# Extramural papers of the month

*By Nancy Lamontagne*



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## Cigarette smoke affects genes associated with heart and lung health

An NIEHS-funded mouse study provides evidence that sidestream cigarette smoke, the secondhand smoke from burning tobacco, affects the activity of hundreds of genes that protect the heart and lungs. Obese mice on a high-fat diet showed the strongest response after inhaling sidestream smoke.

Smoking and obesity are risk factors for cardiovascular disease, but the molecular mechanisms behind the increased risks are not well understood. The researchers used mouse models to study early signaling events that occur in the heart and lungs after cigarette smoke exposure. They also looked at the role of obesity in this response. The investigators exposed normal weight and obese mice fed a high-fat diet to the two components of secondhand smoke - exhaled mainstream smoke and the side stream smoke emitted from the burning tip, the latter of which makes up 85 percent of secondhand smoke.

Using whole genome microarray analysis, the investigators found that mice exposed to mainstream smoke showed cellular and molecular inflammatory responses in the lung. The normal weight animals had 1,466 differentially expressed pulmonary genes and 463 differentially expressed cardiac genes. Exposures to sidestream smoke brought a weak pulmonary response (328 genes) but a strong cardiac response (1,590 genes). In general, the most sensitive smoke-induced cardiac transcriptional changes observed in the normal weight mice were not observed in the smoke-exposed obese mice. The smoke exposure also suppressed multiple proteome maintenance genes induced in the hearts of obese mice. Overall, the results showed that the heart is sensitive to sidestream smoke and that adaptive responses in healthy mice were absent in obese mice.

*Citation*: Tilton SC, Karin NJ, Webb-Robertson BJ, Waters KM, Mikheev V, Lee KM, Corley RA, Pounds JG, Bigelow DJ. *(http://www.ncbi.nlm.nih.gov/pubmed/23786483)*
2013. Impaired transcriptional response of the murine heart to cigarette smoke in the setting of high fat diet and obesity. Chem Res Toxicol 26 (7):1034-1042.

## Graphene sheets pierce and enter cells

NIEHS grantees report that graphene materials with micrometer-scale dimensions, known as graphene microsheets, can enter cells when their sharp protrusions pierce the cell membrane. Understanding how these graphene sheets interact with cells can help scientists develop materials that are not harmful to the body.

The researchers' initial simulations suggested that a microsheet would rarely pierce a cell, because the energy barrier required for a sheet to cut the membrane was too high. However, when these simulations took into account the rough edges commonly found on the edges of graphene sheets, the sheets more easily pierced the membrane.

Confocal fluorescence and electron microscopy confirmed that graphene's rough edges and corners could pierce primary human keratinocytes, human lung epithelial cells, and murine macrophages. The imaging also showed that cells could completely internalize graphene sheets with lateral dimensions of 0.5 to 10 micrometers. More research is needed to understand how the microsheets affect cells, but the researchers say that microsheets might disrupt cytoskeleton and cell motility, and cause problems with epithelial barriers.

*Citation*: Li Y, Yuan H, von dem Bussche A, Creighton M, Hurt RH, Kane AB, Gao H. *(http://www.ncbi.nlm.nih.gov/pubmed/23840061)*
2013. Graphene microsheets enter cells through spontaneous membrane penetration at edge asperities and corner sites. Proc Natl Acad Sci U S A 110(30):12295-12300.

## Global cost of childhood lead exposure

According to research supported by NIEHS, low-income and middle-income countries experience the largest burden of lead

exposure, with cost measured in what are known as international dollars. An international dollar is a hypothetical currency used to compare costs from various countries. It has the same purchasing power as a dollar would in the U.S.

The investigators estimate that childhood lead exposure in low-income and middle-income countries is associated with lost lifetime economic productivity of $977 billion international dollars annually, or 1.2 percent of the world's gross domestic product. For comparison, lead-associated loss in lifetime economic productivity is estimated to be $50.9 billion international dollars in the U.S. and $55 billion international dollars in Europe.

The researchers calculated lead-associated loss, by developing a regression model to estimate average blood lead levels and estimating the lead-attributable economic costs with an environmentally attributable fraction model. They examined only the neurodevelopmental effects of lead, which were assessed using IQ points. The investigators estimate that the total lead-associated economic loss ranges from $728.6 to $1,162.5 billion international dollars, including $134.7 billion in Africa, $142.3 billion in Latin America and the Caribbean, and $699.9 billion in Asia.

*Citation*: Attina TM, Trasande L.
*(http://www.ncbi.nlm.nih.gov/pubmed/23797342)*
2013. Economic costs of childhood lead exposure in low- and middle-income countries. Environ Health Perspect; dx.doi.org/10.1289/ehp.1206424 [Online 25 June 2013].

## Understanding the cytotoxicity of hexavalent chromium

In a study funded in part by the NIEHS, researchers report that hexavalent chromium, or CR(VI), cytotoxicity may partially result from its up-regulation of cholesterol biosynthesis. Cr(VI) is generated during industry processes and is carcinogenic. A better understanding of the mechanisms for the cytotoxicity of this heavy metal could be used to develop therapies that decrease health effects after exposure.

The researchers used stable isotope labeling by amino acids in cell culture and liquid chromatography coupled with tandem mass spectrometry to study the cellular mechanisms affected by Cr(VI). This quantitative proteomic technique revealed 4,607 unique proteins involved in Cr(VI) perturbation of cells. Of these, 270 proteins were significantly up-regulated and 127 down-regulated.

The researchers found that Cr(VI) affected cholesterol biosynthesis, G-protein signaling, inflammatory response, and selenoprotein pathways. Cells treated with Cr(VI) had much higher expression of a large number of enzymes involved in cholesterol biosynthesis, and multiple cell lines showed increases in cellular cholesterol levels. In addition, the cholesterol-lowering drug, lovastatin, reduced growth inhibition of cultured human cells brought on by Cr(VI).

*Citation*: Guo L, Xiao Y, Wang Y.
*(http://www.ncbi.nlm.nih.gov/pubmed/23718831)*
2013. Hexavalent chromium-induced alteration of proteomic landscape in human skin fibroblast cells. J Proteome Res 12(7):3511-3518.

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