Evaluation of Reverse Causality in Epidemiological Associations Using PLETHEM

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An increasing number of studies are reporting associations between chemical exposure and adverse human health effects. However, many associations observed in epidemiological studies at low exposures are likely due to differences in chemical kinetics in affected populations rather than true biological response to the chemicals. Our LRI-funded research program developed a new method to quantitatively access potential biases in those epidemiological associations of low-dose chemical exposure and human health effects using pharmacokinetic modeling. Our initial case studies evaluated reproductive health effects associated with persistent chemicals that are reported to be low-dose endocrine disruptors in humans. Recently, however, epidemiological studies have also reported a variety of other adverse health effects including blood dyslipidemia, obesity, cardiovascular effects and diabetes. Building on our success in this program, we have broadened our scope to build strong cases for reverse causality issue in additional case studies. We initiated a case study in 2016 for non-persistent chemicals and nonreproductive endpoints, evaluating phthalate and obesity associations. In 2017, we will complete the phthalate case study, and begin another case study for associations between persistent chemicals and type II diabetes. We will test how much of the observed association between 2,2’4,4’,5,5’-Hexachlorobiphenyl (PCB-153) and type 2 diabetes mellitus can be explained by temporal trends in exposure to PCB-153 and adiposity-dependent kinetics. This new case study will highlight the impact of temporal trends in exposure on reverse causality and demonstrate the utility of the reverse causality modeling module in PLETHEM (Population Life-Course Exposure to Health Effects Model) as a readily adaptable and flexible testing platform to evaluate potential bias or confounding factors in the observed epidemiological associations.

**Implications:** A Monte Carlo PBPK (physiologically-based pharmacokinetic) 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. The ultimate outcome of this research program is a general evaluation platform as an easy to use module in PLETHEM for quantitative evaluation of the chemical-health effects associations reported in epidemiologic studies. Such a tool will help avoid premature attribution of human health effects to chemical exposures.

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