
Infant/children	Parts 1+2a+2b	6.35

PBPK Modeling in Safety Assessments

- Can be used to address several areas of extrapolation in QRA that are historically dealt with by use of conservative defaults (assumptions or UFs):
  - Interspecies extrapolation
  - Route-to-route extrapolation
  - Exposure conditions (e.g., bolus vs. continuous)
  - High-to-low dose extrapolation
  - Intraspecies variability–including life stage

Use of PBPK Modeling: Assessing a Specific Human Exposure
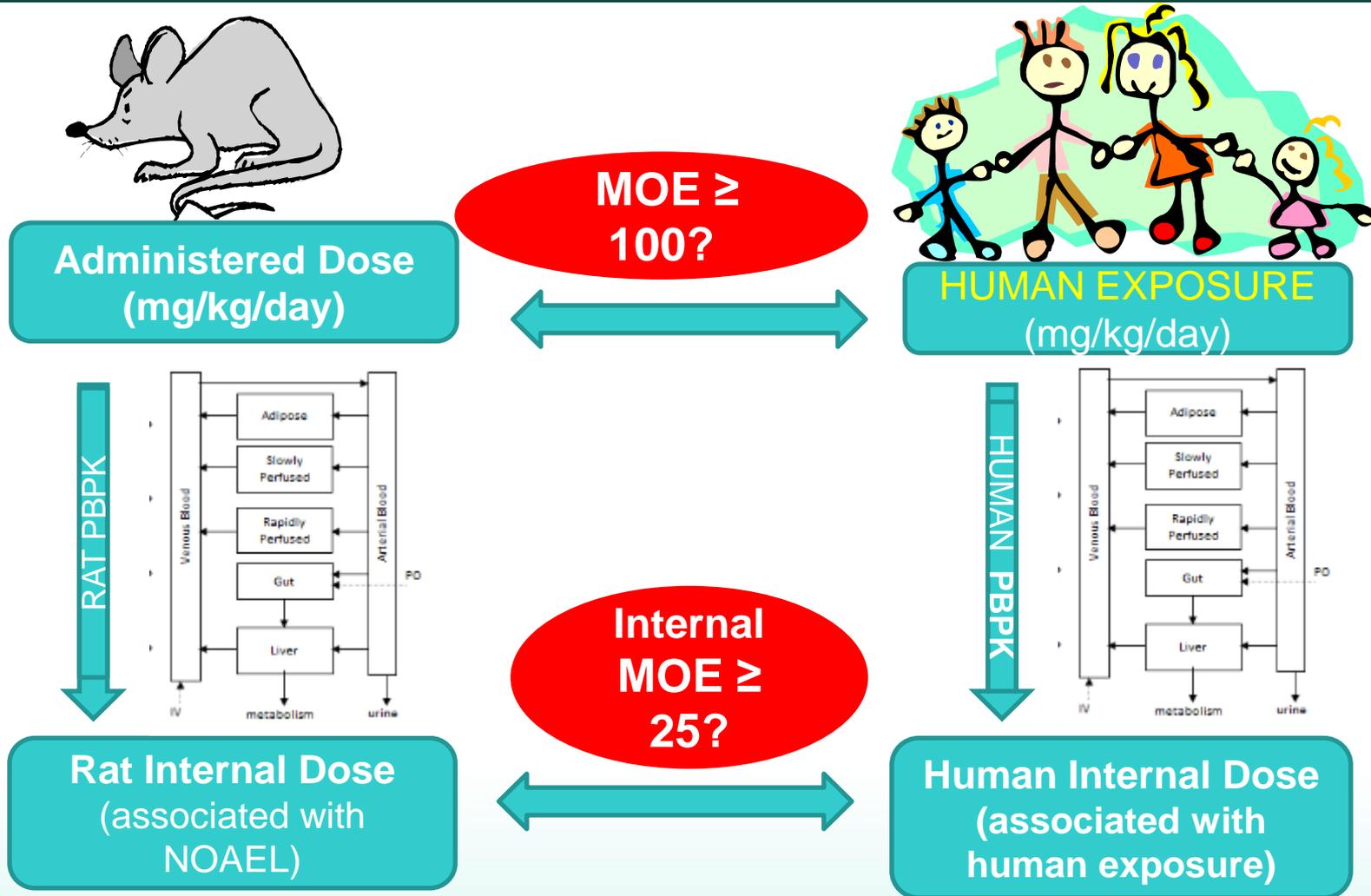
Use of PBPK to Address Lifestage Differences

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Development of a physiologically-based pharmacokinetic model of 2-phenoxyethanol and its metabolite phenoxyacetic acid in rats and humans to address toxicokinetic uncertainty in risk assessment☆

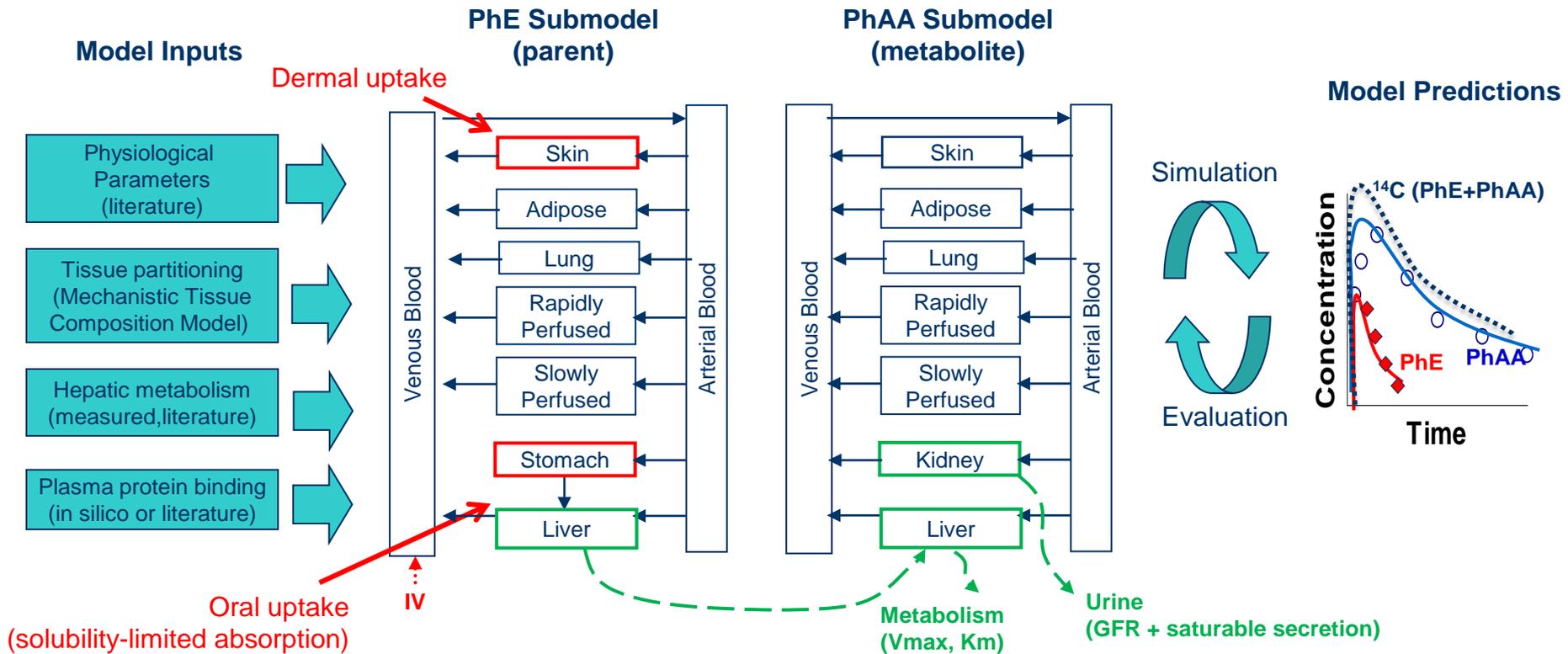John A. Troutman [a,*], David L. Rick [b], Sharon B. Stuard [a], Jeffrey Fisher [c], Michael J. Bartels [b]

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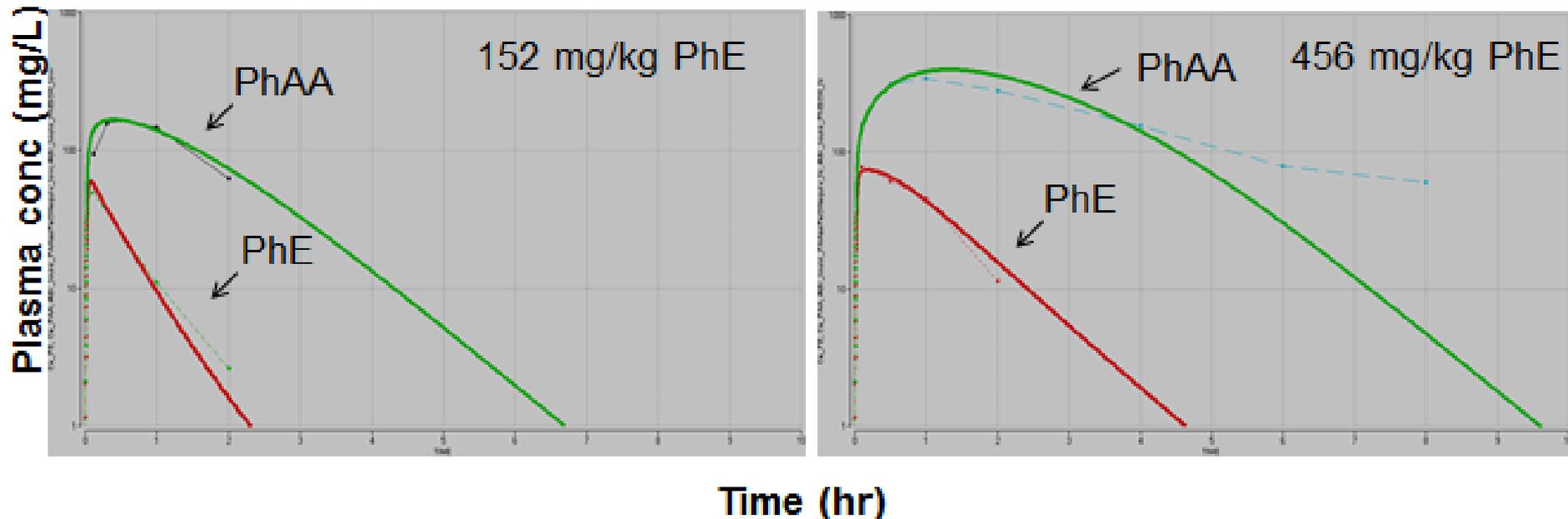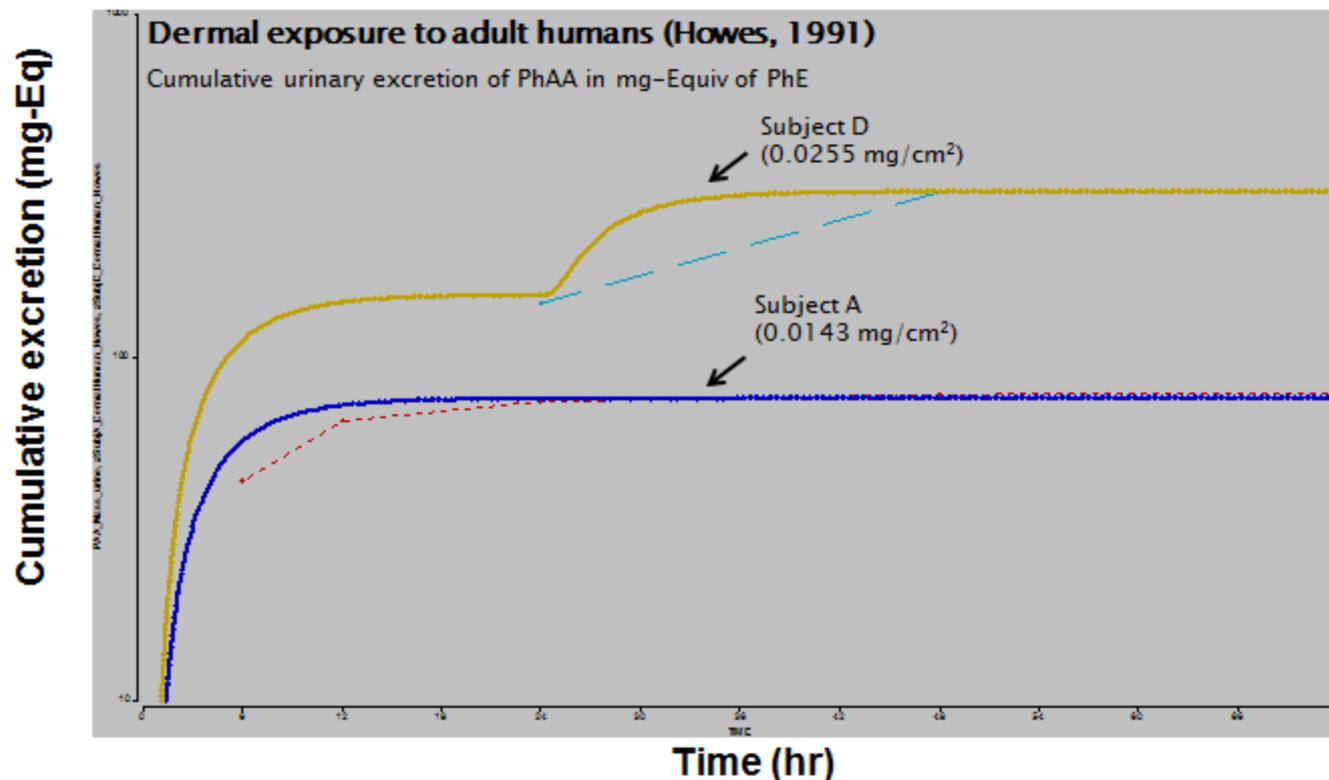
PBPK Model Structure

Model Fit to Rat Oral data

Measured and Predicted Exposure Comparisons for PhE and PhAA in Rats following single oral doses of 152 and 456 mg/kg PhE

Model Fit to Human Dermal Data (Urinary Excretion)

Cumulative Urinary excretion of PhAA in adult humans following dermal application

Application of PBPK in the Safety Assessment of Phenoxyethanol

	Rat External Oral Dose of PhE at NOAEL (mg/kg/d)		Rat PBPK	Rat Internal Dose of PhE at NOAEL (mg*h/L)		Rat Internal Dose of PhAA at NOAEL (mg*h/L)	
Rat	369		➡	61.5		690	
Human Lifestage	Exposure	Consumer exposure (mg/kg/d)	Human PBPK	Internal Dose of PhE from consumer exposure (mg*h/L)	MOE based on PhE internal dose	Internal Dose of PhAA from consumer exposure (mg-Equiv*h/L)	MOE based on PhAA internal dose
Adult	Aggregate (oral+cos-metics)	2.69	➡	0.608	101	8.82	78
Infant (8 kg)	Aggregate (daily baby care+wipes)	6.36		2.29	27	26.3	26

Phenoxyethanol Exposure Assessment

- Based on aggregate exposure estimates assuming use in all products* at 1% (highest allowable level)

  - <u>Adults</u>: Shower gel; hand soap; shampoo; hair conditioner; body lotion; face cream; hand cream; deodorant; hair styling; liquid foundation; make-up remover; eye make-up; mascara; lipstick; eyeliner; toothpaste; mouthwash

  - <u>Infants</u>: face/body cleanser; leave-on products & wipes used in nappy area

- Can refine based on:

  - Actual frequency of use in products

  - Actual level used in products (many are < 1%)

  - Habits & practices; probabilistic modeling of actual consumer exposure

  - Can validate with biomonitoring data

Conclusions

- Differential susceptibility of infants/children compared to adults can be a result of differences in exposure and/or inherent toxicological sensitivity

- Metabolic and excretory functions mature rapidly during the first 6 months; for older infants/ children, they can exceed those of adults

- Most data suggesting potential increased toxicologic susceptibility of infants are from pharma literature or high dose (acute tox) studies that have questionable relevance to lower exposure levels

- Available data and analyses, including global regulatory guidance, support the default 10X intraspecies UF as being adequate to protect infants and children

References

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Questions?