"Mechanisms by which *in utero* exposure to perfluorooctanoic acid (PFOA) programs the offspring to develop non-alcoholic fatty liver disease (NAFLD)"

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Abstract:

Persistent fluorinated compounds (PFCs), including the most widely used compound perfluorooctanoic acid (PFOA), are a subgroup of persistent organic pollutants found in carpets, furniture, shoes, clothing (Gore-Tex), non-stick cookware (Teflon), and food packaging. Rodents exposed to PFCs *in utero* have altered hepatic cholesterol metabolism, increased hepatic *de novo* lipogenesis and increased susceptibility to fatty liver disease later in life but the underlying molecular mechanisms are unknown. Maternal obesity induces marked abnormalities in glucose homeostasis and insulin secretion in the fetus and is linked to obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) in the offspring but little is known about how exposure to maternal obesity *in utero* alters fetal liver metabolism. Exposure to PFOA *in utero* sets the stage for a two-hit hypothesis where increased lipid content in the fetal liver establishes the initial hepatic lipotoxicity and increases susceptibility to an second hit from *in utero* exposure to maternal obesity, thus triggering the development of steatohepatitis. Epigenetic modifications provide a measurable mechanism that allows for the permanent propagation of gene activity states (including transcriptional activation and repression) from one generation of cells to the next and may serve as biological memory of an aberrant intrauterine environment. With the continued increase in the rates of NAFLD in children and adolescence, it is critical to examine the potential role of *in utero* exposure to PFOA and epigenetic programming in the development of these disease processes. We hypothesize that *in utero* exposure to PFOA and maternal obesity triggers exaggerated lipotoxicity in the fetal liver which in turn leads to permanent changes in expression of key metabolic genes in hepatocytes. Further, we hypothesize that the permanent changes in gene expression are driven by changes in DNA methylation,

which ultimately lead to changes in hepatic metabolism and the development of NAFLD later in life.