

group together patients with similar clinical variables. Using this approach, they were able to identify five phenotypes of asthma that differed in multiple ways, including age of asthma onset, gender, body weight, degree of airflow limitation, reversibility of airflow limitation, and asthma exacerbation frequency. For example, one cluster was composed of patients with early onset atopic disease with normal lung function and little difficulty attaining asthma control; another cluster was composed of patients with an older age of onset, obesity, female gender, reversible airflow obstruction, and difficulty attaining asthma control. Yet another cluster had poorly reversible severe airflow obstruction, older age of onset, and a tendency to have systemic hypertension.

Although the authors used 34 clinical variables in their initial analysis, they showed that 80% of subjects could be assigned a cluster using just three variables: pre- and post-bronchodilator FEV<sub>1</sub>% predicted, and age of onset of asthma. In all clusters it was possible to find subjects who would have been classified as severe or treatment refractory by current ATS criteria, highlighting the limitations of currently used classification systems. The implication of these findings is that we can do better in how we use clinical variables to categorize asthma and that these better-defined disease categories may ultimately be shown to have identifiable molecular underpinnings that can be specifically treated. Other groups have previously used similar analytic approaches to identify clinical phenotypes of asthma in research datasets. For example, among a group of difficult to treat subjects with asthma, Haldar and colleagues (6) also found multiple clusters, including one cluster with early onset of asthma and prominent symptoms but minimal eosinophilia, and another cluster with late onset of asthma and minimal symptoms but prominent eosinophilia.

In terms of advancing the concept of disease heterogeneity in asthma, the studies by Moore and colleagues (5) and Haldar and colleagues (6) are steps in the right direction. These studies begin to organize our thinking about how clinical heterogeneity should be tackled, but it is difficult to review the data without being reminded that major deficits persist in our understanding of mechanisms of asthma, and that much work remains to be done. In particular, faster progress is needed to understand the different molecular mechanisms underlying the multiple clinical phenotypes of asthma that are beginning to be consistently identified. To date, the studies that have tackled issues of clinical heterogeneity have been relatively small, have used research databases collected for other purposes, and have had limited ability to assign molecular mechanisms to clinical phenotypes. Now is the time to scale up this clinical research approach significantly. There is a great opportunity to use better methods of disease classification to identify asthma phenotypes that are likely to cluster by causative mechanism. If comprehensive biospecimen analysis is included in careful patient phenotyping protocols, then the heterogeneity of clinical phenotypes can be leveraged to match inflammatory/molecular signatures to specific clinical

phenotypes. This approach should at least point to underlying disease mechanisms that can be further studied in human studies or in disease model systems.

The chronic obstructive pulmonary disease (COPD) community in the United States is beginning a major new project: the NHLBI-sponsored SPIROMICS (SubPopulations and Intermediate Outcome Measures In COPD Study) initiative. This multicenter collaboration supports the prospective collection and analysis of phenotypic, biomarker, genetic, genomic, and clinical data from subjects with COPD for the purpose of identifying subpopulations and intermediate-outcome measures. A strong argument can be made for a similar initiative in asthma, which should include an assessment of the response to currently available asthma treatments. This discovery strategy will compliment other research approaches to uncover unsuspected mechanisms of disease and increase the likelihood that we can ultimately provide personalized programs of care for our patients with asthma.

**Conflict of Interest Statement:** J.V.F. has received \$1,001–\$5,000 in consultant fees from each of the following: GlaxoSmithKline, Oxagen, Amira, Gilead, and Merck; \$5,001–\$10,000 for advisory board activities from Cytokinetics; more than \$100,000 in industry-sponsored grants from each of the following: Genentech, Boehringer Ingelheim, and Roche; and he has a patent pending related to a gene signature for Th2 high asthma.

JOHN V. FAHY, M.D., M.Sc.  
University of California  
San Francisco, California

## References

1. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007; 120:S94–S138.
2. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, Chu HW. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001–1008.
3. Berry M, Morgan A, Shaw DE, Parker D, Green R, Brightling C, Bradding P, Wardlaw AJ, Pavord ID. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007;62:1043–1049.
4. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180:388–395.
5. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, et al.; National Heart Lung and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–323.
6. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.

DOI: 10.1164/rccm.200911-1702ED

## A Second Chance Setting a Protective Ozone Standard

On March 12, 2008, the United States Environmental Protection Agency (EPA) revised the National Ambient Air Quality Standard (NAAQS) for ozone. The new, stricter standard of

0.075 ppm per 8 hours replaced the older standard of 0.084 ppm per 8 hours. Although this stricter standard would provide the basis for requiring reduced ambient ozone levels, it did not, in

our opinion, fulfill the mandate of the Clean Air Act to protect public health with an adequate margin of safety. The new standard fell well short of recommendations from the Clean Air Scientific Advisory Committee (CASAC), which recommended a new standard of between 0.060 and 0.070 ppm. The American Thoracic Society (ATS) and other professional medical organizations concerned with the health effects of air quality recommended a standard of 0.060 ppm per 8 hours. The EPA's decision was inconsistent with a substantial body of evidence from human studies conducted from the 1990s to the present demonstrating detrimental health effects of ozone exposure at levels well below 0.075 ppm per 8 hours.

Under the pressure of an impending lawsuit, the EPA requested an extension on court action to permit time for EPA officials appointed by the new administration to review the 2008 NAAQS ozone standard. Essentially, the EPA has a second chance to establish a public health protective NAAQS for ozone.

In September, 2009, the EPA issued their plan for reconsideration of the 2008 ozone NAAQS in which the agency proposed an assessment of "new" scientific and technical data developed and published since the last review in 2006–2007. However, the published plan is vague as to the full consideration of "new" data and how this will be incorporated in the rulemaking. The EPA prefers to allow "the new information adequate time to receive careful and comprehensive review by CASAC and the public before it is used as a basis... to revise the NAAQS" (1). This approach would potentially ignore recent compelling data that demonstrate adverse health effects of ozone exposures below the current standard. We would encourage the EPA to consider new reports published in peer-reviewed journals of human studies that assessed health effects of ozone exposure below the 2008 standard of 0.75 ppm per 8 hours.

On January 7, 2010, EPA released their proposal for revising the ozone standard. EPA has proposed a stricter primary standard to protect human health between 0.060 and 0.070 ppm per 8 hours.

A previous ATS editorial cited several studies from the early 1990s through 2007, when the editorial was published, that observed significant health risk at exposures below 0.075 ppm per 8 hours (2). Since then, additional studies have demonstrated health risk below the 2008 NAAQS for ozone. Jerrett and colleagues examined the effect of daily maximum ozone concentration on mortality and demonstrated a 2 to 4% increase in the risk of death from respiratory causes with each 10 ppb increase in ozone concentration, and presented evidence suggestive of a threshold at 56 ppb (3). A recent study in healthy, exercising young adults found that inhalation of 70 ppb ozone for 6.6 hours induced statistically significant decreases in FEV<sub>1</sub> (4). Concerns about increased risk to sensitive populations, particularly children or individuals with asthma, were again identified in a study by Sousa and colleagues (2009) that showed increased incidence of asthma symptoms in children living where ozone levels were in the range of 50 to 60 ppb compared with those living where ozone levels were lower (5). Ozone exposures continue to be of concern at both ends of the age spectrum: in children and the elderly.

Recent studies have provided additional evidence that children and elderly adults with preexisting respiratory disease are especially susceptible (6, 7). An investigation of the effect of ozone on hospitalizations in Finland showed the greatest impact among young children with asthma and elderly individuals with asthma and COPD (8). Other studies have found ambient ozone concentration-related exacerbations of asthma in children (7, 9, 10). A very large (n =

1,204,396) birth cohort study of children under the age of 6 years in New York State found that chronic ozone exposure was significantly associated with asthma hospital admissions (odds ratios, 1.16–1.68) and that this effect was strongest among very young children (7). Risks of hospital admissions increased 22% with a 1 ppb increase in mean ozone concentration during the ozone season (April to October). Effects were observed at mean ozone concentrations greater than 37.3 ppb in New York City during the follow-up period. Another study found that for children in California a near twofold increase in the odds of daily/weekly symptoms in children with asthma for each 10 ppb increase in annual average ozone concentration (11).

Although it is clear that ozone exacerbates already existing respiratory disease, what is especially disturbing is the possibility that ozone can increase the incidence of diseases such as allergies and asthma. There is the potential for early exposures to ozone to cause long-term disruption of normal lung and immune system growth. This has been well established for new onset asthma in studies noted in our previous editorial (2). However, now we have the first hints that this is also true for allergies. Parker and colleagues found in a cross-sectional study of more than 73,000 children, 3–17 years of age, that reports of respiratory allergy and hay fever were significantly associated with increased summer ozone levels (12).

Second chances are rare and should not be wasted. That is why the ATS has again urged the EPA to adopt a protective NAAQS for ozone of 0.060 ppm per 8-hour standard. As a growing body of evidence shows, such a standard is needed to protect the public from the known adverse health effects of ozone.

**Conflict of Interest Statement:** R.D. has no financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.V.W. has received up to \$1,000 from McGraw Hill Publishing in royalties; she holds \$50,001–\$100,000 in Amgen stock; she has received over \$100,000 in sponsored grants from NIH, CARB, FAMRI, TRDRP; she has received over \$100,000 in consultancy fees and sponsored grants from US EPA. G.E. is employed by the American Thoracic Society, which receives funding from for-profit organizations; he owns \$1,001–\$5,000 of Pfizer stock. J.B. has received \$10,001–\$50,000 from CA Air Resources Board, and \$1,001–\$5,000 from US EPA for advisory board activities. K.P. has received over \$100,000 from AstraZeneca in grants; he received over \$100,000 from Phillip Morris in sponsored grants between 2004 and 2007 (for research in an animal model of COPD).

RICHARD DEY, PH.D.  
*Department of Neurobiology and Anatomy*  
*West Virginia University*  
*Morgantown, West Virginia*

LAURA VAN WINKLE, PH.D., D.A.B.T.  
*Center for Health and the Environment*  
*University of California, Davis*  
*Davis, California*

GARY EWART, M.H.S.  
*Director of Government Relations,*  
*American Thoracic Society*  
*Washington, D.C.*

JOHN BALMES, M.D.  
*Lung Biology Center*  
*University of California, San Francisco*  
*San Francisco, California*

KENT PINKERTON, PH.D.  
*Center for Health and the Environment*  
*University of California, Davis*  
*Davis, California*

## References

1. Environmental Protection Agency. Integrated review plan for the ozone national ambient air quality standards review: external review draft. Research Triangle Park, NC: National Center for Environmental Assessment, Office of Research and Development and Office of Air Quality Planning and Standards; 2009. US EPA (EPA 452/D-09-001) 1–78.
2. Pinkerton KE, Balmes JR, Fanucchi MV, Rom WN. Ozone, a malady for all ages. *Am J Respir Crit Care Med* 2007;176:107–112.
3. Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085–1095.
4. Schelegle ES, Morales CA, Walby WF, Marion S, Allen RP. 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. *Am J Respir Crit Care Med* 2009;180:265–272.
5. Sousa SI, Alvim-Ferraz MC, Martins FG, Pereira MC. Ozone exposure and its influence on the worsening of childhood asthma. *Allergy* 2009; 64:1046–1055.
6. Villeneuve PJ, Chen L, Rowe BH, Coates F. Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada. *Environ Health* 2007;6:40.
7. Lin S, Liu X, Le LH, Hwang SA. Chronic exposure to ambient ozone and asthma hospital admissions among children. *Environ Health Perspect* 2008;116:1725–1730.
8. Halonen JI, Lanki T, Tiittanen P, Niemi JV, Loh M, Pekkanen J. Ozone and cause-specific cardiorespiratory morbidity and mortality. *J Epidemiol Community Health* 2009; Oct 23. [Epub ahead of print] PMID: 19854743.
9. Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, Tager I. Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California. *Environ Health Perspect* 2008;116:1063–1070.
10. Yamazaki S, Shima M, Ando M, Nitta H. Modifying effect of age on the association between ambient ozone and nighttime primary care visits due to asthma attack. *J Epidemiol* 2009;19:143–151.
11. Wilhelm M, Meng YY, Rull RP, English P, Balmes J, Ritz B. Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. *Environ Health Perspect* 2008;116:1254–1260.
12. Parker JD, Akinbami LJ, Woodruff TJ. Air pollution and childhood respiratory allergies in the United States. *Environ Health Perspect* 2009;117:140–147.

DOI: 10.1164/rccm.201001-0032ED