## 1. ABSTRACT

a) **Funding Opportunity:** EPA-G2022-STAR-A2, Early Career: Development of Innovative Approaches to Assess the Toxicity of Chemical Mixtures

b) **Project Title:** Assessment of Underlying Molecular Mechanisms Promoting Adipogenic Outcomes in Complex Mixtures

c) **Investigators:** Christopher Dennis Kassotis – Lead PI (christopher.kassotis@wayne.edu); Samiran Ghosh – Co-PI (sghos@med.wayne.edu)

d) **Institutions:** Wayne State University, Institute of Environmental Health Sciences and Dept of Pharmacology; Department of Family Medicine and Public Health Sciences

e) **Project Period and Location:** 9/1/2022 – 8/30/2025; Detroit, MI 48202

f) **Project Cost:** $599,925

g) **Project Summary:** Contaminants can interact to produce combination effects other than those predicted by individual component chemicals. This poses a unique challenge for risk assessment, which pre-supposes that contaminants should be assessed individually across a broad dose response range to attempt to discriminate "safe" exposure concentrations. This proposal will directly interrogate the comparability of joint toxicity as well as the development of methods focused various levels of biological organization. (1) We will evaluate mixtures of increasing complexity for ability to promote adipogenesis. Specifically, we will examine mixtures of increasing complexity for their deviations from expected adipogenic effects using concentration addition and independent action models. We hypothesize that mixtures of increasing complexity will shift towards independent action, but that the most complex mixtures will not be well predicted by either model. We will also develop an effect-based model to predict adipogenic activity based on component bioactivities, which we hypothesize will provide a chemical agnostic approach to risk assessments of realistic environmental mixtures. (2) This proposed research program will rigorously assess available mixture models through controlled assessments of contaminants acting through shared, distinct, and mixed mechanisms. We will utilize *in silico* approaches to select chemicals predicted to promote adipogenesis through distinct mechanisms. We will use *in vitro* and *in vivo* models of metabolic health disruption to assess both individual chemicals and their mixtures and compare with predicted outcomes based on concentration addition and independent action. Lastly, we will utilize environmental samples (household dust) to develop a receptor bioactivity component model to predict adipogenic health outcomes. (3) Our results will promote a greater functional understanding of complex mixture effects that can be utilized to bolster risk assessments of diverse contaminant exposures. By using this stepwise approach of increasing mixture complexity, we expect a primary output of clearly describing the weaknesses and strengths of these standard mixture models. Through our testing of dust extracts, we expect that we can support a new method of mixture risk assessments through using component mechanistic effect levels to determine cooperative effects on complex health endpoints and/or outcomes.

h) **Supplemental Keywords:** Adipogenesis; Metabolic Health; Obesogen; Mixture; Dust; Chemicals; Organics; Cumulative Effects; Organism; Cellular; Animal