Evaluation of Physiologically Based Pharmacokinetic and Pharmacodynamic Models of Pregnancy and Lactation for Assessing Dosimetry in the Embryo, Fetus, and Newborn

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The scientific basis for cancer and non-cancer human health risk assessments have been greatly facilitated by the development and application of physiologically based pharmacokinetic (PBPK) and pharmacodynamic (PD) models. PBPK and PD models are powerful computational tools that allow one to simulate either the fate of a chemical once it enters the body (PBPK model) or the dynamic changes to biological systems that the chemical elicits (PD model). These models are based on both generic physiological data, as well as chemical-specific data. While not a replacement for animal testing, they extend data from animals and increase the certainty in risk assessments through their ability to extrapolate from animal species to humans, from high doses to low doses, and from one exposure route to another. With the increased emphasis placed on in utero or neonatal exposure in children’s health, there is every reason to believe that PBPK or PD models can also significantly reduce the uncertainty associated with children’s health risk assessments. Therefore, the purpose of this review was to critically assess the current state-of-the-art in PBPK and PD modeling of pregnancy and lactation and to identify data gaps that, if filled, would aid in the development of these models and significantly improve our abilities to accurately assess health risks associated with in utero or lactational exposures.

Unlike most biologically based models designed for adults, models of pre- and postnatal development must deal with the rapid growth (maternal, embryonic, fetal, and neonatal), changes in the state of differentiation of developing tissues, uniquely expressed or uniquely functioning signal transduction or enzymatic pathways, and unusual routes of exposure (e.g., placental transfer and lactation). Previously published PBPK and PD models have ranged from simplistic, empirical descriptions of the embryo/fetus to more sophisticated biologically based models depending upon the quality and extent of the data available. Although some models attempted to describe target tissues in the developing embryo, fetus or neonate of laboratory animals, extrapolations to humans have largely been limited to maternal blood or milk concentrations given the significant species differences in developmental biology. Thus, future areas of research should extend the progress that has been made by developing new approaches to overcoming the many technical and policy issues surrounding validation of model predictions to human pregnancies or neonatal exposures. Initially, the development and publication of an annotated, critically evaluated database of biological parameters will be of critical importance to the future development of biological models and identification of important biological data gaps. The database should not only include the dynamic changes in anatomy and physiology, but also the ontogeny of metabolizing enzymes, active transport proteins, or other biochemical processes that impact the disposition of chemicals during embryo, fetal, and neonatal development. Considering the dramatic changes that occur during pregnancy and lactation, information of the variability in key biological parameters would allow the use of analytical techniques such as Monte Carlo simulations coupled with PBPK or PD models to evaluate the range of internal doses or biological responses that could be achieved in even potentially sensitive individuals. Where important anatomical, physiological, or biochemical data are missing or not available for the specific species or strain of animal used in toxicity testing, research should be conducted to fill these gaps. In this way, future models can be developed using a commonly available, integrated database of basic biological information and thereby reserve the use of animals for necessary, focused studies.

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For many chemicals, a more thorough, mechanistic understanding of placental or lactational transfer will ultimately be needed to reliably extrapolate across dose, route of exposure or species. Furthermore, studies should be conducted to refine the definition of internal doses that more directly relates exposure to toxicity in target tissues of the developing embryo, fetus or neonate. Although dosimetry estimates from PBPK models are constrained by biological and chemical-specific boundary conditions, some degree of validation in the human will still be necessary before they become more widely applied in human health risk assessments. Extrapolations may be improved using human tissue, blood, or other biological samples in vitro to develop human-specific model parameters. Studying the kinetics of pharmaceuticals that have been approved for use by pregnant and nursing mothers may also add confidence to human extrapolations. Human models could also be constructed using pharmacokinetic data that have already been developed for pediatric drugs and compared with animal PBPK models to validate extrapolations in reverse. Regardless, as more research is conducted that emphasizes the relationships between internal dose and embryo, fetal, and neonatal toxicity, biologically based quantitative models will play an increasingly important role in understanding the complexities of our experimental animal model systems and improve our confidence in predicting outcomes in potentially sensitive human populations.

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