Pollutants and Asthma: Role of Air Toxics

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Asthma is a disease characterized by intermittent bronchoconstriction due to increased airway reactivity to both allergic and nonallergic stimuli. Most asthma exacerbations that result in hospitalization are associated with viral upper respiratory tract infections. Such infections typically induce T-helper type 1 (T_H1) responses in the airway, involving activation of nuclear factor-kappaB (NF-κB). However, a more recently appreciated cause of asthma exacerbation is exposure to pollutants, including ozone and various components of particulate matter (PM), including transition metals, diesel exhaust, and biologicals such as endotoxin. Although the role of air toxics in asthma pathogenesis remains incompletely examined, many components of PM that are active exacerbants of asthma are also prominent air toxics (metal ions and organic residues). These agents have been observed to activate NF-κB. Reviewed in this article are the actions of specific air pollutants on airway inflammation in humans and potential common response pathways for ozone, PM, and several air toxics. ***Key words:*** **air toxics, asthma, exacerbation, T_H1, T_H2.** ***Environ Health Perspect*** **110(suppl 4):565–568 (2002).**
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Asthma is a disease characterized by intermittent bronchoconstriction due to increased airway reactivity to both allergic and nonallergic stimuli. Underlying these phenomena is a chronic, eosinophilic airway inflammation. Perhaps the most common and significant risk factor for development of asthma in children is induction of an immunoglobulin E (IgE; allergic) response against indoor allergens (*1,2*). However, nonallergic stimuli, which do not directly interact with IgE, are common causes of asthma exacerbation. Asthmatic individuals have been identified as a population that is especially sensitive to the effect of ambient air pollutants. Although pollutants might enhance IgE-mediated chronic inflammation via T-helper type 2 (T_H2) processes, they more likely induce exacerbation of asthma. Indeed, many pollutants associated with asthma exacerbation induce neutrophilic inflammation in nonallergic subjects.

Viral infections and pollutants typically induce T_H1-type responses in the airway, involving activation of nuclear factor-kappaB (NF-κB). Yet in asthmatic individuals, these processes may also exacerbate eosinophilic inflammation. This observation suggests that chronic allergic airway inflammation may modify the response to nonallergic stimuli, thus magnifying the impact of such agents. The agents more commonly examined for asthma exacerbation are criteria air pollutants, such as ozone and particulate matter (PM). The role of air toxics in asthma has not been vigorously examined, despite the frequency in which they are encountered. However, many of the agents identified in PM can also be considered air toxics and demonstrate that this important class of pollutants likely has a significant impact on asthma. Reviewed in this article are studies that exemplify the impact of ozone, particulates, and toxic components of particulates on asthma.

Ozone and Asthma

Epidemiologic studies clearly demonstrate that increases in ambient air ozone are linked with increased occurrence of acute asthma exacerbations. Markers for such events, including increased hospitalizations and emergency room visits, are usually noted 24 hr after the increase in inflammation, suggesting that inflammation may play a role in such events (*3–8*). During the 1996 Summer Olympic games, an effort to decrease automobile traffic in Atlanta, Georgia, resulted in decreases in ambient ozone levels. Asthma exacerbations decreased as well, again demonstrating a link between ambient ozone levels and asthma exacerbations (*9*).

Exposure to ozone is known to induce increases in airway inflammation (*10–12*). In asthmatic individuals, the effect of ozone exposure is exaggerated, resulting in either increased neutrophilic inflammation (*13–15*) or an augmentation of eosinophilic inflammation (*16,17*). In addition to asthmatic individuals being more sensitive to ozone per se, ozone appears to augment both the immediate and late-phase response to allergens. Initially, Molfino and colleagues (*18*) described increased sensitivity to inhaled allergen after exposure to a relatively low level of ozone (0.12 ppm for 2 hr). Although other studies examining this dose of ozone do not reveal such an effect (*19*), higher levels of ozone clearly enhance the immediate effect of inhaled allergen on bronchoconstriction (*20,21*). Nasal challenge studies also demonstrate that ozone exposure might enhance the late-phase response to allergen (*22,23*). Thus, persons with allergic inflammation of the airway are differentially susceptible to the effect of ozone, an agent that in nonallergic subjects induces neutrophilic inflammation (*24–26*).

Toxic Components of Particulate Matter and Asthma

Particulate matter is an important pollutant and is associated with increased morbidity and mortality (*24,27–30*). PM is also associated with increased disease severity in asthma (*31–33*). Indeed, increased admissions to hospital for asthma are linked to increased PM exposure, as are decreased peak flow measurements in children (*31,34,35*). An interesting study in the Utah Valley, Utah, showed a marked decrease in admissions to hospital for asthma and respiratory tract illnesses when a local steel mill was closed, with subsequent increase in such events when it reopened (*32,33*).

Although a clear mechanism for the action of PM in asthma exacerbation has not been identified, studies with model pollutants, including residual oil fly ash (ROFA) and Utah Valley dust (UVD) particles, suggest that PM enhances T_H1-like, neutrophilic inflammation. Many of the active agents in various PM species also fall into the broad category of air toxics. ROFA is a potent proinflammatory agent that has oxidant activity, likely mediated by vanadium species and nickel (*36–40*). UVD is another PM in which its biological activity is associated with metal content and oxidant character (*41–44*). Diesel exhaust particles (DEPs) contain polyaromatic aromatic hydrocarbons. Each of these PM components can be considered air toxics. The specific impact of these agents in humans is outlined below.

ROFA particles have been shown *in vitro* to affect prostaglandin metabolism and induce cytokine production in epithelial cells (*45–48*). Animal studies have also demonstrated that ROFA is associated with increased

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neutrophilic airway inflammation (*49*). Animal studies also show that ROFA can exacerbate allergic inflammation in mice and that it enhances sensitization to allergens in a rat model (*50–52*).

UVD has also been shown to induce airway inflammation in animal studies and to induce proinflammatory changes in epithelial cells *in vitro.* Perhaps most intriguing is the decreased effect of UVD particles collected during the time that the local steel mill was closed (*44,53,54*). In humans, instillation of extracts made from UVD collected during the years the mill was open versus those collected when it was closed was consistent with animal and *in vitro* studies demonstrating that influx of neutrophils was associated with dust collected during active years and was blunted in extracts made from UVD collected during a year the mill was closed (*42*). Humans exposed to concentrated ambient air particles also show subtle evidence of increased respiratory tract inflammation (*43*). Thus, it seems clear that PM can induce inflammation, not unlike ozone. This proinflammatory effect of PM may account for its ability to exacerbate asthma.

Diesel exhaust and resultant DEPs are also an interesting component of PM. Human challenge studies with diesel exhaust reveal increases in airway inflammation, including increases in airway neutrophils and mast cells (*55–57*). Diesel exhaust exposure has been shown to enhance nonspecific airway reactivity in asthmatic individuals as well (*58*). DEPs, in nasal instillation studies, have been shown to induce increases in total and antigen-specific IgE, increase cellular response to nasally applied allergen, and enhance production of T_H2 cytokines such as interleukin (IL)-4 and IL-13 (*59–64*). DEPs also enhance sensitization to a neoantigen, keyhole limpet hemocyanin (KLH), such that antigen-specific IgE against KLH is generated (*65*). *In vitro* studies suggest that the active agents in DEPs that affect IgE production are polyaromatic hydrocarbons (*66*). Animal studies also demonstrate that polyaromatic hydrocarbons enhance IgE production in animals via actions on B lymphocytes (*67*). Taken together, these data suggest that diesel particles and DEPs may play a significant role not only in asthma exacerbation but also in T_H2 inflammation via the actions of polyaromatic hydrocarbons on B lymphocytes.

Endotoxin and Asthma

Endotoxin is a common component of PM and is also encountered in domestic (*68,69*) and occupational settings (*70,71*). A number of studies have demonstrated increased airway symptoms in workers who encounter high levels of endotoxin in the workplace (*70,72–77*). Endotoxin is known to stimulate innate immune responses that have a T_H1-type character (neutrophilic inflammation, lack of IL-4 and IL-13). Endotoxin induces neutrophilic airway inflammation in nonallergic, nonasthmatic volunteers (*78–85*). This agent also has been found to enhance nonspecific airway reactivity in asthmatic individuals (*86–88*).

Recent studies suggest that endotoxin may be a factor in increasing asthma morbidity and wheeze (*89,90*). Conversely, exposure to endotoxin at a very young age may protect against development of allergic responses to allergens (*68*). However, in persons with ongoing allergic inflammation, the degree of allergic inflammation, as determined by enumeration of airway eosinophils, appears to correlate with increased response to endotoxin (*91*). Allergen challenge enhances expression of CD14, an important endotoxin receptor, in asthmatic individuals (*92–94*) and enhances nasal inflammatory responses to endotoxin, including increases in neutrophils and eosinophils (*95*). Treatment of asthmatic individuals with corticosteroids blunts response to endotoxin and decreases CD14 expression in the airway (*96*). Taken together, these observations suggest that allergic inflammation modifies the response to endotoxin, enhancing the impact of this agent on asthma symptoms and morbidity.

Potential Common Mechanisms

Each of the pollutants outlined above can induce neutrophilic inflammation. NF-κB is a key aspect of such activation. Ozone has been shown to activate NF-κB in epithelial cells (*97*) and to induce this transcription factor *in vivo* in animal respiratory tissue (*98,99*). This activation is blunted by treatment with corticosteroids. Metal ions and diesel exhaust also appear to induce NF-κB (*48*). Endotoxin is a classic stimulus for NF-κB activation (*100*). Signal transduction of endotoxin after it binds to the CD14 cell surface depends on interaction with the toll-like receptor (TLR) 4. An intriguing linkage between TLR 4, a key receptor for endotoxin, and the action of ozone suggests that TLR4 (or other similar membrane-spanning molecules) may mediate the ultimate activation of NF-κB by ozone as well (*101,102*). Future studies on the effect of environmental stimuli in exacerbating asthma should examine potential common response elements such as the TLR 4, which may mediate the effect of a number of apparently disparate pollutants.

Summary

This article has outlined some of the examined effects of ozone, PM, and biological agents on asthma exacerbation. The role of air toxics, an important and commonly encountered air pollutant, in asthma has not been aggressively studied. Its potential importance is demonstrated by studies of PM in which the active agents are biologically active metal ions and organic residues, both of which can be considered air toxics. This class of compounds may have significant effects on asthma, especially modulating immune function, as demonstrated by the role of polyaromatic hydrocarbons from diesel exhaust in IgE production. Examination of the effect of air toxics in asthma as they exist either in gas, vapor, or particulate form warrants further study.

References and Notes

1. Busse WW, Lemanske RF Jr. Asthma. N Engl J Med 344:350–362 (2001).
2. Gern JE, Lemanske RF Jr, Busse WW. Early life origins of asthma. J Clin Invest 104:837–843 (1999).
3. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology 12:200–208 (2001).
4. Tolbert PE, Mulholland JA, MacIntosh DL, Xu F, Daniels D, Devine OJ, Carlin BP, Klein M, Dorley J, Butler AJ, et al. Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia, USA. Am J Epidemiol 151:798–810 (2000).
5. Romieu I, Meneses F, Ruiz S, Huerta J, Sienra JJ, White M, Etzel R, Hernandez M. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch Environ Health 52:368–376 (1997).
6. Romieu I, Meneses F, Ruiz S, Sienra JJ, Huerta J, White MC, Etzel RA. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am J Respir Crit Care Med 154:300–307 (1996).
7. Romieu I, Meneses F, Sienra-Monge JJ, Huerta J, Ruiz VS, White MC, Etzel RA, Hernandez-Avila M. Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. Am J Epidemiol 141:546–553 (1995).
8. White MC, Etzel RA, Wilcox WD, Lloyd C. Exacerbations of childhood asthma and ozone pollution in Atlanta. Environ Res 65:56–68 (1994).
9. Perkins RC, Scheule RK, Hamilton R, Gomes G, Freidman G, Holian A. Human alveolar macrophage cytokine release in response to in vitro and in vivo asbestos exposure. Exp Lung Res 19:55–65 (1993).
10. Koren HS. Environmental risk factors in atopic asthma. Int Arch Allergy Immunol 113:65–68 (1997).
11. Koren HS. Associations between criteria air pollutants and asthma. Environ Health Perspect 103(suppl 6):235–242 (1995).
12. Koren HS, Bromberg PA. Respiratory responses of asthmatics to ozone. Int Arch Allergy Immunol 107:236–238 (1995).
13. Scannell C, Chen L, Aris RM, Tager I, Christian D, Ferrando R, Welch B, Kelly T, Balmes JR. Greater ozone-induced inflammatory responses in subjects with asthma. Am J Respir Crit Care Med 154:24–29 (1996).
14. Balmes JR, Aris RM, Chen LL, Scannell C, Tager IB, Finkbeiner W, Christian D, Kelly T, Hearne PQ, Ferrando R, et al. Effects of ozone on normal and potentially sensitive human subjects. Part I: Airway inflammation and responsiveness to ozone in normal and asthmatic subjects. Res Rep Health Eff Inst 78:1–37 (1997).
15. Basha MA, Gross KB, Gwizdala CJ, Haidar AH, Popovich J Jr. Bronchoalveolar lavage neutrophilia in asthmatic and healthy volunteers after controlled exposure to ozone and filtered purified air. Chest 106:1757–1765 (1994).
16. Peden DB, Boehlecke B, Horstman D, Devlin R. Prolonged acute exposure to 0.16 ppm ozone induces eosinophilic airway inflammation in asthmatic subjects with allergies. J Allergy Clin Immunol 100:802–808 (1997).
17. Frampton MW, Balmes JR, Cox C, Krein PM, Speers DM, Tsai Y, Utell MJ. Effects of ozone on normal and potentially sensitive human subjects. Part III: Mediators of inflammation in bronchoalveolar lavage fluid from non-

smokers, smokers, and asthmatic subjects exposed to ozone: a collaborative study. Res Rep Health Eff Inst 78:73–79 (1997).
18. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, Szalai JP, Raizenne M, Slutsky AS, Zamel N. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 338:199–203 (1991).
19. Ball BA, Folinsbee LJ, Peden DB, Kehrl HR. Allergen bronchoprovocation of patients with mild allergic asthma after ozone exposure. J Allergy Clin Immunol 98:563–572 (1996).
20. Jorres R, Nowak D, Magnussen H. The effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. Am J Respir Crit Care Med 153:56–64 (1996).
21. Kehrl HR, Peden DB, Ball B, Folinsbee LJ, Horstman D. Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. J Allergy Clin Immunol 104:1198–1204 (1999).
22. Bascom R, Naclerio RM, Fitzgerald TK, Kagey-Sobotka A, Proud D. Effect of ozone inhalation on the response to nasal challenge with antigen of allergic subjects. Am Rev Respir Dis 142:594–601 (1990).
23. Peden DB, Setzer RW Jr, Devlin RB. Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics. Am J Respir Crit Care Med 151:1336–1345 (1995).
24. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. Am J Respir Crit Care Med 153:3–50 (1996).
25. Koren HS, Devlin RB, Graham DE, Mann R, McGee MP, Horstman DH, Kozumbo WJ, Becker S, House DE, McDonnell WF. Ozone-induced inflammation in the lower airways of human subjects. Am Rev Respir Dis 139:407–415 (1989).
26. Devlin RB, McDonnell WF, Mann R, Becker S, House DE, Schreinemachers D, Koren HS. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. Am J Respir Cell Mol Biol 4:72–81 (1991).
27. Dockery DW. Epidemiologic evidence of cardiovascular effects of particulate air pollution. Environ Health Perspect 109(suppl 4):483–486 (2001).
28. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810–2815 (2001).
29. Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwartz J, Zanobetti A. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. Res Rep Health Eff Inst 94:5–70 (2000).
30. Dockery DW, Schwartz J. Particulate air pollution and mortality: more than the Philadelphia story. Epidemiology 6:629–632 (1995).
31. Hoek G, Dockery DW, Pope A, Neas L, Roemer W, Brunekreef B. Association between PM_{10} and decrements in peak expiratory flow rates in children: reanalysis of data from five panel studies. Eur Respir J 11:1307–1311 (1998).
32. Pope CA III. Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache valleys. Arch Environ Health 46:90–97 (1991).
33. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 79:623–628 (1989).
34. Guo YL, Lin YC, Sung FC, Huang SL, Ko YC, Lai JS, Su HJ, Shaw CK, Lin RS, Dockery DW. Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ Health Perspect 107:1001–1006 (1999).
35. Peters A, Dockery DW, Heinrich J, Wichmann HE. Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur Respir J 10:872–879 (1997).
36. Dye JA, Adler KB, Richards JH, Dreher KL. Epithelial injury induced by exposure to residual oil fly-ash particles: role of reactive oxygen species? Am J Respir Cell Mol Biol 17:625–633 (1997).
37. Gavett SH, Madison SL, Dreher KL, Winsett DW, McGee JK, Costa DL. Metal and sulfate composition of residual oil fly ash determines airway hyperreactivity and lung injury in rats. Environ Res 72:162–172 (1997).
38. Kodavanti UP, Schladweiler MC, Richards JR, Costa DL. Acute lung injury from intratracheal exposure to fugitive residual oil fly ash and its constituent metals in normo- and spontaneously hypertensive rats. Inhal Toxicol 13:37–54 (2001).
39. Galbreath KC, Toman DL, Zygarlicke CJ, Huggins FE, Huffman GP, Wong JL. Nickel speciation of residual oil fly ash and ambient particulate matter using X-ray absorption spectroscopy. J Air Waste Manag Assoc 50:1876–1886 (2000).
40. Ghio AJ, Silbajoris R, Carson JL, Samet JM. Biologic effects of oil fly ash. Environ Health Perspect 110(suppl 1): 89–94 (2002).
41. Soukup JM, Ghio AJ, Becker S. Soluble components of Utah Valley particulate pollution alter alveolar macrophage function in vivo and in vitro. Inhal Toxicol 12:401–414 (2000).
42. Ghio AJ, Devlin RB. Inflammatory lung injury after bronchial instillation of air pollution particles. Am J Respir Crit Care Med 164:704–708 (2001).
43. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J Respir Crit Care Med 162:981–988 (2000).
44. Frampton MW, Ghio AJ, Samet JM, Carson JL, Carter JD, Devlin RB. Effects of aqueous extracts of PM(10) filters from the Utah Valley on human airway epithelial cells. Am J Physiol 277:L960–L967 (1999).
45. Samet JM, Graves LM, Quay J, Dailey LA, Devlin RB, Ghio AJ, Wu W, Bromberg PA, Reed W. Activation of MAPKs in human bronchial epithelial cells exposed to metals. Am J Physiol 275:L551–L558 (1998).
46. Silbajoris R, Ghio AJ, Samet JM, Jaskot R, Dreher KL, Brighton LE. In vivo and in vitro correlation of pulmonary MAP kinase activation following metallic exposure. Inhal Toxicol 12:453–468 (2000).
47. Wu W, Graves LM, Jaspers I, Devlin RB, Reed W, Samet JM. Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to metals. Am J Physiol 277:L924–L931 (1999).
48. Quay JL, Reed W, Samet J, Devlin RB. Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-kappaB activation. Am J Respir Cell Mol Biol 19:98–106 (1998).
49. Costa DL, Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. Environ Health Perspect 105(suppl 5):1053–1060 (1997).
50. Gavett SH, Madison SL, Stevens MA, Costa DL. Residual oil fly ash amplifies allergic cytokines, airway responsiveness, and inflammation in mice. Am J Respir Crit Care Med 160:1897–1904 (1999).
51. Lambert AL, Dong W, Selgrade MK, Gilmour MI. Enhanced allergic sensitization by residual oil fly ash particles is mediated by soluble metal constituents. Toxicol Appl Pharmacol 165:84–93 (2000).
52. Lambert AL, Dong W, Winsett DW, Selgrade MK, Gilmour MI. Residual oil fly ash exposure enhances allergic sensitization to house dust mite. Toxicol Appl Pharmacol 158:269–277 (1999).
53. Dye JA, Lehmann JR, McGee JK, Winsett DW, Ledbetter AD, Everitt JI, Ghio AJ, Costa DL. Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiologic studies in Utah Valley residents. Environ Health Perspect 109(suppl 3):395–403 (2001).
54. Ghio AJ, Stonehuerner J, Dailey LA, Carter JD. Metals associated with both the water-soluble and insoluble fractions of an ambient air pollution particle catalyze an oxidative stress. Inhal Toxicol 11:37–49 (1999).
55. Nordenhall C, Pourazar J, Blomberg A, Levin JO, Sandstrom T, Adelroth E. Airway inflammation following exposure to diesel exhaust: a study of time kinetics using induced sputum. Eur Respir J 15:1046–1051 (2000).
56. Salvi S, Blomberg A, Rudell B, Kelly F, Sandstrom T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 159:702–709 (1999).
57. Salvi SS, Nordenhall C, Blomberg A, Rudell B, Pourazar J, Kelly FJ, Wilson S, Sandstrom T, Holgate ST, Frew AJ. Acute exposure to diesel exhaust increases IL-8 and GRO-alpha production in healthy human airways. Am J Respir Crit Care Med 161:550–557 (2000).
58. Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. Eur Respir J 17:909–915 (2001).
59. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J Immunol 158:2406–2413 (1997).
60. Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. J Clin Invest 94:1417–1425 (1994).
61. Diaz-Sanchez D, Penichet-Garcia M, Saxon A. Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. J Allergy Clin Immunol 106:1140–1146 (2000).
62. Diaz-Sanchez D, Tsien A, Casillas A, Dotson AR, Saxon A. Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. J Allergy Clin Immunol 98:114–123 (1996).
63. Diaz-Sanchez D, Jyrala M, Ng D, Nel A, Saxon A. In vivo nasal challenge with diesel exhaust particles enhances expression of the CC chemokines rantes, MIP-1alpha, and MCP-3 in humans. Clin Immunol 97:140–145 (2000).
64. Fujieda S, Diaz-Sanchez D, Saxon A. Combined nasal challenge with diesel exhaust particles and allergen induces in vivo IgE isotype switching. Am J Respir Cell Mol Biol 19:507–512 (1998).
65. Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. J Allergy Clin Immunol 104:1183–1188 (1999).
66. Tsien A, Diaz-Sanchez D, Ma J, Saxon A. The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances IgE production by IgE-secreting EBV-transformed human B cells in vitro. Toxicol Appl Pharmacol 142:256–263 (1997).
67. Takenaka H, Zhang K, Diaz-Sanchez D, Tsien A, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. J Allergy Clin Immunol 95:103–115 (1995).
68. Gereda JE, Leung DY, Thatayatikom A, Streib JE, Price MR, Klinnert MD, Liu AH. Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. Lancet 355:1680–1683 (2000).
69. Park JH, Spiegelman DL, Burge HA, Gold DR, Chew GL, Milton DK. Longitudinal study of dust and airborne endotoxin in the home. Environ Health Perspect 108:1023–1028 (2000).
70. Milton DK, Christiani DC, Greaves IA. Airborne endotoxin associated with industrial-scale production of protein products in gram-negative bacteria. Am Ind Hyg Assoc J 50:A-596 (1989).
71. Milton DK, Chawla RK. Cotton dust contains proteolytic and elastolytic enzymes not inhibited by alpha-1-proteinase inhibitor. Am J Ind Med 9:247–260 (1986).
72. Cormier Y, Merlaux A, Duchaine C. Respiratory health impact of working in sawmills in eastern Canada. Arch Environ Health 55:424–430 (2000).
73. Rylander R, Vesterlund J. Airborne endotoxins in various occupational environments. Prog Clin Biol Res 93:399–409 (1982).
74. Rylander R, Haglind P. Airborne endotoxins and humidifier disease. Clin Allergy 14:109–112 (1984).
75. Teeuw KB, Vandenbroucke-Grauls CM, Verhoef J. Airborne gram-negative bacteria and endotoxin in sick building syndrome. A study in Dutch governmental office buildings. Arch Intern Med 154:2339–2345 (1994).
76. Vogelzang PF, van der Gulden JW, Folgering H, Kolk JJ, Heederik D, Preller L, Tielen MJ, van Schayck CP. Endotoxin exposure as a major determinant of lung function decline in pig farmers. Am J Respir Crit Care Med 157:15–18 (1998).
77. Wang Z, Larsson K, Palmberg L, Malmberg P, Larsson P, Larsson L. Inhalation of swine dust induces cytokine release in the upper and lower airways. Eur Respir J 10:381–387 (1997).
78. Sandstrom T, Bjermer L, Rylander R. Lipopolysaccharide (LPS) inhalation in healthy subjects increases neutrophils, lymphocytes and fibronectin levels in bronchoalveolar lavage fluid. Eur Respir J 5:992–996 (1992).
79. Sandstrom T, Bjermer L, Rylander R. Lipopolysaccharide (LPS) inhalation in healthy subjects causes bronchoalveolar neutrophilia, lymphocytosis, and fibronectin increase. Am J Ind Med 25:103–104 (1994).
80. Michel O, Nagy AM, Schroeven M, Duchateau J, Neve J, Fondu P, Sergysels R. Dose-response relationship to inhaled endotoxin in normal subjects. Am J Respir Crit

Care Med 156:1157–1164 (1997).
81. Michel O, Dentener M, Corazza F, Buurman W, Rylander R. Healthy subjects express differences in clinical responses to inhaled lipopolysaccharide that are related with inflammation and with atopy. J Allergy Clin Immunol 107:797–804 (2001).
82. Michel O. Systemic and local airways inflammatory response to endotoxin. Toxicology 152:25–30 (2000).
83. Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, Frees K, Watt JL, Schwartz DA. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet 25:187–191 (2000).
84. Kline JN, Cowden JD, Hunninghake GW, Schutte BC, Watt JL, Wohlford-Lenane CL, Powers LS, Jones MP, Schwartz DA. Variable airway responsiveness to inhaled lipopolysaccharide. Am J Respir Crit Care Med 160:297–303 (1999).
85. Schwartz DA, Thorne PS, Yagla SJ, Burmeister LF, Olenchock SA, Watt JL, Quinn TJ. The role of endotoxin in grain dust-induced lung disease. Am J Respir Crit Care Med 152:603–608 (1995).
86. Michel O, Duchateau J, Sergysels R. Effect of inhaled endotoxin on bronchial reactivity in asthmatic and normal subjects. J Appl Physiol 66:1059–1064 (1989).
87. Michel O, Ginanni R, Le Bon B, Content J, Duchateau J, Sergysels R. Inflammatory response to acute inhalation of endotoxin in asthmatic patients. Am Rev Respir Dis 146:352–357 (1992).
88. Michel O, Ginanni R, Sergysels R. Relation between the bronchial obstructive response to inhaled lipopolysaccharide and bronchial responsiveness to histamine. Thorax 47:288–291 (1992).
89. Park JH, Gold DR, Spiegelman DL, Burge HA, Milton DK. House dust endotoxin and wheeze in the first year of life. Am J Respir Crit Care Med 163:322–328 (2001).
90. Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, Pauwels R, Sergysels R. Severity of asthma is related to endotoxin in house dust. Am J Respir Crit Care Med 154:1641–1646 (1996).
91. Alexis N, Eldridge M, Reed W, Bromberg P, Peden DB. CD14-dependent airway neutrophil response to inhaled LPS: role of atopy. J Allergy Clin Immunol 107:31–35 (2001).
92. Dubin W, Martin TR, Swoveland P, Leturcq DJ, Moriarty AM, Tobias PS, Bleecker ER, Goldblum SE, Hasday JD. Asthma and endotoxin: lipopolysaccharide-binding protein and soluble CD14 in bronchoalveolar compartment. Am J Physiol 270:L736–L744 (1996).
93. Virchow JC Jr, Julius P, Matthys H, Kroegel C, Luttmann W. CD14 expression and soluble CD14 after segmental allergen provocation in atopic asthma. Eur Respir J 11:317–323 (1998).
94. Lensmar C, Prieto J, Dahlen B, Eklund A, Grunewald J, Roquet A. Airway inflammation and altered alveolar macrophage phenotype pattern after repeated low-dose allergen exposure of atopic asthmatic subjects. Clin Exp Allergy 29:1632–1640 (1999).
95. Eldridge MW, Peden DB. Allergen provocation augments endotoxin-induced nasal inflammation in subjects with atopic asthma. J Allergy Clin Immunol 105:475–481 (2000).
96. Alexis NE, Peden DB. Blunting airway eosinophilic inflammation results in a decreased airway neutrophil response to inhaled LPS in patients with atopic asthma: a role for CD14. J Allergy Clin Immunol 108:577–580 (2001).
97. Nichols BG, Woods JS, Luchtel DL, Corral J, Koenig JQ. Effects of ozone exposure on nuclear factor-kappaB activation and tumor necrosis factor-alpha expression in human nasal epithelial cells. Toxicol Sci 60:356–362 (2001).
98. Chung KF, Adcock IM. Induction of nuclear factor-kappa B by exposure to ozone and inhibition by glucocorticoids. Methods Enzymol 319:551–562 (2000).
99. Haddad EB, Salmon M, Koto H, Barnes PJ, Adcock I, Chung KF. Ozone induction of cytokine-induced neutrophil chemoattractant (CINC) and nuclear factor-kappa b in rat lung: inhibition by corticosteroids. FEBS Lett 379:265–268 (1996).
100. Muller JM, Ziegler-Heitbrock HW, Baeuerle PA. Nuclear factor kappa B, a mediator of lipopolysaccharide effects. Immunobiology 187:233–256 (1993).
101. Kleeberger SR, Reddy S, Zhang LY, Jedlicka AE. Genetic susceptibility to ozone-induced lung hyperpermeability: role of toll-like receptor 4. Am J Respir Cell Mol Biol 22:620–627 (2000).
102. Kleeberger SR, Reddy SP, Zhang LY, Cho HY, Jedlicka AE. Toll-like receptor 4 mediates ozone-induced murine lung hyperpermeability via inducible nitric oxide synthase. Am J Physiol Lung Cell Mol Physiol 280:L326–L333 (2001).