

Research Brief 185: Childhood Exposures to Pesticides May Contribute to Obesity and Diabetes in Adults

Release Date: 05/05/2010



<http://www.niehs.nih.gov/srp/>

Background

Dr. Ted Slotkin at the Duke University SRP studies the neurotoxic and neurodevelopmental impacts of exposure to organophosphate (OP) pesticides. His research team has made significant discoveries – identifying mechanisms of neurotoxicity that do not involve cholinesterase inhibition; determining that organophosphates are damaging to neural cell replication and differentiation at exposure levels below the threshold for significant inhibition of cholinesterase; and demonstrating that the adverse effects of organophosphates on neurodevelopment are shared by other Superfund chemicals that can target similar events, such as divalent heavy metals and organochlorines.

Organophosphate insecticides represent nearly 50% of worldwide insecticide use.

In a recent series of studies, Dr. Slotkin's research team investigated the toxic effects of organophosphate exposures that extend beyond the nervous system. It is increasingly clear that environmental chemical exposures early in life contribute to the explosive increase in the incidence of obesity and diabetes. As childhood exposure to organophosphates is virtually ubiquitous, the researchers explored whether low level exposures early in life, alone or in combination with poor dietary choices, can lead to changes in metabolic function that could contribute to obesity and diabetes. They focused their attention on adipokines – the hormones that signal changes in fatty-tissue mass and energy status to control fuel usage:

According to an April, 2010 report issued by the Institute of Medicine, ~68 percent of adults in the United States aged 20 years or older are either overweight or obese. Among children, the rate is nearly 32 percent.

- **Leptin** – controls body weight by regulating both feeding behavior and energy expenditure.
- **Adiponectin** – modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism.
- **Tumor necrosis factor- α (TNF α)** – regulates the function of other adipokines and insulin, contributing to insulin resistance and diabetes.

Advances

The researchers exposed neonatal rats to organophosphates at levels ranging from doses that barely induce detectable cholinesterase inhibition to doses known to induce systemic intoxication. In adulthood, one group of animals was switched to a diet high in saturated fat. The researchers then evaluated the concentrations of serum adipokines and of TNF α in adipose tissues. They also assessed membrane lipid peroxidation in adipose tissues, brain regions, skeletal muscle, heart, liver, and kidney.

The researchers found that fetal or neonatal exposures to chlorpyrifos, diazinon, or parathion resulted in sex-selective changes in serum lipids, leading to changes in responses to dietary fat intake and increased body weight in adulthood. Detailed analysis of serum metabolites suggested that organophosphates likely target lipid metabolism in a complex manner.

In a study in which the researchers exposed neonatal rats to parathion, they found: decreased serum adiponectin levels in adult males regardless of diet; increased adipose TNF α in adult males and females regardless of diet; increased serum leptin levels in adult males fed a high fat diet; and decreased serum leptin levels in adult females fed a high fat diet. That is, neonatal organophosphate exposure not only altered basal adipokine concentrations, but also altered their reactivity to dietary factors.

Following neonatal parathion exposure, the researchers noted elevated TNF α levels in the fatty tissues, indicative of a chronic adipose inflammatory state similar to that associated with diabetes and obesity. This suggests that early-life parathion exposure induces a state of chronic adipose inflammation even in the absence of dietary manipulations and

that these effects that could well provide a driving force for many of the other metabolic abnormalities. For example, systemic changes in lipid metabolism and adiposity affect the composition of synaptic membranes within the brain, altering the function of the neurotransmitter receptors and signaling molecules. Thus, early-life organophosphate exposure, metabolic disruption, and neurobehavioral consequences may be related.

Significance

These results support the view that early-life organophosphate exposure disrupts lipid metabolism in adulthood. Combined with Dr. Slotkin's prior findings that showed how early-life parathion and chlorpyrifos produce serum metabolic profiles resembling the initial stages of diabetes, it is evident that organophosphates, generally classified as developmental neurotoxicants, target important homeostatic mechanisms that govern metabolism, growth, and the risk factors contributing to diabetes, obesity, and cardiovascular disease.

For more information, contact:

Theodore A. Slotkin, Ph.D.

Department of Pharmacology & Cancer Biology
Box 3813 DUMC
Durham, NC 27710
Tel: 919-681-8015
Email: t.slotkin@duke.edu

To learn more about this research, please refer to the following sources:

Lassiter, T.L., I.T. Ryde, E.D. Levin, F.J. Seidler, and T.A. Slotkin. 2010. Neonatal exposure to parathion alters lipid metabolism in adulthood: Interactions with dietary fat intake and implications for neurodevelopmental deficits. *Brain Research Bulletin* 81(1):85-91.
doi:10.1016/j.brainresbull.2009.07.002

Lassiter, T.L., I.T. Ryde, E.A. MacKillop, K.K. Brown, E.D. Levin, F.J. Seidler, and T.A. Slotkin. 2008. Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. *Environmental Health Perspectives*. 116:1456-1462.
doi:10.1289/ehp.11673

T.A. Slotkin, K.K. Brown, and F.J. Seidler. 2005. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. *Environmental Health Perspectives*. 113 (2005) 1291-1294.
doi: 10.1289/ehp.8133.

Shiriki K. Kumanyika, Lynn Parker, and Leslie J. Sim. 2010. Bridging the Evidence Gap in Obesity Prevention: A Framework to Inform Decision Making. Editors; Committee on an Evidence Framework for Obesity Prevention Decision Making; Institute of Medicine
http://www.nap.edu/catalog.php?record_id=12847



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

