The accurate assessment of disease risks attributable to chemical exposures remains paramount to the protection of global public health. Risk assessments evaluate the likelihoods of both exposure and disease, with results directly impacting how chemicals are regulated in the chemical manufacturing, food, beverage, and pharmaceutical industries. Historically, when chemicals are nominated for risk assessment through government regulatory agencies, the entire risk assessment process has required years to complete, often requiring over a decade per chemical. As there are an estimated 100,000 chemicals in commerce, traditional risk assessment methods are inadequate to address the safety of all chemicals humans are exposed to. To address this public health issue, we are currently in the midst of a paradigm shift in how chemicals are evaluated for safety. A recent push has been prioritized, both globally and in the U.S., for new approach methods (NAMs) that allow for the more efficient evaluation of chemical exposure, toxicity, and overall risk. Our research at UNC directly addresses this aim through the implementation of novel exposure science and toxicology methods that more efficiently evaluate larger chemical domains. Specific examples will be presented of our ongoing efforts; first, through the more efficient characterization of chemical toxicity using cell-based models, toxicogenomics, and computational modeling to link understudied exposure conditions to disease outcomes. Second, studies will be discussed that are incorporating more efficient exposure science methods to evaluate as many chemicals as possible within our external (e.g., household dust) and internal (e.g., human tissue) exposome. Third, methods in which we can incorporate these toxicology and exposure science-based NAMs into evaluating the overall risk of disease associated with understudied chemicals will be presented. These case studies provide important examples of how we can more efficiently identify new chemical-disease relationships, improve health risk characterizations, and prioritize regulation and intervention strategies to reduce the extent to which humans are exposed to harmful chemicals.