

Road RAGE?

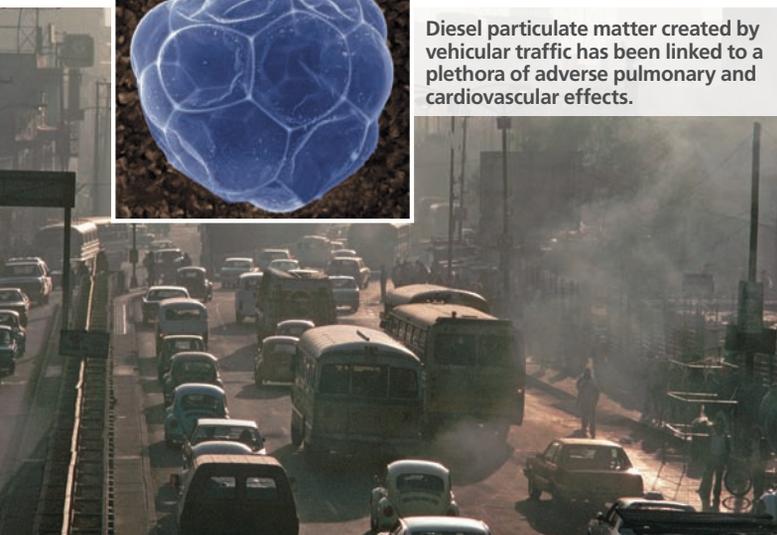
The Role of Diesel Particulate Matter in Lung Inflammation

Diesel particulate matter (DPM) is a nearly ubiquitous environmental pollutant. It is known to be inflammatory and is linked to a plethora of health effects including asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis. New research sheds light on which components of DPM are harmful to the lung and what mechanisms they trigger [*EHP* 119(3):332–336; Reynolds et al.].

The authors focused on receptors for advanced glycation end-products (RAGE), cell-surface proteins expressed in many cell types.

Previous research performed in the same laboratory documented that

Diesel particulate matter created by vehicular traffic has been linked to a plethora of adverse pulmonary and cardiovascular effects.



Climate Change and Children's Health

Protecting and Preparing Our Youngest

Climate change is expected to bring increased frequency and intensity of rainstorms, snowstorms, heat waves, and other extreme weather events. Numerous studies indicate climate change is already contributing to a greater overall burden of disease. A new review uses a children's health framework to summarize the latest data on the projected increasing burden of climate change–related disease for children [*EHP* 119(3):291–298; Sheffield and Landrigan]. The authors also discuss prevention strategies they believe should be incorporated into public health programs.

For 2000 the World Health Organization (WHO) estimated climate change contributed to more than 150,000 deaths and 5.5 million lost disability-adjusted life years worldwide. More than 88% of this burden occurs in children under age 5 years, even though the overall pediatric burden of disease is only 5% in high-income countries and 31% in low- and medium-income countries.

Children are inherently sensitive to the climate because they are physiologically and metabolically less effective than adults at adapting to heat and other climate-related exposures. Rapid development and higher exposures per unit of body weight make them more vulnerable to environmental exposures, and their diet and behavior may expose them to different agents than adults might typically encounter. More expected future years of life provides more time

RAGE can be activated in response to cellular stress resulting from exposure to particles in cigarette smoke. The authors hypothesized that exposure to DPM generated by fuel combustion could induce RAGE in the epithelial cells lining the lungs.

The team studied effects of DPM exposure in human primary pulmonary epithelial cells and R3/1 cells, an immortalized alveolar type 1 cell line derived from rats. They found that the quantities of *RAGE* messenger RNA and protein increased by approximately 100% in both cell types after exposure to DPM for 2 hours, compared with controls. By demonstrating that RAGE is indeed upregulated following exposure to DPM, the authors identified a surface signaling mechanism involved in inflammatory responses triggered by DPM exposure.

From there, the scientists identified some of the downstream signaling effects associated with RAGE upregulation. Their gene reporter experiments showed DPM exposure caused significant translocation of nuclear factor κ B (NF- κ B), a potent proinflammatory mediator, into the nucleus of R3/1 cells, where it can promote the expression of more than 200 genes. Through experiments involving the inhibition of RAGE with small interfering RNA (siRNA), the team confirmed that DPM-induced NF- κ B activation is mediated in part by RAGE expression.

The scientists also documented that exposure to DPM increased the synthesis and secretion of two NF- κ B targets (IL-8, a chemokine, and MCP-1, a cytokine) by the R3/1 cells. These molecules were secreted to a lesser extent, but were not completely inhibited, in cells transfected with siRNA for RAGE prior to DPM exposure, which suggests other factors and pathways also are involved in inflammatory responses to DPM.

The new research is also significant for contradicting conventional wisdom that only “fresh” DPM is biologically active. The work suggests that even “aged” DPM that has been suspended in the atmosphere for more than a decade is capable of biological activity, which has important public health implications given the abundance of this pollutant in the atmosphere.

Kellyn S. Betts has written about environmental contaminants, hazards, and technology for solving environmental problems for publications including *EHP* and *Environmental Science & Technology* for more than a dozen years.

for exposure to new or worsening hazards, and a dependence on caregivers means children can't always control their surroundings or remove themselves from harm.

In the current review, the authors analyzed health outcomes expected to result from increased temperatures, increasing frequency and severity of extreme weather, and sea-level rise. These include higher rates of vectorborne diseases such as malaria and dengue and of diarrheal disease, more exposure to extreme weather and to toxic chemicals (for instance, as weather changes affect patterns of pesticide use), and greater risks of poverty and of displacement due to sea-level rise, crop failure, and food insecurity. Other impacts include malnutrition and problems related to increased exposures to allergens and air pollution. Risk varies across socioeconomic levels and geographic locations.

The authors write that prevention strategies to help alleviate children's burden of disease should incorporate climate change adaptation into current programs as well as monitor children's exposures and environmental health indicators in a manner that is internationally consistent—as proposed by the WHO. They emphasize that new climate-sensitive disease-prevention programs should strive not only to protect children and parents in the short term but also prepare children to be resilient adults in the years to come. They also point to health impact assessments as an emerging tool to help shape smart policies that can solve multiple existing problems and head off future burdens.

Tanya Tillett, MA, of Durham, NC, is a staff writer/editor for *EHP*. She has been on the *EHP* staff since 2000 and has represented the journal at national and international conferences.

Not Just for Workers

Maternal Exposure to Ambient Benzene Linked to Spina Bifida in Infants

Occupational exposure to hazardous air pollutants such as benzene has been linked in some studies to neural tube defects (NTDs), yet to date no one had studied whether exposure to ambient levels of benzene may similarly lead to adverse outcomes. A new study now reveals a positive association between exposure to ambient benzene in outdoor air and increased prevalence of spina bifida [*EHP* 119(3):397–402; Lupo et al.].

NTDs are a common type of birth defect. They arise when the neural tube fails to close during fetal development, leading to spina bifida (incomplete spinal column formation) or anencephaly (incomplete brain and skull formation). Both genetic and environmental factors, particularly inadequate folic acid intake, appear to play a role in NTDs.

The Texas Birth Defects Registry provided data from 1 January 1999 to 31 December 2004 on 1,108 newborn infants, stillborn infants, and electively terminated fetuses with NTDs. A random set of 4,132 unaffected infants born during the same period served as a control group. Ambient air levels of benzene, toluene, ethylbenzene, and xylene were estimated at the census-tract level using the U.S. Environmental Protection Agency's 1999 Assessment System for Population Exposure Nationwide (ASPEN) paired with mothers' residential addresses at the time they gave birth. After exclusions for missing data and known

chromosomal abnormalities or syndromes, 533 spina bifida cases, 303 anencephaly cases, and 3,695 control cases remained for analysis.

Mothers with the highest estimated benzene exposure ($\geq 3 \mu\text{g}/\text{m}^3$ in ambient air) were 2.3 times as likely as mothers in the reference group to bear children with spina bifida. The relationship between benzene exposure and spina bifida was statistically significant for most levels of exposure above the reference value, but the dose–response relationship was not monotonic (that is, the odds of risk did not increase consistently with each increase in exposure level). Associations between other solvents and spina bifida and between individual solvents and anencephaly also were observed but were not statistically significant.

The study has several potential limitations including possible exposure misclassification, the availability of pollutant data for only 1 year of the study period, and limited information on potential confounders, such as maternal folic acid intake. However, these limitations are at least partially offset by ASPEN's high-quality exposure estimates, the likelihood that pollutant levels were stable during the study years, and mandatory folic acid fortification of foods.

This study is the first to suggest spina bifida prevalence is associated with maternal exposure to ambient air benzene levels. Further study of exposure, genotypes, and maternal nutrient status are needed to confirm this finding.

Julia R. Barrett, MS, ELS, a Madison, WI–based science writer and editor, has written for *EHP* since 1996. She is a member of the National Association of Science Writers and the Board of Editors in the Life Sciences.

A Whale Tale

Using Blubber Biopsies to Characterize Pacific Ocean Pollutant Trends

Expression of the enzyme CYP1A1 in the skin of marine mammals has been shown by multiple studies to indicate exposure to organic pollutants in a dose-dependent manner. A new large-scale monitoring study investigated whether analysis of dermal CYP1A1 expression and organic pollutants in sperm whales (*Physeter macrocephalus*) could reveal oceanwide geographical trends in chemical exposure [*EHP* 119(3):337–343; Godard-Coddig et al]. This is the first known study to assess broad geographic trends in CYP1A1 expression, stable carbon and nitrogen isotopes, and organic pollutant burdens in a threatened whale species.

The authors used immunochemistry to analyze CYP1A1 expression in skin and blubber samples collected from 234 sperm whales from five Pacific Ocean regions. Variation in the whales' trophic level (position in the food chain) was examined by using mass spectrometry to measure nitrogen isotopes in skin samples; enrichment of an animal's tissue nitrogen is known to occur as the animal eats higher on the food chain. The general latitude frequented by the whales—a reflection of where the whales were likely to have been exposed to pollution—was determined by analyzing carbon isotope ratios.

The whales exhibited significant regional differences in CYP1A1 expression. Expression was highest among whales from the Galapagos Islands, a United Nations World Heritage marine reserve, and lowest among whales from sites farthest away from continents. Differences in the whales' age, sex, and diet did not appear to explain regional differences but could not be ruled out unequivocally.

This study did not show a significant correlation between CYP1A1 expression in skin cells and actual pollutant burden in blubber, as measured by analyzing eight sex-specific pooled samples for burdens of polycyclic

aromatic hydrocarbons, hexachlorobenzene, polychlorinated biphenyls, and the pesticide DDT, then comparing them with CYP1A1 immunohistochemistry scores estimated for the pooled samples.

However, the small size of the individual biopsies allowed under standards for humane biopsying of marine mammals prevented detailed chemical analyses and limited the power to detect significant associations. Also, the biopsies were limited to the outer blubber layer, which is less metabolically active than deeper tissue. Studies in bottlenose dolphins have shown that CYP1A1 expression in the skin is more strongly related to pollutants measured in deeper blubber than in blubber closer to the skin surface; whether such stratification happens in other cetaceans requires further study.

The study succeeded at identifying regional differences in CYP1A1 expression, providing a baseline for this known biomarker of exposure to organic pollutants. Future studies that profile CYP1A1 expression in cetacean skin biopsies oceanwide are warranted to explore the global distribution of biochemically relevant levels of these chemicals.

Angela Spivey writes from North Carolina about science, medicine, and higher education. She has written for *EHP* since 2001 and is a member of the National Association of Science Writers.



Carnivorous sperm whales are at the top of their food chain.