**Development of Physiologically Based Dosimetry Models for the Perinatal Period**

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Exposure to xenobiotics during critical phases of development can result in adverse effects. There is a critical need to identify factors that may predispose the developing organism to xenobiotic-induced injury. Differences in exposure patterns, pharmacokinetics, and pharmacodynamics all play a role in the unique sensitivity of developing animals to environmental chemicals. This project is primarily focused on developmental dosimetry modeling with an overall goal of developing models that predict the fate of environmental chemicals under relevant exposure conditions and during pregnancy, a critical period of development. Specific aims associated with this project are as follows: (1) Create generic, physiologically based pharmacokinetic (PBPK) models for the pregnant rat and human; (2) Develop a data base of biological parameters for the development of PBPK models for pregnant rats and humans. Examination of the available literature revealed that currently little data exists on pulmonary function in rats during pregnancy, an animal model often used for developmental studies. Respiration will affect the pharmacokinetics of volatile compounds, and accurate estimates of minute ventilation will improve physiologically based pharmacokinetic models that predict target tissue concentrations for extrapolation to human exposure scenarios. We conducted a longitudinal study to evaluate pulmonary function in rats during pregnancy (Leavens et al., 2006). Whole-body plethysmography was used to measure the breathing frequency, tidal volume, and minute ventilation approximately every other day from gestation day (GD) 1 to 21 in 16 timed pregnant and 16 nonpregnant female, Sprague-Dawley rats. Scaled minute ventilation was calculated from the minute ventilation and body weight of each rat. Multivariate analysis of variance methods for a repeated measures design were used to analyze the collected data. On GD 1, breathing frequency, tidal volume, minute ventilation, and scaled ventilation were 100 ± 2.3 bpm, 1.45 ± 0.04 ml, 142 ± 3.0 ml/min, and 35.9 ± 1.0 L/hr/kg for pregnant rats, and 101 ± 3.1 bpm, 1.47 ± 0.04 ml, 146 ± 9.7 ml/min, and 38.5 ± 2.5 L/h/kg for nonpregnant rats. On GD 21, breathing frequency, tidal volume, minute ventilation, and scaled ventilation were 105 ± 4.0 bpm, 1.97 ± 0.05 ml, 205 ± 11 ml/min, and 30.2 ± 1.5 L/hr/kg for pregnant rats, and 98 ± 3.4 bpm, 1.68 ± 0.06 ml, 162 ± 7.9 ml/min, and 35.9 ± 1.4 L/hr/kg for nonpregnant rats. Tidal volume increased significantly during the study but was not significantly different between the pregnant and nonpregnant rats. Minute ventilation was significantly greater in pregnant rats compared to nonpregnant rats. The scaled ventilation was significantly lower in pregnant compared to nonpregnant rats. This study provides important reference values to be used in pharmacokinetic models during pregnancy.

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Presentation(s):

Leavens, T., Parkinson, C., James, A., House, D., and Dorman, D. (2005). Pulmonary function in rats during pregnancy. *Toxicol. Sci.* 84 (S-1), 176. (Abstract 863).

Struve, M. F., Turner, K. H., Dodson, P. K., and Dorman, D. C. (2005). Prenatal exposure to fenitrothion: Are changes in the SDN-POA a concern? Presentation, 22nd International Neurotoxicology Conference – Environment and Neurodevelopmental Disorders, Research Triangle Park, NC, September 12.

Elswick, B., Leavens, T. L., and Dorman, D. (2004). Compiling a database of physiological parameters for pharmacokinetic models of rat pregnancy. Poster presentation at 13th annual meeting of the Triangle Consortium for Reproductive Biology, Research Triangle Park, NC, February 7.

Leavens, T., Elswick, B., and Dorman, D. (2004). Physiological parameters of rats for pharmacokinetic models of prenatal exposure. *Toxicol. Sci.* 78 (S-1), 417. Supplement–*The Toxicologist.* (Abstract 2026).

Andersen, M. E. (2003). Developing PBPK models for testosterone dosimetry in the perinatal period in the rat and systems biology approaches to EAC risk assessment. Poster presentation at first annual science meeting of the Long-Range Research Initiative, American Chemistry Council, Herndon, VA, June 24–25.

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