Predicting Age-Appropriate Pharmacokinetics of Six Volatile Organic Compounds in the Rat Utilizing Physiologically-Based Pharmacokinetic Modeling

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research & development

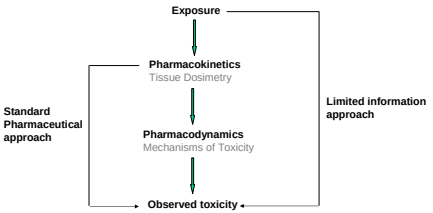
Science Question

• The pediatric and elderly populations require special considerations in risk assessment since they can exhibit increased or decreased sensitivity to the toxic actions of xenobiotics when compared to young adults. The difference in sensitivity may be due to age-dependent changes in pharmacokinetics and/or pharmacodynamics.

• Physiologically-based pharmacokinetic (PBPK) models represent valuable tools to describe the pharmacokinetics (absorption, distribution, metabolism, and elimination) of xenobiotics and can incorporate age-dependent changes in physiological and chemical-specific parameters.

• PBPK modeling of experimental animals represents an important anchor point for correlating tissue dosimetry to the toxic effects of a particular chemical.

Risk Assessment Approach

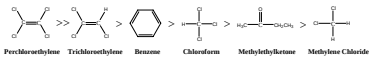


Volatile Organic Compounds (VOCs)

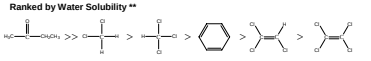
- Produced in high volume every year
- Used as paint thinners, dry cleaning solvents, and synthetic intermediates
- High vapor pressure to significantly enter the atmosphere
- Common soil and water contaminants
- Varying lipophilicity – Can easily cross cellular membranes including blood brain barrier
- Implicated in several toxicities: developmental, carcinogenesis, and CNS depression

VOCs examined in this study:

Ranked by Lipophilicity *



Ranked by Water Solubility **



* Based on fat:air partition coefficients measured in adult Sprague Dawley rats as reported by *Mahley et al.* (5).
** Based on water or saline solubility as reported by *Poulin et al.* (1).

Research Goals

• To assemble age-appropriate physiological and chemical-specific parameters for the rat for incoporation into a PBPK model for evaluating how predicted internal dosimetry of VOCs might change across different lifestages of the rat.

• To identify the critical physiological and chemical-specific parameters responsible for the age-dependent differences in tissue dosimetry.

Methods/Approach

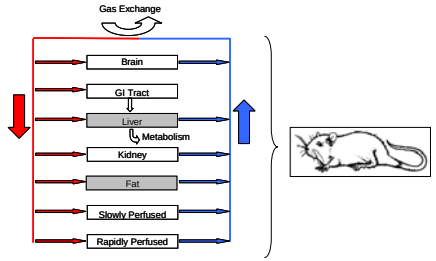
Physiological Parameters
Adult and Aged: Cardiac output (CO), fractional blood flows, and tissue volumes for a 187 and 438g 344 Fisher rat were taken from *Delp et al.* (2) and scaled to body weight (BW) to simulate a 200 (adult) and 450g (aged) rat, respectively. CO and alveolar ventilation rate (QPI) were assumed to be equal.
PND10: CO for postnatal day 10 (PND10) was estimated by plotting CO versus BW and analyzing by nonlinear regression for fit to the equation $CO=COmax*BW/(BW_{50}+BW)$ (Graphpad Prism, San Diego, CA). Fractional blood flows were taken from *Stulcova* (3) and assumed to be the same as PND9. QPI was estimated from a report by *Bandla et al.* (4) and was approximately equal to CO.

Chemical-Specific Parameters
Tissue:blood partition coefficients: partition coefficients corresponding to PND10, adult (60 days old), and aged (22 months old) Sprague Dawley rats were taken from *Mahle et al.* (5).
Metabolism: *In vivo* metabolic parameters (Km and Vmax) for methylene chloride, chloroform, trichloroethylene, and perchloroethylene for a standard adult rat were taken from *Gargas et al.* (6), and those for benzene and methyl ethyl ketone were taken from *Medinsky et al.* (7) and *Thrall et al.* (8), respectively. Vmax values were adjusted for age-dependent differences as follows:

$Vmax_x = Ra*Rlp*Rvl*Vmax_{adult}$ Where x refers to PND10 or aged rat, and

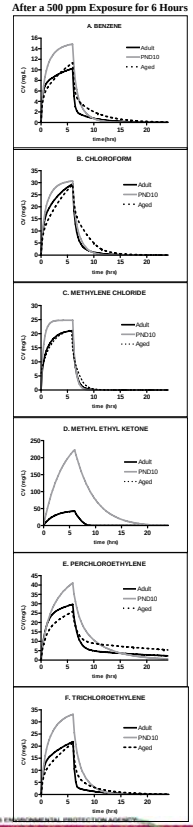
$$Ra = \frac{(Vmax\ (in\ vitro))x}{(Vmax\ (in\ vitro))adult}, \quad Rlp = \frac{(Liver\ fraction\ protein\ content)x}{(Liver\ fraction\ protein\ content)adult}, \quad Rvl = \frac{(Liver\ Volume)x}{(Liver\ Volume)adult}$$

PBPK Model Structure
The PBPK model proposed by *Ramsey and Andersen* (9) was modified for this study.



Results/Conclusions

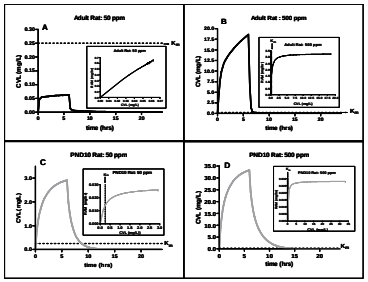
Predicted Venous Concentration of VOCs After a 500 ppm Exposure for 6 Hours



Predicted Peak Venous Blood Concentrations (mg/L) of VOCs for Different Ages of the Rat following a 50 or 500 ppm Inhalation Exposure for 6 h

VOC		PND10	Adult	Aged	Aged / Adult	PND10 / Adult
Perchloroethylene	500 ppm	41	30	26	0.9	1.4
	50 ppm	4.1	3.0	2.6	0.9	1.4
Trichloroethylene	500 ppm	33	22	20	0.9	1.5
	50 ppm	3.0	0.80	0.80	1.0	3.8
Benzene	500 ppm	15	10	11	1.1	1.5
	50 ppm	1.4	0.7	0.8	1.1	2.0
Chloroform	500 ppm	31	29	29	1.0	1.1
	50 ppm	2.9	0.80	0.90	1.1	3.6
Methylene Chloride	500 ppm	25	21	21	1.0	1.2
	50 ppm	2.4	0.70	0.80	1.1	3.4
Methyl ethyl ketone	500 ppm	224	43	41	1.0	5.2
	50 ppm	20.5	0.80	0.90	1.1	25.6

Predicted Metabolic Profile for the Adult and PND10 Rat During a 6 h Inhalation Exposure to 50 or 500 ppm Trichloroethylene



Predicted Amount of VOC Metabolized per Unit Liver Volume (mg/L) for Different Ages of the Rat at 24 h following a 50 or 500 ppm Inhalation Exposure for 6 h

VOC		PND10	Adult	Aged	Aged / Adult	PND10 / Adult
Perchloroethylene	500 ppm	12	104	97	0.9	0.1
	50 ppm	1.2	10.4	9.7	0.9	0.1
Trichloroethylene	500 ppm	635	2900	3909	1.3	0.2
	50 ppm	390	420	506	1.2	0.9
Benzene	500 ppm	273	1530	1954	1.3	0.2
	50 ppm	66	195	240	1.2	0.3
Chloroform	500 ppm	317	2004	2661	1.3	0.2
	50 ppm	215	386	460	1.2	0.6
Methylene Chloride	500 ppm	143	1257	1772	1.4	0.1
	50 ppm	99	259	308	1.2	0.4
Methyl ethyl ketone	500 ppm	1461	2557	2987	1.2	0.6
	50 ppm	376	286	333	1.2	1.3

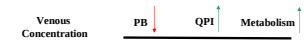
Conclusions

• The predicted differences between the adult and aged rat were not dramatic and were mainly due to differences in blood:air partition coefficients and fat content.

• The highest venous levels of VOCs were predicted for PND10. A lower metabolic capability, largely due to a smaller liver size, and a faster ventilation rate per unit body weight (QPI) were identified as the critical parameters.

Aged versus Adult

PND10 versus Adult



• Toxicity studies conducted during early life are currently analyzed only for the maternal exposure. These modeling efforts begin to predict how dosimetry changes across age and evaluate the potential impact of dose-response analyses using age-appropriate dosimetry.

References

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