A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP8877.

Potential Mechanisms behind Air Pollution Toxicity: Findings from Real-World Chronic Exposures

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https://doi.org/10.1289/EHP8877

Traffic is one of the major contributors to air pollution in urban areas; the dynamic mixture of gases and particles that results from vehicle exhaust and noncombustion emissions such as road and tire wear is known as traffic-related air pollution (TRAP).[1] The impact of TRAP exposure on human health has been the subject of epidemiological studies for two decades, but the mechanisms by which TRAP-associated particulate matter (PM) alters heart and lung function remain to be elucidated. In a recent pilot study reported in *Environmental Health Perspectives*, investigators sought to address this issue using a real-world model of TRAP exposure in rats.[2]

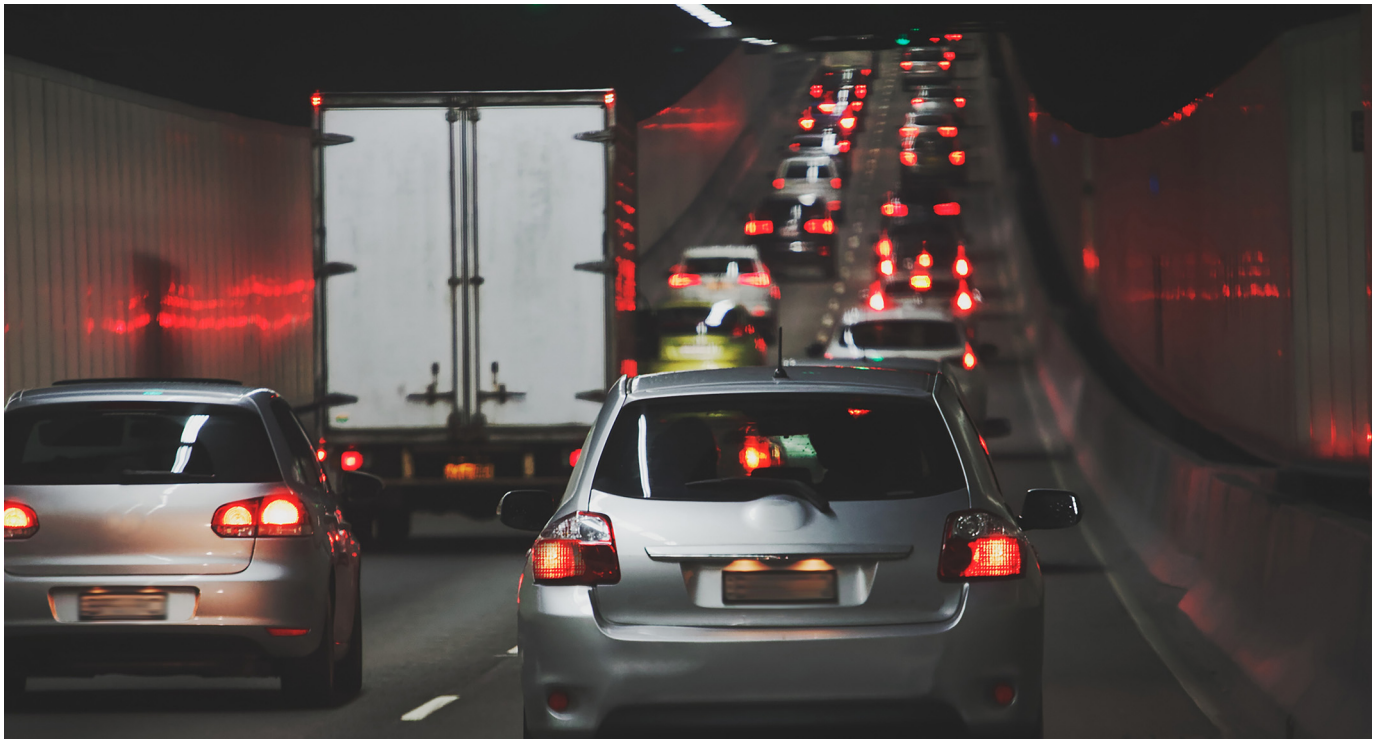
Worldwide, ambient air pollution is estimated to cause 3.8 million premature deaths per year due to cardiovascular and respiratory diseases.[3,4] Several studies have reported an association between acute exposure to highly concentrated PM and development of cardiopulmonary dysfunction in humans and animals.[5,6,7,8,9]

Tunnel traffic has been used before to characterize single or well-defined mixtures of TRAP pollutants as well as associated health effects in humans and animals.[5,6,7,8,10] The new study, in contrast, examined health effects of chronic exposure to environmentally relevant doses of real-world TRAP. The animals' average exposures to fine PM roughly approximated the primary National Ambient Air Quality Standard of 12 $\mu g/m^3$ per day per year set by the U.S. Environmental Protection Agency (EPA).[11]

David Diaz-Sanchez, director of the Public Health and Integrated Toxicology Division at the EPA Center for Public Health and Environmental Assessment, says the inclusion of both males and females is another unique feature of this study. "Some epidemiological studies have looked at [sex-dependent differences on TRAP exposure effects], but their results are often confounded by lifestyle differences between men and women," notes Diaz-Sanchez, who was not involved in the study. "The majority of animal models and preclinical studies look at male data, so there is a real need to try to understand the differences between male and female responses."

For the new study, researchers created a vivarium beside a heavily traveled tunnel in Northern California, which allowed for collection and delivery of TRAP into chambers housing male and female rats. Starting at 4 weeks of age, animals were exposed continuously to either tunnel air or filtered air. After about 14 months, the investigators performed histological and biochemical assays to evaluate oxidative stress, inflammation, and fibrosis as markers of cardiopulmonary function.

Surprisingly, although lungs exposed to TRAP showed formation of black nodules, markers of pulmonary function were not affected. In contrast, cardiac dysfunction markers were elevated in hearts from both males and females exposed to TRAP. "The most important takeaway is that we see pathologic changes in the cardiorespiratory system after chronic exposure to levels of TRAP that are considered safe by the EPA," says senior author Pamela Lein, a professor in the Department of Molecular Biosciences at the University of California, Davis.



The confined air found in highway tunnels contains levels of TRAP comparable to daily exposures for people who commute or live near busy roads. Image: © ddisq/Shutterstock.

Moreover, there were strong sex differences in this response, with female hearts showing greater effects than male hearts. These findings are consistent with emerging epidemiologic data[12] that suggest women may be more susceptible to TRAP-related health effects and further support the relevance of this model to the human condition, Lein says.

Even though the study presented limitations such as small sample size and lack of direct assessment of cardiopulmonary function, it could open the door for mechanistic studies aimed at understanding the basis for the sex differences observed. Lein concludes that identifying the TRAP constituent that is driving these changes is the logical next step, as it will likely inform necessary changes to air quality regulatory guidelines.

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