



Age-Dependent Differences in the Pharmacokinetics of Volatile Organic Compounds Utilizing Physiologically-Based Pharmacokinetic Modeling of Rat

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research development

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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 adults. The difference in sensitivity may be due to age-dependent changes in physiological (e.g., body weight, cardiac output, and ventilation rate) and chemical-specific parameters (e.g., metabolism and tissue:blood partition coefficients) that can significantly alter the pharmacokinetics of xenobiotics.
- 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.

Research Goals

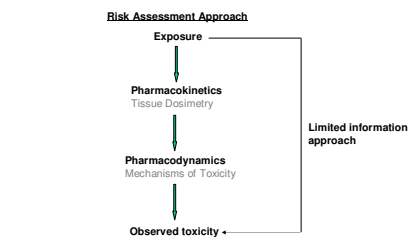
- To assemble available information on age-dependent differences in physiological and chemical-specific parameters for the Sprague Dawley rat.
- To incorporate age-appropriate parameters into a PBPK model for evaluating how predicted internal dosimetry of VOCs might change across different lifestages of the Sprague Dawley rat.
- To identify the critical physiological and chemical-specific parameters responsible for the age-dependent differences in tissue dosimetry.

Methods/Approach

Physiological Parameters: Cardiac output (CO), alveolar ventilation rate, and tissue volumes were scaled to body weight (BW).
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.* (1) and used to simulate a 200 (adult) and 450g (aged) Sprague Dawley rat, respectively.

PND10: CO for postnatal day 10 (PND10) was estimated by plotting CO versus BW and analyzing by nonlinear regression for fit to the equation $CO = C_{max} * BW / (BW_{50} + BW)$ (Graphpad Prism, San Diego, CA). Fractional blood flows were taken from *Stulcova* (2) and assumed to be the same as PND9. Ventilation rate was assumed to be equal to CO and supported by a report by *Banda* et al. (3).

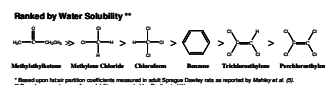
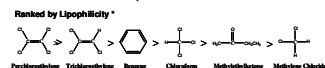
Chemical-Specific Parameters:
Tissue:blood partition coefficients: partition coefficients corresponding to PND10, adult (60 days old), and aged (22 months old) Sprague Dawley rats were taken from *Mahle et al.* (4).
Metabolism: *In vivo* metabolic parameters (Km and Vmax) for methylene chloride, chloroform, trichloroethylene, and perchloroethylene for a standard adult rat were taken from *Gargas et al.* (5), and those for benzene and Methyl ethyl ketone were taken from *Medinsky et al.* (6) and *Thrall et al.* (7), respectively. Vmax values were adjusted for age-dependent differences in CYP2E1 activity according to the literature.



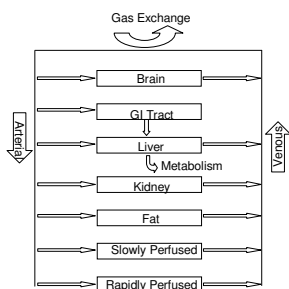
Volatile Organic Compounds (VOCs)

- 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:



The PBPK model proposed by *Ramsey and Andersen* (8) was adapted and parameterized according to age-dependent differences:

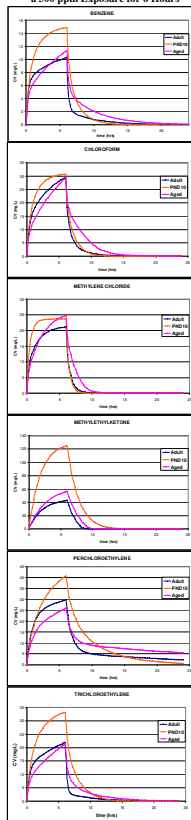


Results/Conclusions

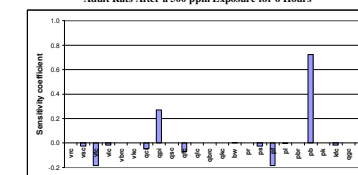
Predicted Peak Venous Concentrations of VOCs After a 500 ppm Exposure for 6 Hours

	CVmax (PND10)	CVmax (Adult)	CVmax (Aged)
Perchloroethylene	41	30	26
Trichloroethylene	33	22	21
Benzene	15	10	11
Chloroform	31	29	29
Methyl ethyl ketone	125	43	56
Methylene Chloride	24	21	25

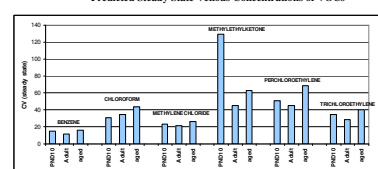
Venous Concentration of VOCs After a 500 ppm Exposure for 6 Hours



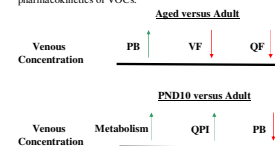
Sensitivity Analysis of Venous Concentration of Perchloroethylene at 6 hours in Adult Rats After a 500 ppm Exposure for 6 Hours



Predicted Steady State Venous Concentrations of VOCs



* Age-dependent differences in physiological and chemical-specific parameters can result in significant differences in the pharmacokinetics of VOCs.



* The difference in the dose metric observed at 6 hr versus steady state achieved with repeated daily exposures may have significant implications on the interpretation of dosimetry in toxicity studies. In particular, on a single day PND10 rats are predicted to achieve steady state levels faster compared to the adult and aged rat. However, it is uncertain if the young animal approximate steady state with repeated exposures due to more rapid clearance than the adults and aged.

Impact and Outcomes

- 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.
- These analyses found relatively small differences in average daily steady state area under the curve (AUC), except for methyl ethyl ketone, while peak concentration at the end of 6 hour exposures were more variable, with pnd10 rats having the highest predicted blood concentrations.

Future Directions

- Analysis of other dose metrics will be performed
- The results of this study will be published.
- Age-dependent differences will be incorporated in the study of other xenobiotics of toxicological interest, particularly perfluorinated compounds which reportedly exhibit early life toxicity.

References

1. Poulin, P., Kitchman, K. A. Tissue Composition-Based Algorithms for Predicting Tissue:Air Partition Coefficients of Organic Chemicals. *Toxicology and Applied Pharmacology* 136, 126-130 (1996).
2. Delp, M. D., Evans, M. V., Duan, C. Effects of aging on cardiac output, regional blood flow, and body composition in Fischer-344 rats. *J Appl Physiol* 85(5), 1813-22, 1998.
3. Stulcova, B. Postnatal development of cardiac output distribution measured by radioactive microspheres in rats. *Biol Neonate* 32(3-4), 119-24, 1977.
4. Banda, H.P., Simakajornboon, N., Graff, G.R., and Gozal, D. Protein Kinase C Modulates Ventilatory Pattern in the Developing Rat. *Am J Respir Crit Care Med* 159, 968-973 1999.
5. Mahle, D.A., Gearhart, J.M., Giggaby, C., Mattie, D., Barton, H.A., Lipscomb, J.C., Cook, R.S. Unpublished data.
6. Gargas, M.L., Chewell, H.J., Andersen, M.E. Gas uptake inhalation techniques and the rates of metabolism of chloroethanes, chloroethanes, and chloroethylenes in the rat. *Inhalation Toxicology* 2, 295-319, 1990.
7. Medinsky, M. A., Sabourin, P. J., Lucier, G., Birnbaum, L. S., Henderson, R. F. A physiological model for simulation of benzene metabolism by rats and mice. *Toxicol Appl Pharmacol* 99(2), 193-206, 1989.
8. Thrall, K. D., Soelberg, J. J., Weitz, K. K., Woodstock, A. D. Development of a physiologically based pharmacokinetic model for methyl ethyl ketone in F344 rats. *J Toxicol Environ Health A* 65(13), 881-96, 2002.
9. Ramsey, J. C., Andersen, M. E. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol Appl Pharmacol* 73(1), 159-75, 1984.

Long Term Goal III



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