

## Concept Clearance

**Branch:** Population Health Branch

**Council Period:** 201601

**Concept Title:** Preconceptional Exposure and Health of the Offspring Concept

### Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis postulates that early-life stressors influence later-life health outcomes. It is now evident that risk for developing a number of developmental diseases is affected by a variety of chemical and nutritional imbalances during fetal or postnatal development. These responses to environmental exposures permanently change the body's growth patterns, physiology, and metabolism. Studies in animals and epidemiological evidence strongly support the DOHaD hypothesis.

Similar to early life development, the preconceptional period (before fertilization) is a time of rapid cell growth, meiotic division, hormonal, and epigenetic changes. Exposures during this "sensitive" window can have lasting impacts on health. Because unfertilized male and female germ cells also respond to an environmental insult, and these effects can be transmitted to future generations, the DOHaD hypothesis can be expanded to include preconceptional exposures.

At fertilization, the male and female gametes each provide their genome, epigenome, and other gamete content, which has been modified during spermatogenesis and oogenesis, respectively. Even minor alterations to these constituents by various environmental factors can have significant effects on the resulting offspring. In this regard, brief exposures of maturing sperm cells and oocytes can alter transmissible material temporally and permanently, resulting in significant phenotypic changes in the first generation offspring.

Exposures during this "sensitive" window can have lasting impacts on health. For example, it is well established that exposures during the prenatal period can lead to changes in pubertal development, neurobehavioral effects, cause cancers and lead to many other health outcomes. Evidence has long shown that chemical exposures during reproductive years can alter germ cell quality, reduce fertility, and have teratogenic effects on the offspring. These effects influence the developing organs, tissues, and cells in a process known as reprogramming and can lead to differences in adult phenotypes.

There is a significant body of research showing that paternal and maternal preconceptional exposure to drugs, social instability, nutritional status, and smoking can have adverse effects on the offspring. For example, maternal smoking is associated with increased risk of congenital heart defects, and paternal smoking is associated with type 2 diabetes in the offspring. However, only a few studies have reported associations between preconceptional environmental chemical exposures to germ cells and their effects on life-long health.

### Research Goals and Scope

For this concept, only studies in non-human model systems will be considered. Studies must test the hypothesis that preconceptional environmental exposures (pre-fertilization) to germ cells can lead to later-life health outcomes in the first generation offspring. It is not necessary for these effects to be transgenerational (although they could be), therefore the focus should not be on imprinted genes or multiple generations of offspring. The environmental factor/insult (e.g., endocrine disruptor, pesticide, air pollution, fungicide, combined exposures, etc.) to be administered should lead to a reproducible phenotype in the first generation offspring. Researchers are encouraged to test emerging, understudied, and non-genotoxic chemical exposures to germ cells and link alterations in transmitted material to developmental changes in the offspring.

Any well-defined mechanistic change(s) occurring in pre-fertilized germ cells can be analyzed, such as changes in:

- DNA methylation
- chromatin structure
- micro and non-coding RNA populations
- oxidative states or other cellular milieu
- mitochondrial function, non-redox states
- gene copy number variations (CNVs)
- mutations (non-teratogenic)
- other potential reprogramming events

Germ cell alterations should be linked to physiological changes in the direct offspring, such as, but not limited to the following:

- cardiovascular disease or stroke
- metabolic diseases such as diabetes, obesity
- reproductive and pubertal development
- cancer

- neurodevelopmental disease
- endocrine diseases and disorders
- kidney disease
- osteoporosis or other bone diseases

Due to the limited project period, detailed examination of the mechanism underlying a particular mechanistic change is not required.

#### **Mechanism and Justification**

This initiative will use a 3 year R01 mechanism with a cap of \$250,000 (direct cost/year). The program is estimated at \$2.5M annually to support 6–8 R01 projects. A 3 year R01 will ensure that researchers have the time and resources to link a preconceptional exposure mechanism with health effects in the offspring.