

## Extramural papers of the month

By Nancy Lamontagne

- Prenatal BPA exposure linked with higher levels of oxidative damage
- Vitamin B protects against DDT-associated fertility problems
- BPA may be especially harmful to heart health of females
- People and mice share epigenetic differences tied to obesity

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Superfund Research Program  
Research Brief. New issues  
are published on the first  
Wednesday of each month.

### Prenatal BPA exposure linked with higher levels of oxidative damage

NIEHS grantees report that exposure during pregnancy to the endocrine-disrupting chemical bisphenol A (BPA) can cause oxidative damage that may increase the child's risk of developing diabetes or heart disease later in life. The researchers tested multiple species of animals to replicate and strengthen human studies showing BPA exposure during pregnancy can bring about a specific type of oxidative stress.

Oxidative stress is associated with insulin resistance and inflammation, which are risk factors for diabetes and other metabolic disorders, as well as cardiovascular disease. For the human study, the researchers analyzed blood samples from 24 mother and infant pairs. The women were divided into two groups based on levels of BPA, determined from blood draws taken during the first trimester of pregnancy. Mothers and their infants with higher levels of BPA showed increased levels of a marker of nitrosative stress, known as 3-nitrotyrosine. Nitrosative stress is a type of oxidative stress brought about by the free radical nitric oxide or reactive species derived from it. For the animal studies, the researchers examined the effects of BPA on sheep, rats, and mice by prenatally treating the animals with BPA at doses similar to what people would experience. The animals showed increased systemic nitrosative stress, which indicates a causal link between BPA exposure and this type of oxidative stress.

Overall, the findings demonstrate an association between increased BPA exposure and increased systemic nitrosative stress. The results also support the potential use of maternal 3-nitrotyrosine as a health status biomarker for future offspring.

*Citation:* Veiga-Lopez A, Pennathur S, Kannan K, Patisaul HB, Dolinoy DC, Zeng L, Padmanabhan V.  
(<http://www.ncbi.nlm.nih.gov/pubmed/25603046>)

2015. Impact of gestational bisphenol A on oxidative stress and free fatty acids: human association and interspecies animal testing studies. *Endocrinology* 156(3):911-922.

### Vitamin B protects against DDT-associated fertility problems

New research, supported in part by NIEHS, shows that B vitamins can help protect against increased risk of miscarriage, which is associated with high levels of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) in the body.

From 1996 to 1998, the researchers followed female Chinese textile workers who were trying to get pregnant. They measured preconception concentrations of vitamin B-6, vitamin B-12, and folate in blood plasma, as well as serum total DDT. Among the 291 women in the study, there were 385 conceptions, of which 31 percent were lost before six weeks. The time to conception was longer and the frequency of pregnancy was lower in women with B-vitamin deficiency and high DDT blood levels, than in women with adequate B-vitamin levels and low DDT. For the women with high DDT, conception frequency increased by 47 percent for every 17.8 nanomoles per liter increase in vitamin B-6, and the likelihood of an early pregnancy loss was reduced by 45 percent with every 4.8 nanomoles per liter increase in folate.

Researchers suggest that higher preconception intake of B vitamins, through fortified foods and improved nutrition, could help improve pregnancy outcomes in countries where DDT is still used.

*Citation:* Ouyang F, Longnecker MP, Venners SA, Johnson S, Korrick S, Zhang J, Xu X, Christian P, Wang MC, Wang X.  
(<http://www.ncbi.nlm.nih.gov/pubmed/25411282>)

2014. Preconception serum 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane and B-vitamin status: independent and joint effects on women's reproductive outcomes. *Am J Clin Nutr* 100(6):1470-1478.

### BPA may be especially harmful to heart health of females

An NIEHS grantee and colleagues report that exposure to the endocrine disruptor bisphenol A (BPA) from birth through young adulthood affects the heart function and blood pressure of male mice differently from that of female mice. The results add more

evidence that BPA can adversely affect the cardiovascular system and suggest that females are particularly sensitive to heart damage from BPA.

The researchers fed mice with food containing various amounts of BPA, which resulted in exposures ranging from 4 to 5,000 micrograms per kilogram of body weight per day. They observed changes in the control of heart rate and blood pressure in both male and female BPA-exposed mice. Male mice exposed to BPA above 5 micrograms and female mice exposed to the highest amounts of BPA showed decreased systolic blood pressure.

To mimic some of the effects of a heart attack, the researchers administered isoproterenol, a drug that leads to tissue enlargement. In BPA-exposed female mice, isoproterenol caused increased heart muscle damage along with accumulation of collagen, which indicates fibrosis or scarring. In male mice, BPA exposure without isoproterenol increased fibrosis, but isoproterenol treatments didn't cause any additional increase in fibrosis, ischemic damage, or hypertrophy. The researchers also conducted a RNA sequence analysis, which identified significant sex-specific changes in gene expression in mice exposed to BPA.

*Citation:* [Belcher SM, Gear R, Kendig EL.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/25594700>)

2015. Bisphenol A alters autonomic tone and extracellular matrix structure and induces sex-specific effects on cardiovascular function in male and female CD-1 mice. *Endocrinology* 156(3):882-895

## People and mice share epigenetic differences tied to obesity

Research, supported in part by NIEHS, found a surprising similarity between obesity-induced epigenetic marks in mice and humans. These findings might provide new routes to prevent and study obesity, as well as insight into how the environment might bring about epigenetic changes that can lead to obesity-related diseases, such as type 2 diabetes.

Epigenetic marks are chemical modifications, such as the addition of a methyl group, that change how DNA is expressed without changing the genetic code. The researchers analyzed more than 7 million sites in the DNA of fat cells in lean and obese mice and found clear differences in methylation patterns. They also looked at changes in DNA methylation in people before and after gastric bypass surgery. Of the 625 regions of DNA with methylation patterns associated with obesity in the mice, 249 regions showed significant conserved methylation changes associated with obesity in people.

The researchers used genetic association data from a large type 2 diabetes genome-wide association study to link their findings with disease. This revealed that some of the obesity-associated methylation patterns affected genes known to raise diabetes risk, while others affected genes that had not been conclusively linked to the disease but did have roles in metabolism. It also identified some DNA regions that might be susceptible to environmental factors that influence methylation.

*Citation:* [Multhaup ML, Seldin MM, Jaffe AE, Lei X, Kirchner H, Mondal P, Li Y, Rodriguez V, Drong A, Hussain M, Lindgren C, McCarthy M, Naslund E, Zierath JR, Wong GW, Feinberg AP.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/25565211>)

2015. Mouse-human experimental epigenetic analysis unmask dietary targets and genetic liability for diabetic phenotypes. *Cell Metab.* 21(1):138-149.

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