# Small Particles with Big Effects

The Clean Air Act directs the Environmental Protection Agency (EPA) to promulgate National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) that are evidence-based and that protect the public health with "an adequate margin of safety," regardless of cost. The PM NAAQS, last revised in 1997, has recently been reviewed in a multi-year process, and initial recommendations for the next NAAQS were just made by the EPA. The latest proposal includes a slight tightening of the existing fine particle standard (for $PM_{2.5}$, i.e., particles $< 2.5$ μm in aerodynamic diameter) and the addition of a standard for coarse PM in urban areas in the size range $PM_{10-2.5}$. The new recommendations, however, are not as stringent as recommended by the Agency staff and the Clean Air Scientific Advisory Committee (CASAC), which provides peer review and guidance on the NAAQS. We call for, as has the American Thoracic Society, a more stringent NAAQS than Administrator Johnson's proposal.

The PM NAAQS has a central role in the management of air quality in the United States. Particles have multiple sources, both natural and related to human activities, and the consequences of a new NAAQS are potentially sweeping. Consequently, the PM NAAQS is of great interest to stakeholders that include affected industries, municipalities, environmental groups, and nongovernmental organizations, particularly the American Lung Association, and the public generally. Over the six-year process leading to the most recent proposal for revision of the NAAQS, there has again been substantial discussion and controversy concerning the new scientific evidence since the prior NAAQS and the extent to which key uncertainties have been addressed. The new evidence is substantial, in part because Congress called for a national research agenda on PM that was to be developed by the EPA with guidance from a committee of the National Research Council (1).

PM has now been linked to a broad range of adverse health effects, both respiratory and cardiovascular, in epidemiologic and toxicologic research. The diversity of effects may reflect the complexity of airborne PM, which is made up of a rich mixture of primary and secondary particles. Combustion sources—vehicles, power generation, and industry—are major contributors to urban PM. Monitoring data show that $PM_{2.5}$ differs in concentration and characteristics across regions of the country, within urban areas and by season. The U.S. median annual average $PM_{2.5}$ concentration is 13 $\mu g/m^3$ (range, 4–28 $\mu g/m^3$), with higher levels in urban areas and in the eastern United States and California. Physical and chemical properties of PM have been postulated to be determinants of toxicity: for example, metal content, oxidative potential, or being in the ultrafine size mode ($< 0.10$ μm). Consequently, management of sources of more toxic particles may be critical to public health and effects of PM on health may vary across the country.

The primary impetus for the 1997 PM NAAQS and the current proposed revision has been epidemiologic evidence that associates PM with increased risk for mortality (2). Time-series studies reported in the early 1990s showed that day-to-day variation in PM concentration was associated with mortality counts (3). These studies in selected cities have now been followed by national-level time-series analyses in the United States and Europe that pool data from broad regions to produce national estimates of the effect of PM on daily mortality. For example, in 90 U.S. cities, the National Morbidity and Mortality Air Pollution Study (NMMAPS) estimated a 0.2% increase of all-cause mortality per 10 $\mu g/m^3$ increase in $PM_{10}$ (4). Risk was highest in the northeast and for cardiovascular and respiratory causes of death. Findings of follow-up studies, including most notably the Harvard Six Cities Study (5) and the American Cancer Society's Cancer Prevention (CPS) II Study (6), show that the resulting loss of life may be substantial. The World Health Organization estimated that inhalation of PM in ambient air causes 500,000 premature deaths per year. The time-series studies show a linear relationship between PM concentration and risk at concentrations measured routinely in many U.S. cities (7).

There is a now a substantial, parallel literature on PM and morbidity. Studies have addressed PM and risk for hospitalization and other clinical outcomes and preclinical biomarkers (8). Since the 1997 PM NAAQS, there has been an explosion of research on cardiovascular consequences of exposure to PM (9) indicating short-term and long-term effects of PM on cardiovascular health.

Expanding toxicologic research indicates multiple mechanisms by which PM might cause disease. The evidence on $PM_{2.5}$ and cardiovascular health effects is illustrative of the complexity of underlying pathogenetic mechanisms (9): cardiovascular effects of PM exposure may result from systemic inflammation, autonomic effects, or accelerated atherosclerosis. Particles mobilize monocytes, band cells, and neutrophils from the bone marrow, elevate serum 1L-1β and IL-6, and upregulate endothelial adhesion molecules that recruit leukocytes into atherosclerotic plaques (10). After breathing $PM_{2.5}$ for 6 mo, ApoE atherosclerosis-prone knockout mice had an increased composite plaque area compared with controls breathing filtered air (11). In humans, a parallel association has been observed between carotid artery intimal medial layer thickening and estimated long-term exposure to particles (12). Effects of PM exposure on heart rate variability, an indicator of activity of the autonomic nervous system, have also been observed (9).

Numerous studies have shown that PM exposure activates inflammatory pathways in the respiratory system. For example, *in vitro* exposure of normal human bronchial epithelial (NHBE) cells stimulates release of oxidants, hemeoxygenase, cytokines, and upregulation of NF-κB (13). Experimental 2-h human exposures to PM increases the numbers of neutrophils in lavage fluid (14). Direct instillation of particles collected in an area where a smelter was a principal pollution source of $PM_{2.5}$ increased neutrophils, cytokines, and oxidant species on lung lavage of the exposed volunteers one day later (15). In healthy volunteers and volunteers with asthma, diesel exhaust particles increased airway hyperresponsiveness to methacholine, airway resistance, and bronchial tissue mast cell, neutrophil, and lymphocyte counts (16). Diesel particulate caused airway inflammation 6 h later and increased immunohistochemical staining for MAP kinases, NF-κB and AP-1. Simultaneous diesel exhaust and allergen exposure can mediate a Th2 switch.

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In the face of the extensive evidence on PM and health and the strong mandate of the Clean Air Act for public health protection, the PM NAAQS proposed by Administrator Johnson appear lax. Based on the same evidence, the American Thoracic Society and other health organizations have recommended 12 and 25 $\mu g/m^3$ for the average annual and 24-h $PM_{2.5}$ standards, respectively. The proposed, less stringent standard does not protect the nation's health, as required by the Clean Air Act.

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# Exhaled Breath Condensate pH

## Reflecting Acidification of the Airway at All Levels

Airway lining fluid acidification can and does affect airway function by numerous pathways, including damaging epithelial cells, enhancing oxidative injury, decreasing ciliary motility, altering inflammatory cell recruitment and function, and triggering cough and bronchospasm (1). Airway acidification occurs when gastric acid is aspirated (2), and is a likely mechanism of lung injury associated with chlorine gas inhalation (3), which symptomatically behaves much like acute asthma. Acidification is a common finding in inflamed fluids throughout the body, and it is reasonable to expect the same in the lung in asthma and other inflammatory airway diseases.

Obtaining direct data regarding airway lining fluid pH in health and, more particularly, in acute disease is fraught with difficulties arising from the poorly accessible and large surface area of the lungs, and the invasiveness of passing pH probes. Assays of the pH of exhaled breath condensate (EBC) therefore have been used in an attempt to overcome the nearly complete lack of understanding we have regarding this central, and therapeutically addressable, chemical characteristic of the airways and lungs. EBC can be collected safely even from critically ill patients, and EBC pH has been found to be low in multiple lung diseases.

As with any assay or procedure, caution is warranted regarding the interpretation of EBC pH, and there needs to be awareness of factors that can influence this measurement. That EBC acidification reflects lower respiratory tract disease is supported by several arguments: (*1*) low EBC pH is found in diseases of the lower airway and lung, such as asthma (4) and COPD (5), in which salivary acidification is not a known component; (*2*) low EBC pH is identified in samples collected from the isolated lower airway (6, 7) in endotracheally intubated, ill patients; and (*3*) EBC pH correlates with lower airway acidification measured directly by pH probe placed against the epithelium, at least in the cow (8).

It is clear that acidification of the airway at any level, including the hypopharynx, oropharynx, or tracheobronchial tree, could cause volatilization of acids that are then exhaled. In consideration of this potential for upper airway contamination, it is common practice to avoid collecting EBC samples within an hour of eating or drinking so as to prevent effects of acidic food or drink. In this issue of the *AJRCCM* (pp. 386–392), Effros and coworkers provide some data in an effort to directly support what was previously assumed: that salivary acids, in addition to lower airway acids, also could contribute to EBC acidification (9).

Exhaled breath passes through the hypopharynx and oropharynx unless there is an artificial airway. How can these portions of human anatomy then *not* have potential to contribute to exhaled breath assays? Certainly, if breath sampling were