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Concept Clearance

Research Program to Understand the Role of Environmental Exposures in the  
Development of Obesity, Type 2 Diabetes and Metabolic Syndrome

**Introduction**

The prevalence of obesity has risen dramatically in the United States and in other regions of the world over the past two decades. In the United States, 30% of adults have been defined as clinically obese and 65% defined as overweight. Perhaps more important is that obesity and related diseases, such as diabetes, are rising dramatically in our children. More than 60% of children 10 years and older either are or will become obese later in life. There is considerable evidence that obesity risk may begin early in life, during pregnancy, and early childhood. There are numerous studies showing that rapid weight gain in the first few months of life is associated with obesity later in life.

The prevalence of type 2 diabetes has also risen dramatically in the United States over the past few decades. Diabetes poses a tremendous and increasing clinical and public health burden for Americans; 19.3 million Americans over the age of 20 years are affected, one third of whom are undiagnosed. Seventy percent of type 2 diabetes risk is attributed to overweight/obesity suggesting a metabolic link between weight gain and type 2 diabetes. Indeed, obesity is the leading cause of type 2 diabetes. Of particular concern is the fact that the incidence of type 2 diabetes is increasing in children and adolescents along with the rise in obesity. One in four overweight children has impaired glucose tolerance. Type 2 diabetes is more common in girls than boys and girls are less insulin sensitive as early as 5 years of age.

Metabolic syndrome is also associated with the rise in obesity and may progress to type 2 diabetes. It is defined clinically as a combination of at least three of the following five dysfunctions: hypertension, central adiposity, increased serum triglycerides and low serum HDL, and high fasting blood sugar. There is significant data supporting the idea that metabolic syndrome is programmed during development and that there is a role for maternal diet in its etiology.

There is a strong relationship between obesity, type 2 diabetes and metabolic syndrome. Indeed, "diseaseome" analysis shows significant overlap between the three conditions. In addition, preliminary data in animal models suggest that environmental exposures that cause one of these diseases also, in many cases, cause the others.

The NIEHS interest in this disease area dates back to 2004 when we cosponsored a Spring Symposium, "Obesity: Developmental Origins and Environmental Influences" as part of the Duke University Integrated Toxicology Program Seminar Series. We also organized sessions on this topic at the Society of Toxicology and AAAS annual meetings and a day long satellite symposium at the European Obesity Society annual meeting. We are a member of the NIH Obesity Task Force and contributed a section to the White House Document on Obesity. We also have an obesity listserv and have presented numerous invited lectures on the "Obesogen Hypothesis" around the world.

Last month the NTP held a workshop entitled "Role of Environmental Chemicals in the Development of Diabetes and Obesity". This workshop produced not only a state-of-the-art document but also a listing of data gaps and ideas for a research strategy. The results of this workshop should have an important impact to stimulate interest and research in the role of environment in these diseases.

### **Research Goals and Scope**

The overall goal of this Concept Clearance is to present a research program to understand the role of environmental exposures in the development of obesity, type 2 diabetes and metabolic syndrome. This research area falls under the umbrella of the developmental basis of disease, endocrine disruptor and epigenetics research programs.

The hypothesis tested is that the obesity epidemic is due, in part, to environmental chemical exposures during development. We hypothesize that environmental exposures act during development to control fat cell development and metabolism thereby altering the programming of the weight gain and glucose tolerance/insulin sensitivity "set point". Certainly food intake and exercise are important in the obesity epidemic but environmental chemical exposures during development can alter the "set point" for gaining weight. It can control how much food it takes to put on weight and how much exercise is needed to reduce weight.

Thus, the overall goal is to determine the importance of this emerging hypothesis, now called "the Obesogen Hypothesis" in the current epidemic of obesity and type 2 diabetes and the associated metabolic syndrome.

This hypothesis changes the focus from genetics (the traditional focus) to gene-environment interactions. It also changes the focus from intervention (which does not work well!) to prevention. It focuses on pregnancy and the first few years of life and puberty as sensitive periods for the development of these diseases. Once we identify the chemicals that play an important role in the development of these diseases we can focus on prevention by reducing exposures during critical time periods.

## **Mechanism and Justification**

NIEHS proposes a multicomponent program to address the role of environmental exposures in the development of obesity, type 2 diabetes and metabolic syndrome. These include the use of SBIR grants to develop screens for obesogens and other chemicals that play a role in these diseases, NTP Tox 21 program to assess chemicals that have the potential to play a role in these diseases and FOAs which would use the R21 and R01 mechanism.

The program will be initiated with a program announcement (PA) with an R21 and R01 program. The advantage of a PA is that it will be active for 3 years allowing applicants both times to submit and the ability to resubmit if their first application does not fare well.

The goals of the proposed R21 and R01 program were developed as a result of DERT analysis of the research needs and the results of the recent NTP Workshop.

- The R21 program would focus on identifying additional environmental chemicals that have the capacity to alter adipose tissue development and/or metabolism, glucose tolerance/insulin resistance and/or lipid metabolism at the cellular and molecular level and also to develop high throughput screens to detect chemicals that can affect weight gain and/or glucose and lipid metabolism.
- The R01 program would focus on understanding the site(s) and mechanism(s) whereby environmental chemicals can alter weight gain, glucose metabolism/insulin sensitivity and lipid metabolism using an integrated molecular approach. It would also focus on development of predictive biomarkers of weight gain and insulin insensitivity, and the interaction of genetic background, nutritional status, stress, drugs, infections, alterations in circadian systems and alterations in the immune system with environmental exposures during development that would lead to weight gain, type 2 diabetes and metabolic syndrome.

For both mechanisms Multi PI applications (one with expertise in basic biology and endocrinology of obesity, type 2 diabetes and metabolic syndrome and another with expertise in toxicology and endocrine disruptor research) will be encouraged. We also expect applicants to use dose responses, measure internal levels of the environmental chemicals to assess both genders and to use modern molecular approaches to assess site and mechanisms.

We also expect to work closely with the NTP to develop and incorporate new screens into their high throughput screening assays to detect chemicals that can alter the molecular pathways known to play important roles in these diseases.