MODELING

Pharmacokinetics and Modeling for Interspecies Extrapolation in Evaluating Children's Health Risks

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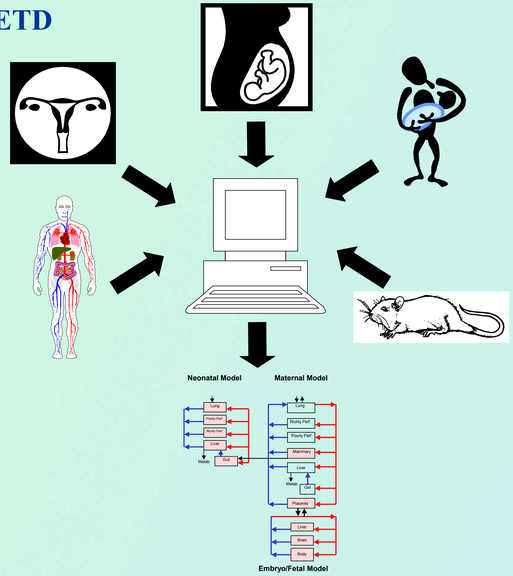
ENVIRONMENTAL ISSUE: Evaluation of potential environmental risks to children's health has been a focus of risk assessment within the U.S. EPA. Three general approaches exist for evaluating potential hazards - 1) using data from children available from epidemiological studies, 2) animal toxicity testing during early development (i.e. *in utero* and postnatal periods through puberty), and 3) assuming the toxicity observed in the adult would occur with some differential incidence (or severity) if early pre- and post-natal exposures were accounted for based upon dosimetry. Each of these approaches involves estimation of exposure and internal doses and, in the latter two cases, extrapolations from animals or adults to children.

STUDY GOAL: Computer simulation models, such as physiologically based pharmacokinetic (PBPK) models, provide a rigorous and internally logical methodology for describing the numerous factors that can be important in extrapolating tissue dose from animals or adults to human children. The goal of this research is to develop PBPK models for the *in utero* and postnatal lactational and weaning periods in rodents, such that developmental studies can be simulated to obtain estimates of internal dose for a diverse range of chemicals. Simulations of two-generation reproductive studies in rats would be particularly valuable as these involve all of these early life stages.

A. Physiological & Metabolic Parameters for PBPK Models of Neonates

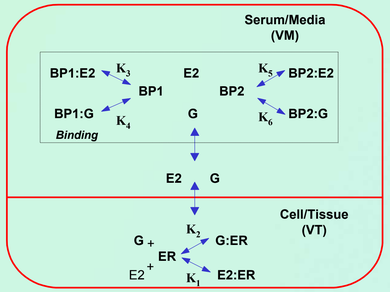
Efforts to obtain these values for different early life stages in rats, mice, and humans are a part of a cross-ORD research effort.

- Values for physiological parameters for growing mice and rats are being obtained from reviews of the published literature. An ACCESS database for mice and Sprague-Dawley was created by contract in collaboration with NHEERL and NCEA scientists. Tissue volumes, blood flows, glomerular filtration, inhalation rates, and water and food intake values have been compiled. Plans are to expand it to Fisher 344 and Wistar rats.
- Measurements of age-dependent partition coefficients for six chemicals (methylene chloride, methyl ethyl ketone, chloroform, benzene, trichloroethylene, perchloroethylene) are being made at the Operational Toxicology Branch, Air Force Research Laboratory, WPAFB in a collaboration with NHEERL and NCEA scientists. Pediatric and adult human blood:air partitions and postnatal day 10 and adult F344 rat blood:air and tissue:air partitions are being determined.
- Age-dependent changes in metabolism are another critical need. Studies of developmental profiles in rat liver and lung for selected enzymes (e.g. glucuronyl transferases, aldehyde dehydrogenases, epoxide hydrolase) have recently been initiated.



C. Case Example: Serum Binding Proteins Lifestage, and Species

- Free endocrine active compounds in blood are available for tissue distribution, so protein binding can limit tissue availability and diminish clearance
- When clearance occurs in a tissue, protein-bound compound may dissociate from protein and enter tissue (greater apparent availability than instantaneous free fraction)
- Modeling of *in vitro* and *in vivo* systems evaluated ability to predict free and bound compound across lifestages and species.
- *In vitro* modeling showed good results with adult human and rat serum, but poor fits to experimental data for fetal or early postnatal rat serum likely due, in part, to competition by endogenous compounds that also bind the protein (e.g. fatty acids binding to alpha-fetoprotein).



Rat Serum	AFP (nM)	Exp.* E2 (pg/ml)	Exp.* E2 (nM)	Exp.* Free E2 (nM)	Exp.* Free E2 (%)	Model Free E2 (nM)	Model Free E2 (%)
Proestrus	0.25	60	0.22	0.0083	3.9±0.12	0.0087	4.0
Diestrus	0.25	14	0.050	0.0019	4.0±0.17	0.0020	4.0
gd19	61,300	155	0.57	0.0020	0.35±0.01	0.00015	0.027
	4,460					0.0020	0.35
pnd 1	44,700	126	0.46	0.0080	1.77±0.20	0.00016	0.035
	700					0.008	1.73

*Montano et al. Biol Reprod 53, 1198-1207 (1995)

Experimental and modeled results for free estradiol in rat serum:

- Good concordance for adult female sera (diestrus and proestrus)
- Reduced estimate of free alpha-fetoprotein (AFP) available for binding was required to simulate early life stages, gestational day 19 (gd19) and postnatal day 1 (pnd 1)

B. Models Under Development

Age-dependent *in vivo* and *in vitro* models are being developed for several classes of compounds.

- Serum Binding Proteins: Impacts of rat and human serum protein binding on predicted potency for estrogen receptor binding relative to estradiol were modeled (Teeguarden and Barton, 2003). Some results from this work are presented below.
- Perfluorinated Hydrocarbons: Another poster presents initial literature reviewing and model conceptualization for perfluorooctane sulfonate (PFOS). Compartmental modeling approaches for estimating blood concentrations at different lifestages for perfluorooctanoic acid (PFOA) are being utilized in collaboration with Office of Pesticide Programs.
- TCDD: Modeling of rodent exposures to dioxin prior to and during pregnancy to estimate tissue dose metrics is presented in another poster.
- Conazoles: *In vivo* pharmacokinetic studies are being planned by a new postdoc to complement planned developmental studies with triazole pesticides and to provide data for modeling. The developmental studies will involve feed-based exposure of rats during pregnancy, lactation, and early development through age 90 days. Quantitation of parent compound and selected metabolites in blood, milk, and other tissues will be undertaken.

CONCLUSIONS: Efforts are underway to obtain physiological and chemical specific information that will permit development of PBPK models for growing rodent pups as well as nonpregnant, pregnant, and lactating female rodents. Pharmacokinetic models are under development for these lifestages. Rodent models will complement the development of PBPK models for human lifestages, work being done by organizations within and outside U.S. EPA. These models will assist in improving cross-species extrapolations, particularly when the equivalent window of susceptibility has been defined in the different species.

IMPACT: Development of PBPK models for early lifestages will be invaluable for interpreting toxicity studies and addressing a range of important issues for the Agency. For example, recent efforts to evaluate whether perinatal carcinogenicity studies demonstrate increased early life susceptibility would be strengthened by quantitative estimates of the doses during different period. Similarly, dose-response analyses for reproductive studies use estimates of the exposure doses to the mothers but it would be valuable to estimate the range of doses occurring at different periods during the studies.

FUTURE DIRECTIONS: The goal of this effort is to have a template model for two-generation and lifetime toxicity studies. The template will describe changes in physiology and anatomy in growing, adult, and aging rats.

SOLVING AGENCY PROBLEMS