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ACC Science and Research Highlights

Shedding light on studies contending associations of human biomonitoring levels with health effects



Publications correlating measurements of chemicals in human biological specimens (blood, urine) with certain adverse health outcomes have become more prevalent and have contributed to escalating concerns regarding the effects of chemical exposures on human health. Advances in analytical chemistry methods now make it feasible to measure chemical concentrations in blood, urine, and other biomarkers at exquisitely low levels and in small sample volumes. So it is not surprising that the collection and reporting of biomonitoring data from individuals has proliferated. In addition, national biomonitoring programs such as the National Health and Nutrition Examination Survey (NHANES), which collect and make available to the public a huge wealth of chemical, exposure, and health data have also contributed to the recent growth in exposure-response association studies. At the 30,000 foot level, **such studies typically ask, "Is exposure to chemical X related to health status Y?"** These cross-sectional studies make use of individual human biomonitoring data to try to identify relationships between exposures and health status.

Ensuring newfound associations are accurately characterized and communicated has become challenging. It is commonly understood within the scientific community that correlation is not equivalent to causation; discerning a link between

two variables does not necessarily provide insight into the nature of the relationship between them.

As part of ACC's LRI program, researchers at The Hamner (now ScitoVation) have used tools and knowledge of chemical absorption, distribution, and metabolism in the body as a function of physiological status to better understand the relationships between levels detected in biomonitoring studies and actual exposures. One aspect of this work is building physiologically based pharmacokinetic (PBPK) models, including both individual life stage variability as well as population characteristics, to simulate the concentration of a particular chemical in biological specimens.

This research has shown that **physiological determinants can greatly influence the detection and concentration of chemicals in various biological specimens.** An important component of this research initiative includes developing exposure models that can be used to understand how the physiological changes that occur during pregnancy, lactation, and parturition can impact concentrations of chemicals in biomonitoring specimens ([Verner et al. 2013](#)). For a lipophilic substance, this research shows when physiological changes in growth and development of the mother and fetus are taken into account, differing chemical levels observed in serum can result from inter-individual variations in physiological changes alone, and are not associated with changes in external exposures. Thus, human variations in physiological status alone could produce an apparent association

[Click here to learn more about NHANES.](#)

between biomonitoring levels found in a study population and an effect, or contribute to such an association. **Referred to as reverse causality, this concept explains how some health outcome associations observed in epidemiology studies at low exposures could be due to differences in physiological status and kinetics in different individuals and populations, rather than true chemically-induced responses.**

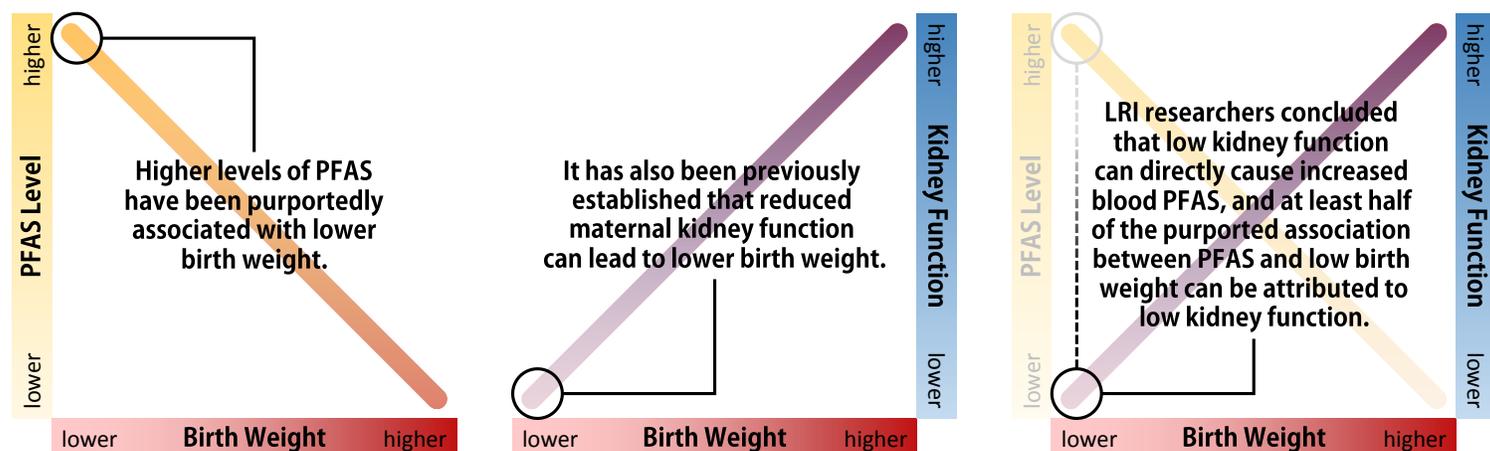
This research has now been applied to evaluate a number of purported associations between biomonitoring results and certain adverse health outcomes to ask “to what extent can these links be explained by normal physiological changes and population variability?” A number of investigations have shown that much of the observed association purported to be due to exposure can actually be explained by reverse causality and physiological considerations. For example, [Wu et al. 2015](#) showed that at least one third of the suspected relationship between exposure to a chemical and menarche delay could be explained by physiological status and age alone. Similarly, using the reverse causality technology methods developed through support by the ACC LRI, [Verner et al. 2015](#) found that a substantial proportion of the purported association between prenatal exposure and low birth weight could be attributable to decreased kidney function (Figure 1). In other

words, the degree of decrease in kidney function in a subset of women during pregnancy affected the concentration of chemical in their serum. Because a decrease in kidney function is established as a cause of decreased birth weight, the decreased kidney function is the major contributor to lower birthweight as opposed to the higher degree of exposure to the chemical. This is an example of the reverse of the causality that was initially inferred, showing that the higher levels of chemical in serum are not necessarily a true higher level of exposure, but rather a consequence of the decreased kidney function.

As exposure-response research continues to grow, it is important that investigators accurately characterize the nature of any observed associations before drawing conclusions regarding chemicals and health outcomes. By their very nature, observational cross-sectional epidemiologic studies are limited in their ability to draw conclusions regarding causation, and the possibility of reverse causality always exists.

The human exposure modeling research supported by ACC’s LRI that’s being conducted by ScitoVation investigators can be utilized to address reverse causality and promote greater understanding of the scientific limits that apply to interpreting correlations of chemicals in humans with adverse health outcomes.

Figure 1. Schematic of Reverse Causality Technology in Practice. This figure was adapted from a slide by Dr. Miyoung Yoon (ScitoVation), based on [Verner et al. 2015](#).



The relationship between birth weight and PFAS levels is confounded by GFR
PFAS – polyfluoroalkyl substances