Author Disclosure: The author does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

> MANUELA CERNADAS, M.D. Brigham and Women's Hospital Harvard Medical School Boston, Massachusetts

References

- Endt K, et al. The microbiota mediates pathogen clearance from the gut lumen after non-typhoidal Salmonella diarrhea. PLoS Pathog 2010;6.
- Oyama N, Sudo N, Sogawa H, Kubo C. Antibiotic use during infancy promotes a shift in the T(H)1/T(H)2 balance toward T(H)2-dominant immunity in mice. J Allergy Clin Immunol 2001;107:153–159.
- Huang YJ, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. J Allergy Clin Immunol 2011;127:372–381.
- Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci USA* 2010;107:12204–12209.
- Leech MD, Benson RA, De Vries A, Fitch PM, Howie SE. Resolution of Der p1-induced allergic airway inflammation is dependent on CD4+CD25+Foxp3+ regulatory cells. J Immunol 2007;179:7050–7058.
- Round JL, et al. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 2011;332:974–977.

- Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* 2004;118:229–241.
- Sung SS, *et al.* A major lung CD103 (alphaE)-beta7 integrin-positive epithelial dendritic cell population expressing Langerin and tight junction proteins. *J Immunol* 2006;176:2161–2172.
- Jakubzick C, *et al.* Blood monocyte subsets differentially give rise to CD103+ and CD103- pulmonary dendritic cell populations. *J Immunol* 2008;180:3019–3027.
- Rescigno M, *et al.* Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. *Nat Immunol* 2001;2:361–367.
- Annacker O, et al. Essential role for CD103 in the T cell-mediated regulation of experimental colitis. J Exp Med 2005;202:1051–1061.
- 12. Hintzen G, *et al.* Induction of tolerance to innocuous inhaled antigen relies on a CCR7-dependent dendritic cell-mediated antigen transport to the bronchial lymph node. *J Immunol* 2006;177:7346–7354.
- de Heer HJ, *et al.* Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. *J Exp Med* 2004;200:89–98.
- Macpherson AJ, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science* 2004;303:1662–1665.
- Wei B, et al. Commensal microbiota and CD8+ T cells shape the formation of invariant NKT cells. J Immunol 2010;184:1218–1226.

DOI: 10.1164/rccm.201105-0828ED

Ozone Air Pollution: How Low Can You Go?

A new human clinical study of the respiratory effects of exposure to ozone appeared in a recent issue of the *Journal* (1). Fifty-nine healthy young adults breathed clean air and 0.06 ppm ozone, on separate occasions, for 6.6 hours with intermittent exercise. In comparison with clean air exposure, the mean FEV_1 decreased following ozone exposure a small but statistically significant 1.75%, and the percentage of neutrophils in induced sputum, collected the morning after exposure, increased 15.7%. Neither lung function change nor inflammation was affected by presence of the glutathione-S-transferase null gene polymorphism.

Why does this article warrant space in the premier respiratory journal? We already know that breathing ozone while exercising can cause airway inflammation (2) and decrements in lung function (3) in susceptible people, and that these effects appear to be independent of each other (2, 4). Responsiveness to ozone is quite variable among people, but reproducible within individuals. With repeated daily exposures, the declines in FEV₁ and the increases in airway neutrophils are attenuated, but other markers of airway inflammation and injury persist or increase, including neutrophils in airway mucosal biopsies (5). Smokers experience minimal lung function effects (6), but remain susceptible to the airway inflammatory effects (2). Genetic differences in antioxidant protective mechanisms have been hypothesized to contribute to susceptibility (7). There is increasing evidence that ozone may adversely affect the cardiovascular system (8); the Health Effects Institute has recently funded a multicenter clinical study of the acute cardiovascular effects of ozone exposure in elderly people (9). The importance of the study by Kim and colleagues in this issue lies, not in any new mechanistic insights, but in its regulatory impact: it demonstrates health effects at an exposure concentration that is

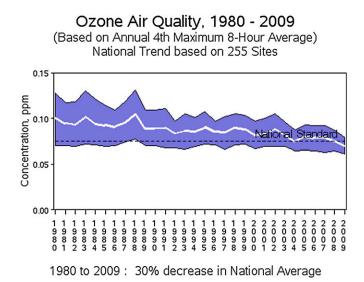
well below the current U.S. National Ambient Air Quality Standard (NAAQS) of 0.075 ppm over 8 hours.

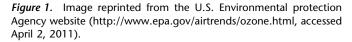
The history of ozone regulation has been one of ever-tightening standards based on findings of health effects at ever-lower levels, punctuated by controversy and lawsuits. Implementation of emission control technologies has been successful, and ozone air pollution has been getting better in the United States, the result of reduced emissions of precursor pollutants that drive tropospheric ozone formation. As shown in Figure 1, average ozone concentrations have declined 30% over the past 30 years. However, much of the U.S. population resides in communities that fail to comply with the current standard, and compliance will worsen if the standard is tightened further.

The Clean Air Act was passed in 1970 (10), mandating the establishment of air quality standards "...allowing an adequate margin of safety... to protect the public health." The EPA first specified a 1-hour NAAQS for ozone of 0.12 ppm in 1979 (11). In 1991, amid increasing evidence of health effects below 0.12 ppm, the American Lung Association went to court to compel the EPA to lower the standard. The EPA published an ozone criteria document in 1996, finding strong evidence of adverse health effects below 0.12 ppm. In 1997 the EPA revised the ozone NAAQS, setting an 8-hour standard at 0.08 ppm. This was challenged in court by industry and some states. The case found its way in 2001 to the U.S. Supreme Court, which upheld the constitutionality of the Clean Air Act, and reaffirmed that the EPA must set standards based solely on public health considerations, without consideration of costs.

The most recent scientific review by the EPA of ozone health effects was completed in 2006 (12). The Clean Air Scientific Advisory Committee (CASAC) unanimously recommended to the EPA, based on the scientific review and in concurrence with the recommendations in the EPA staff paper in 2007, that a new 1-hour standard be established in the range of 0.060 to 0.070 ppm. In a break with tradition, rather than choosing a level within the

Supported by grants R01ES017428 and RC1ES018519 from the National Institutes of Health.





range recommended by CASAC and the EPA's own staff, former Administrator Steven L. Johnson promulgated a new ozone 8hour standard of 0.075 ppm. This triggered more litigation. Now with a different administration in the White House and a new EPA Administrator, the ozone standard is being reconsidered, based on the scientific review completed in 2006. CASAC has reaffirmed concurrence with an ozone standard in the range of 0.060 to 0.070 ppm (13), while recognizing that ever tighter standards create more problems with implementation. Given the new evidence presented in this issue, it seems likely that the ozone NAAQS will need to go even lower following the next EPA review cycle, to comply with the legislative requirements of the Clean Air Act. The problem: it may not be possible to achieve an "adequate margin of safety." The scientific evidence suggests that, for ozone at least, there may be no identifiable safe threshold concentration.

Further tightening of the standard would be costly. Attempts to achieve compliance would require major reductions in emissions of precursor air pollutants, with increased costs to industry and transportation sectors at a time of high unemployment and a fragile economic recovery. More importantly, the science is telling us we need to rethink how we regulate air pollution. The authors of the Clean Air Act made an assumption that seemed reasonable at the time, that there is a safe threshold concentration for air pollutants, below which there are no significant health effects, even for the most susceptible groups. However, more sophisticated and targeted studies, including those reported by Kim and colleagues in this issue, are demonstrating effects at lower and lower ambient concentrations.

We can never make our air completely free of air pollutants. There is a background tropospheric ozone level in North America that is not related to local human activities (14). This background ozone comes from lightning strikes, emissions from vegetation, stratospheric intrusions, and transport from other continents. The EPA has estimated the "policy relevant" background level for North America to be between 0.015 and 0.045 ppm. As the ozone NAAQS gets closer to background concentrations, the regulatory burdens and cost of control implementation increase exponentially, while the health benefits of further reductions decrease. NAAQS compliance becomes a near impossibility for many communities.

We need to balance the health benefits with the economic and welfare costs of regulation, to allocate resources to maximize benefits. We need to consider new regulatory approaches in achieving the cleanest air possible and minimizing harm. One example is the "multipollutant approach," which was discussed in a previous editorial in the *Journal* (15). Continuing to reduce the ozone NAAQS to concentrations that are unattainable threatens the effectiveness of, and regard for, the regulatory process. Maybe it's time to reconsider the way we regulate criteria pollutants, and rewrite the Clean Air Act.

Author Disclosure: M.W.F. has received consultancy fees from the Health Effects Institute and from the American Petroleum Institute; his institution has received grants from the Health Effects Institute, the Environmental Protection Agency, and Exxon-Mobil.

Acknowledgment: Dr. Mark Utell (University of Rochester Medical Center) reviewed a draft of this editorial and provided helpful comments.

MARK W. FRAMPTON, M.D. Departments of Medicine and Environmental Medicine University of Rochester Medical Center Rochester, New York

References

- Kim CS, Alexis NE, Rappold AG, Kehrl H, Hazucha MJ, Lay JC, Schmitt MT, Case M, Devlin RB, Peden DB, *et al.* Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *Am J Respir Crit Care Med* 2011;183:1215–1221.
- Torres A, Utell MJ, Morrow PE, Voter KZ, Whitin JC, Cox C, Looney RJ, Speers DM, Tsai Y, Frampton MW. Airway inflammation in smokers and nonsmokers with varying responsiveness to ozone. *Am J Respir Crit Care Med* 1997;156:728–736.
- McDonnell WF, Smith MV. Description of acute ozone response as a function of exposure rate and total inhaled dose. J Appl Physiol 1994;76:2776–2784.
- Balmes JR, Chen LL, Scannell C, Tager I, Christian D, Hearne PQ, Kelly T, Aris RM. Ozone-induced decrements in FEV₁ and FVC do not correlate with measures of inflammation. *Am J Respir Crit Care Med* 1996;153:904–909.
- Jörres RA, Holz O, Zachgo W, Timm P, Koschyk S, Müller B, Grimminger F, Seeger W, Kelly FJ, Dunster C, et al. The effect of repeated ozone exposures on inflammatory markers in bronchoalveolar lavage fluid and mucosal biopsies. Am J Respir Crit Care Med 2000;161:1855–1861.
- Frampton MW, Morrow PE, Torres A, Cox C, Voter KZ, Utell MJ. Ozone responsiveness in smokers and nonsmokers. *Am J Respir Crit Care Med* 1997;155:116–121.
- Bauer AK, Kleeberger SR. Genetic mechanisms of susceptibility to ozone-induced lung disease. Ann N Y Acad Sci 2010;1203:113–119.
- 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.
- 9. Health Effects Institute. New multicenter ozone study. HEI Update. Boston, MA; Winter 2010–2011. p. 8.
- Clean air act. U S C 42: § § 7408–7409; 1970. (Accessed April 3, 2011.) Available from: http://www.law.cornell.edu/uscode/42/ch85.html.
- US EPA. History of Ground-level Ozone Standards. 2011. (Accessed April 3, 2011.) Available from: http://www.epa.gov/groundlevelozone/history. html.
- US EPA. Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 Final). Document number: EPA/600/R-05/004aF-cF. US Environmental Protection Agency, Washington, DC, 2006.
- US EPA Clean Air Scientific Advisory Committee (CASAC). Final Reports by Fiscal Year. 2010. (Accessed April 3, 2011.) Available from: http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYear CASAC!OpenView.
- McClellan RO, Frampton MW, Koutrakis P, McDonnell WF, Moolgavkar S, North DW, Smith AE, Smith RL, Utell MJ. Critical considerations in evaluating scientific evidence of health effects of ambient ozone: a conference report. *Inhal Toxicol* 2009;21:1–36.
- Vedal S, Kaufman JD. What does multi-pollutant air pollution research mean? Am J Respir Crit Care Med 2011;183:4–6.

DOI: 10.1164/rccm.201104-0606ED