# Concept Clearance

**Branch:** Population Health Branch

**Council Period:** 201601

**Concept Title:** Collaborative Research in Environmental Mixtures

## Introduction

A well-known issue in environmental epidemiology is that real-world exposures occur in mixtures. Data collected in epidemiological studies may include a number of correlated exposures with non-uniform distribution. Commonly used statistical approaches that evaluate each exposure independently and/or assume linearity may not be appropriate and toxicological information may need to be considered. As a result, epidemiologists and statisticians are implementing Bayesian methods, principal components analysis, clustering, weighting, and other approaches to determine how specific exposures acting within a mixture and combined exposures influence health outcomes.

The NIEHS supported environmental chemical mixtures research with two workshops (2011 and 2015). The 2011 workshop, "Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects" brought experts from epidemiology, toxicology, exposure science, risk assessment, and statistics together to identify key challenges in mixtures research and suggest approaches for addressing challenges. Important findings from the 2011 workshop included the need for cross-disciplinary collaboration, the development of novel statistical approaches to predict and evaluate effects associated with exposure to mixtures, and the comparison of existing statistical methods. This aided the development of the 2015 workshop, "Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies." The objective was to identify and compare statistical approaches to analyzing chemical mixture data in epidemiology. Using two simulated datasets and one real world dataset, investigators were given a challenge to analyze the data using their specific approaches. Participants submitted abstracts and were asked to address questions such as "Which exposures contributed to the outcome and by how much? Was there evidence of interaction? What was the effect of joint/cumulative exposure to the mixture? What are the strengths/limitations of the method?" Outcomes from the 2015 workshop were that 1) no one method outperformed another for the simulated datasets and the real-world dataset; 2) many approaches can be used and considered valid; and 3) greater complexity of the data led to greater variability in the results. However, clear data gaps and limitations remain in the field including 1) the need for real-world context including toxicological information on exposures and demographic information of the study population; 2) the need for larger sample size to examine mixtures with adequate statistical power; 3) the importance of interdisciplinary teams to assess mixtures comprehensively; and 4) the opportunity to continue novel statistical methods development.

Following subsequent program review, there is evidence that a focused funding opportunity for collaborative research is needed to address the specific challenges in this field. We propose to support consortia-based research in environmental mixtures with particular attention to statistical methodology and application in epidemiology.

## Research Goals and Scope

The goal for this program is to develop a highly productive consortium focused on mixtures with specific attention to methodological issues and solutions. The interdisciplinary group should include epidemiologists, statisticians, toxicologists, and related scientists. We expect the major outcomes of this program to include 1) advancing the underlying statistical methods including a broader comparison of existing methods and the development of novel approaches; 2) a comprehensive understanding of the strengths and weaknesses of various statistical approaches to mixtures within a specific disease context; 3) consideration of complex combinations of NIEHS-relevant exposures and health outcomes, and 4) software package development for broad implementation (i.e. *R* packages) where not already available. Under the R01 model (described below) cross-consortia efforts are also anticipated and would be highly encouraged. Overall, this program will facilitate cutting-edge interdisciplinary science needed to move the mixtures research forward in ways most relevant to the NIEHS. There will be significant program involvement to promote and strengthen collaboration.

## Mechanism and Justification

We propose the development of a Funding Opportunity Announcement (FOA) to support one of two options that will be presented to council: 1) 3-4 R01s, or 2) 3-4 U01s. Under the R01 model, each R01 will have a specific disease focus and will include 3-4 independent epidemiological study populations to form a focused consortium. The goal of each consortium will be to work cooperatively to combine data with pooling or meta-analysis to evaluate the impact of specific environmental mixtures on health outcomes. Suggested health outcomes include those of interest to the NIEHS and currently evaluated with independent populations in the NIEHS epidemiology portfolios – for example, cardiovascular, obesity, diabetes, cancer, reproduction, and neurological outcomes. Consortia should have sufficient sample size and statistical power for analyses at the time of application. The PI will be responsible for administrative activities. Each consortium should include 3-4 epidemiologists (subject-matter knowledge of exposure and disease, ability to implement statistical models), 2-3 statisticians (knowledge of statistical

model selection and novel methods development), 1-2 toxicologists (subject-matter knowledge on biology/toxicology), and possibly other researchers in environmental health or fields relevant for these efforts such as bioinformatics. Applications may also include costs to support 1-2 pre- or post-docs. Cross-consortia collaboration will be encouraged and assisted with program involvement.

Under the U01 cooperative agreement model, the collaboration will represent one large consortium. Each U01 application can focus on one or more of the following expertise areas: Statisticians, epidemiologists, or toxicologists. The outcomes of the consortium under the U01 model are the same as those proposed for the R01 model.

This FOA will contribute to goal 4 (understanding how combined environmental exposures affect disease pathogenesis and goal 7 (data science). The anticipated time line is to publish the FOA in the NIH guide in the summer of 2016. The proposed total cost is $2.1 million for 4 awards; $350K direct ($525K total cost) per award. An alternative cost per award is $300K direct for science permitting an amount for administrative oversight given the collaborative nature of the project.