Quantitative Bias Assessment for Epidemiological Associations of Chemical Exposure and Human Health Effects: Extension of Reverse Causality Modeling and Incorporation into PLETHEM Model Suite

Miyoun Yoon, Harvey Clewell III, Christopher Ruark, Yuansheng Zhao, and Xueying Sun. ScitoVation.

Published epidemiological studies have identified associations between blood concentrations of persistent organic pollutants such as perfluorinated compounds (PFCs), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs) and a variety of human health effects. The health effects include increased time-to-pregnancy, decreased birth weight, increased age at menarche, and decreased age at menopause. The effects have been observed at blood concentrations far below which any effects were observed in experimental animal models. The observed associations between human health outcomes and chemical concentrations can be explained by pharmacokinetic variability in humans as physiological or biochemical factors related to the health outcome also affect the disposition or clearance of the chemical. ScitoVation established a research program to evaluate pharmacokinetic bias for such epidemiological associations in collaboration with Dr. Matthew Longnecker at the National Institutes of Environmental Health Sciences (NIEHS). The key tool in this assessment was physiologically-based pharmacokinetic (PBPK) models that are used to assess whether associations reported in epidemiologic studies of exposures to chemicals may be due to normal changes in physiology and their impact on chemical disposition rather than the true effect of the chemical. This research program combined the ScitoVation’s expertise in life-stage PBPK modeling and reverse dosimetry derived from previous ACC LRI-funded research projects as well as the experience with reverse causality modeling of perfluorinated chemicals in other programs at ScitoVation.

Under this project, research efforts evaluated the epidemiological associations between the early life exposure to environmental chemicals (PBDEs) and altered timing of puberty. The life stage MC-platform was jointly supported by the industry sponsors and the ACC-LRI, the result of which effort was published (Wu et al., 2015). For the PBDE study, in addition to the published cross-sectional study of NHANES by Chen et al. (2011), we added evaluation of a recently published longitudinal study (Windham et al., 2015). We found little evidence of bias due to kinetics in epidemiologic results on BDE-47 and age at menarche, while the two epidemiologic studies reported conflicting results. We identified two important data gaps: 1) how best to model exposure (as a function of individual body weight or of mean weight for a given age), and 2) the relation of serum PBDE concentration to body composition. To address these issues, we: 1) continued discussions with the U.S. Environmental Protection Agency (EPA) exposure group (SHEDS) on how best to estimate individual exposure during rapid growth and 2) designed in vitro studies to test the manner in which lipid/lipoprotein levels affect blood chemical concentration of lipophilic compounds among individuals. These in vitro studies used our in-house developed Caco-2/CES2 cells to determine the degree of lipoprotein involvement in in vivo disposition of highly lipophilic chemicals.

Implications: A Monte Carlo PBPK modeling approach can provide a tool to critically assess whether findings in epidemiology studies can be attributed to extant correlations between individual pharmacokinetics and health outcomes. Other health endpoints such as diabetes, obesity and cardiovascular disease for other persistent chemicals as well as concerns for reverse causality for short half-life chemicals such as the phthalates can be addressed in a similar manner. Based upon the experience built with a few case studies, a general modeling platform can be built to support evaluation and prediction of potential (spurious) associations for chemicals.

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