HHS Public Access

Author manuscript

*Obesity (Silver Spring)*. Author manuscript; available in PMC 2013 December 01.

Published in final edited form as:

*Obesity (Silver Spring)*. 2013 June ; 21(6): 1079–1080. doi:10.1002/oby.20222.

# The Perfect Storm for Obesity

**Jerrold J. Heindel**[1] and **Thaddeus T. Schug**[1,*]

[1]Division of Extramural Research and Training, Cellular, Organ and Systems Pathobiology Branch, National Institute of Environmental Sciences, Research Triangle Park, NC, USA

Obesity rates have risen steadily in the United States and around the world over the past century, with a marked escalation within the past two decades. Conventional wisdom within the medical community is that the burgeoning obesity epidemic is the product of poor nutrition and lack of exercise, but increasingly researchers are questioning whether those factors are wholly responsible. Emerging research about alternative factors is setting the stage for today's "Perfect Storm" for obesity.

## Endocrine Disrupting Chemicals and Obesity

Scientists are discovering that there is a subclass of endocrine disrupting chemicals (EDCs) that interfere with endocrine signaling, which can disrupt hormonally-regulated metabolic processes, especially during early development. These chemicals, called "obesogens," may predispose some people to gain weight due to their effects on metabolic tissues despite efforts to limit caloric intake and increase physical activity [1]. Others are finding parallels between chemical exposures early in life and later life onset of obsessive eating in obese individuals and other addictive behaviors [2].

The role of environmental chemicals in obesity is also beginning to attract the attention of academic, policy, and funding organizations. The Presidential Task Force on Childhood Obesity and the National Institutes of Health Strategic Plan for Obesity Research both acknowledge that environmental exposures could play an underlying role in the development of metabolic diseases. The National Toxicology Program recently reported on many studies in both humans and animal models that provide "real biological plausibility" [3] for linkages between environmental exposures and type 2 diabetes and obesity.

Early development is a highly orchestrated series of biochemical, physical, and organizational events that must be tightly coordinated to ensure proper growth. Because the developmental period is a "plastic" phase, an organism is critically sensitive to alterations in hormones that can lead to changes in gene expression and protein levels, which persist as tissues and organs develop. Indeed, early life exposures (in utero and/or first few years of life) to environmental perturbations (nutrition or environmental chemicals) can be directly associated with increased risk for many of today's most common diseases.



*Corresponding Address: Thaddeus T Schug, Ph.D., Celluar, Organs and Systems Pathobiology Branch, National Institute of Environemntal Health Sceinces/NIH, Division of Extrameural Research and Training, POB 12233 MD K3-15, Research Triangle Park, NC, 27709, 919-541-9469 (P), 919-541-5064 (F), schugt@niehs.nih.gov.

Exposure to obesogens *in utero* and in early infancy into childhood can disrupt metabolic programming events that subsequently lead to increased risk of obesity later in life. For example, a recent study in mice demonstrated that a single prenatal exposure to the fungicide tibutyltin (TBT), in the range of human exposures, results in premature accumulation of adipose tissue. Developmental exposure to TBT alters the fate of mesenchymal stem cells, which normally have the ability to differentiate into a variety of tissue types to become fat cells at the expense of bone cells [4].

There are now nearly 20 chemicals shown to cause long-term weight gain based on exposures during critical periods of development due to their ability to disrupt normal hormone and neuronal signaling pathways. Smoking and nicotine, persistent organophosphate pesticides, flame retardants, plasticizers and plastics, and fungicides, for example, have all been linked to obesity in animals. Certainly, this could be just the tip of the iceberg as there are close to 800 chemicals in commerce with reported EDC properties [1].

Obesogens may also be more harmful for those who are already overweight or obese because they are lipid-soluble. For instance, toxic industrial chemicals, such as organochlorines, are stored in fat cells, where they can continue to disrupt tissue function for decades and escape into the bloodstream when those cells lose fat during weight loss [5]. These higher concentrations may increase the likelihood that formerly overweight individuals will regain shed pounds. It is plausible that fat leaching chemicals may interfere with both the thyroid gland, which helps regulate the body's metabolism, and individual cells' mitochondria, which convert fuel into energy.

Studies show that exposure to EDCs, including bisphenol-A (BPA), disrupts the organization and function of dopaminergic pathways throughout the brain, resulting in a wide range of behavioral effects including elevated impulsivity, anxiety, and disrupted sociality. BPA alters both pre- and post-synaptic dopamine activity in brain regions associated with addiction and impulse control, suggesting that this may be a mechanism by which BPA exposure alters feeding behavior.

The actions of EDCs on the developing brain have been shown to trigger changes in the hypothalamus, the region of the brain that plays a particularly important role in feeding behaviors. Improper hypothalamic programming may adjust metabolic "set-points" in adolescents and adults. These adjustments may manifest and help explain differences between the eating behavior of lean and obese individuals.

Nutrition during development also plays an important role in the obesity epidemic. Maternal diabetes, a disease with links to both dietary factors and EDC exposures, is highly associated with above average birth weight and childhood obesity. Nutritional studies show that high pre-pregnancy body mass index and excessive weight gain during pregnancy are also associated with above average birth weight. In turn, an above average birth weight can be an indicator for overweight or obesity in childhood and adulthood. Paradoxically, people born gestationally small also have an increased risk of obesity, possibly because of rapid compensatory postnatal growth. Many disease patterns linked to poor nutrition have also

been traced to maternal chemical exposure, suggesting a common mechanism for chemical and nutritional stress that ultimately leads to long-term obesity.

The developmental time period is critically sensitive to both nutritional and environmental influences that affect long-term disease etiology. We propose that the confluence of these factors during development (in utero and first few years of life) association with overnutrition and decreased activity along with additional environmental exposures throughout life creates “The Perfect Storm” that is driving the obesity epidemic throughout the world. Dealing with this storm will require more research into understanding how nutritional and environmental chemical exposures affect the basic mechanisms underlying adipose tissue development and function as well as eating behavior. The implications of the obesity epidemic are great, and new research into its causes offers a window on prevention and/or intervention strategies.

## References

1. Grun F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocr Metab Disord. 2007; 8(2):161–71. [PubMed: 17657605]
2. Aschengrau A, et al. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. Environ Health. 2011; 10:102. [PubMed: 22136431]
3. Thayer KA, et al. Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Report. Environ Health Perspect. 2012; 1:1.
4. Kirchner S, et al. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol. 2010; 24(3):526–39. Epub 2010 Feb 16. [PubMed: 20160124]
5. Tremblay A, et al. Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution. Int J Obes Relat Metab Disord. 2004; 28(7):936–9. [PubMed: 15148504]