Epidemiologic Evidence for Asthma and Exposure to Air Toxics: Linkages between Occupational, Indoor, and Community Air Pollution Research

Ralph J. Delfino

Epidemiology Division, Department of Medicine, University of California, Irvine, California USA

Outdoor ambient air pollutant exposures in communities are relevant to the acute exacerbation and possibly the onset of asthma. However, the complexity of pollutant mixtures and etiologic heterogeneity of asthma has made it difficult to identify causal components in those mixtures. Occupational exposures associated with asthma may yield clues to causal components in ambient air pollution because such exposures are often identifiable as single-chemical agents (e.g., metal compounds). However, translating occupational to community exposure–response relationships is limited. Of the air toxics found to cause occupational asthma, only formaldehyde has been frequently investigated in epidemiologic studies of allergic respiratory responses to indoor air, where general consistency can be shown despite lower ambient exposures. The specific volatile organic compounds (VOCs) identified in association with occupational asthma are generally not the same as those in studies showing respiratory effects of VOC mixtures on nonoccupational adult and pediatric asthma. In addition, experimental evidence indicates that airborne polycyclic aromatic hydrocarbon (PAH) exposures linked to diesel exhaust particles (DEPs) have proinflammatory effects on airways, but there is insufficient supporting evidence from the occupational literature of effects of DEPs on asthma or lung function. In contrast, nonoccupational epidemiologic studies have frequently shown associations between allergic responses or asthma with exposures to ambient air pollutant mixtures with PAH components, including black smoke, high home or school traffic density (particularly truck traffic), and environmental tobacco smoke. Other particle-phase and gaseous co-pollutants are likely causal in these associations as well. Epidemiologic research on the relationship of both asthma onset and exacerbation to air pollution is needed to disentangle effects of air toxics from monitored criteria air pollutants such as particle mass. Community studies should focus on air toxics expected to have adverse respiratory effects based on biological mechanisms, particularly irritant and immunological pathways to asthma onset and exacerbation. *Key words:* **asthma, diesel, epidemiology, toxic air pollutants, volatile organic compounds.** *Environ Health Perspect* **110(suppl 4):573–589 (2002).**
http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/573-589delfino/abstract.html

Importance

Asthma morbidity and mortality have steadily increased since the mid-1970s (*1*), possibly reaching a plateau recently, but the causes of this rise are largely unknown. The rise in allergic rhinitis may have begun after the inception of the industrial revolution (*2*). The possibility of a linkage between the rise in asthma and in allergic rhinitis is supported by the consensus that the two diseases share certain genetic and environmental determinants (*3*). During the time that asthma increased, regulated ambient criteria air pollutants generally decreased in the United States. Because the two time trends are not positively related, arguably the rise in asthma could not be due to exposure to ambient air pollutants. This argument is not valid because correlations between time series are subject to ecologic fallacy. This biased interpretation can occur when associations at an aggregate level do not represent associations on an individual level because of unrelated causal factors that independently drive one or both of the aggregate trends. The bias may be amplified if trends in synergistic or antagonistic factors are ignored. For example, a lifestyle risk factor or other environmental exposure may have increased over the same period, and that factor could have positively interacted with effects of the regulated air pollutants. Many factors associated with Western industrial life other than environmental pollution have been identified as potential causes for the asthma epidemic, including allergens from indoor carpeting and pets coupled with increases in indoor residence time and in building tightness, early antibiotic use that prevents differentiation toward T-helper type 1 lymphocytes (T_H1), declining physical fitness, and diet (*4*).

Acute asthma morbidity has been associated with specific regulated air pollutants in aggregate time series and in individual-level repeated measures studies [reviewed by Bascom et al. (*5*)]. The risk of asthma onset or chronic effects on asthma from ambient air pollution exposure has been less clearly identified in epidemiologic studies, although few studies are prospective cohort designs (*6–13*). A cohort study of nonsmoking adult Seventh Day Adventists in California followed 10 or more years found associations between the development of asthma and outdoor concentrations of total suspended particulates (*11*), total suspended sulfate (*12*), and ozone (O_3) (*13*). The association for O_3 was found in males but not in females, possibly because males in that study spent significantly more time outdoors than females (*13*). Three cohort studies looked at lung function growth in children and found significant reductions in growth of forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC) in relation to increasing levels of ambient air pollutants, including nitrogen dioxide (NO_2), particulate matter (PM) < 10 and < 2.5 μm in aerodynamic diameter (PM_{10} and $PM_{2.5}$, respectively), O_3, sulfur dioxide (SO_2), and black smoke (an indicator of soot, including diesel exhaust [DE]) (*8–10*). Diminished lung function growth is one of the possible adverse outcomes of poorly controlled asthma (*14*).

Epidemiologic studies of asthma and ambient air pollution have focused primarily on five of six principal criteria air pollutants (excluding lead) for which the U.S. Environmental Protection Agency (U.S. EPA) has established so-called National Ambient Air Quality Standards (NAAQS): O_3, PM, carbon monoxide (CO), NO_2, and SO_2. Studies in Europe have also used black smoke, which can represent sources of complex exposures such as DE that have a high elemental carbon content. The causal components in the epidemiologic studies have not been clearly identified, partly because the measurements have included only those major pollutant types that *a*) co-vary with other photochemically produced pollutants (e.g., O_3 with aldehydes); *b*) involve complex particle mixtures that vary by space and time (e.g., black smoke, PM_{10}, or $PM_{2.5}$); or *c*) are correlated with other cogenerated primary pollutants (e.g., NO_2 or SO_2 with organic compounds from fossil fuel combustion). The availability of government monitoring data and the regulatory focus partly explains the lack of epidemiologic data concerning other potentially important exposures such as air toxics. Experimental research on the respiratory effects of air toxics is largely limited to animal models or *in vitro* studies. This is not surprising given that many air toxics have potentially serious adverse consequences such

This article is part of the monograph *Environmental Air Toxics: Role in Asthma Occurrence?*

Address correspondence to R.J. Delfino, Epidemiology Division, Dept. of Medicine, University of California, Irvine, 224 Irvine Hall, Irvine, CA 92697-7550 USA. Telephone: (714) 824-7401. Fax: (714) 824-4773. E-mail: rdelfino@uci.edu

Received 3 October 2001; accepted 12 December 2001.

as carcinogenic, reproductive, or neurological effects. The occupational literature, on the other hand, has data on high exposures that may be less frequently encountered in nonoccupational settings.

Given the lack of information on the causal role in asthma of a large number of potentially important air pollutants, it is important at this stage to identify information that future research can build upon. This article provides a review of the literature relevant to this issue. A major objective is to establish conceptual linkages concerning potential adverse respiratory effects of air toxics between different foci of research, including occupational, indoor, and community air pollution research.

Overview of Asthma and Air Toxics

Air toxics can be defined as having three characteristics: *a*) they have the potential to cause serious adverse health effects in the general population or to organisms in the environment as a result of airborne exposures; *b*) they are released from anthropogenic sources; and *c*) they include 189 hazardous air pollutants listed in section 112.b.1 of the Clean Air Act of 1990. It is conceivable that personal exposures to some air toxics (toxic air pollutants) may have increased over the last several decades and been partly responsible for the increase in asthma. Most notably, the U.S. Department of Transportation reports that the number of ton-miles carried by intercity trucks has steadily increased from 285 billion ton-miles in 1960 to 1,027 billion ton-miles in 1998, and the amount of diesel fuel consumed also increased in parallel (*15*). Over the same period, the total motor vehicle fuel consumption nearly tripled (58 to 155 billion gallons/year) (*15*). Traffic density has also increased in many cities along with stagnation in fuel economy since the early 1980s (*15*). As a result, it is expected that concentrations of traffic-related pollutants will have increased in certain urban microenvironments. It is relevant that minority groups most at risk for poor asthma management and subsequent disease progression are more likely to live in areas failing to meet the NAAQS. This includes 80% of Hispanics and 65% of Blacks compared with 57% of Whites in the United States (*16*).

Asthma has been defined as having three phenotypic characteristics: intermittent and reversible airway obstruction; increased airway responsiveness to contractile stimuli; and airway inflammation. Pulmonary inflammation is a hallmark of asthma and is directly related to asthma severity as a function of acute and chronic airflow obstruction. One potential mechanism of action for air toxics is through enhancement of airway inflammation. Inflammation in asthma, however, has diverse pathways, mirroring the complexity of the disease. Three general mechanisms of inflammation in asthma include immunoglobulin E (IgE)-mediated, neurogenic, and irritant induced.

The principal inflammatory mechanism in asthma is an IgE-mediated reaction whereby an antigen cross-links with an IgE antibody specific to that antigen on the surface of mast cells and other immune cells. Commonly recognized antigens that induce acute exacerbations of asthma are high molecular weight allergens such as pollen, fungal and animal proteins. Low molecular weight agents involved in IgE-mediated reactions, including certain air toxics, act as haptens. Haptens must first react with endogenous or exogenous proteins to form a complete antigen (e.g., formaldehyde-albumin). IgE-mediated mechanisms are key in early-phase asthmatic reactions (within minutes). Other processes follow over several hours and involve the recruitment of eosinophils, $CD4^+$T cells, neutrophils, basophils, and macrophages, and the release of proinflammatory mediators and cytokines. T-cell activation leads to the release of T-helper cell type 2 (T_H2)-like cytokines, which may be involved in a more prolonged chronic phase of inflammatory response over days (*14*). The involvement of T_H2 cells is important because a key pathway to the development of the asthma phenotype is believed to be the early differentiation of T-helper lymphocytes into T_H2 rather than T_H1 cells, although this is still controversial (*17*). T_H1 cells participate in delayed-type hypersensitivity reactions. T_H2 cells promote antibody immune responses, and because they secrete eosinophil-active cytokines and enhance IgE synthesis, they are implicated in the genesis of allergic inflammation. Putative progenitor T cells develop into early T_H0 cells with the first antigen encounter. T_H0 cells then differentiate into T_H1- or T_H2-type lymphocytes after repetitive antigen stimulation (*18*). Interleukin (IL)-4 shifts the differentiation from T_H1 to T_H2. The balance toward T_H2 cells may be tipped by early environmental influences, including exposure to air pollutants (*19*), coupled with genetic susceptibilities. This is presumed to be key in the development of asthma.

Neurogenic inflammation involves a spread of the inflammatory response via the release of neurotransmitters or activation of afferent nerves by the action of inflammatory mediators (*20,21*). Inflammatory mediators can trigger the activation of nonadrenergic, noncholinergic nerves to release tachykinins. A cascade of bronchoconstrictive reflexes and of inflammatory events can follow.

Reactive airways dysfunction syndrome (RADS) is a primary example of a type of asthma where toxic irritant-induced inflammation is a key mechanism. RADS has been identified in occupational settings and is defined as an irritant-induced nonimmunologic asthma with no latency period. RADS is nonimmunologic in the sense that bronchial epithelial injury is the primary causal event and typical phases of the immune response are absent, namely, sensitization, latent period, episode of elicitation of an immune response to antigen, and repetitive elicitation (*22*). RADS is an example of an inflammatory mechanism of air toxics, but it is rare and its relevance to nonoccupational asthma is unclear.

There is hypothesized to be a feedback loop between inflammatory processes and neuronal processes that trigger inflammation (Figure 1) (*3*). The inflammatory processes can be either immune mediated (e.g., IgE mediated) or triggered by irritant-induced airway injury. For RADS (*22*), and to some extent oxidant pollutants such as O_3 (*23*), the initiation of bronchial epithelial injury could initiate the release of inflammatory

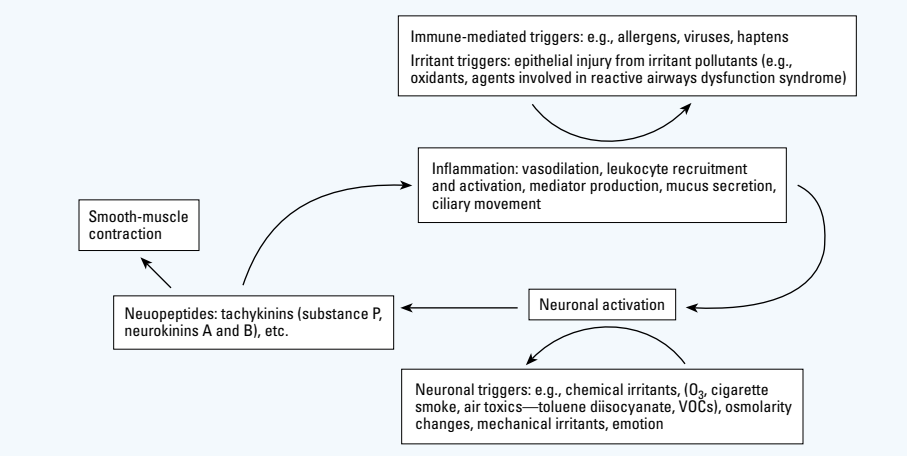

Figure 1. Hypothetical feedback loop between inflammatory processes and neuronal processes that trigger inflammation. Adapted from American Thoracic Society Workshop (*3*).

mediators. This inflammation could then trigger neurogenic inflammation. Chemical irritants may also act as neuronal triggers directly (*3,24*). Irritant-induced induction of tachykinin release could serve to enhance ongoing inflammation in the asthmatic lung caused by known immune triggers. Examples consistent with this hypothetical mechanism include the putative interaction between ozone and pollen in asthma exacerbations (*25*), and the finding in subjects with mild asthma that airway responsiveness to inhaled allergen increases after ozone challenge (*26*). Airborne irritants could also indirectly enhance neuroinflammation by inhibition of neutral endopeptidase (NEP). NEP degrades tachykinins and its levels are decreased following exposure to oxidants (*27*), cigarette smoke (*28*), and an agent responsible for a form of occupational asthma, toluene diisocyanate (TDI) (*29*).

In addition to inflammatory mechanisms, the heterogeneity of asthma is further evidenced by other factors, including

- differences in etiology and clinical outcomes between pediatric and adult asthma, which are poorly delineated to date (*30,31*);
- variability in the importance of atopy, with both allergic and nonallergic types being described, although both show similar profiles of inflammatory mediators with the possible exception of IL-4 (*14*);
- specific inducers of acute asthma, including allergenic, largely high molecular weight agents (e.g., fungal spores, animal proteins), and nonallergenic, largely low molecular weight agents that may act as irritants (e.g., O_3) or as haptens (e.g., formaldehyde) (*32*); and
- severity and response to treatment.

Given the diversity of both causal determinants and clinical characteristics of asthma, it is a great challenge to understand its etiology. Therefore, it should not be surprising that the role that air toxics play in asthma onset and exacerbation is poorly understood.

Occupational Asthma

A recent review of the literature suggests that the proportion of new or exacerbated asthma in adults due to workplace exposures ranges between 5 and 25% (*33*). The basic mechanisms defining new-onset occupational asthma include *a*) IgE-mediated, which occurs after a latency period and is caused by high molecular weight (>5 kDa) allergens, or low molecular weight compounds (e.g., acid anhydrides, metals) that act as haptens; *b*) unknown immunological, which occurs after a latency period, but no IgE- or non–IgE-mediated mechanism is known (e.g., polyisocyanates such as TDI); and *c*) nonimmunologic, namely, the mechanism for RADS, which occurs after single or multiple exposures to high concentrations of nonspecific irritants (e.g., hydrogen sulfide [H_2S], chlorine gas, fire smoke) leading to bronchial epithelial injury and neurogenic inflammation (*22*).

Occupational data have the potential to guide research into asthma and community air toxics exposures. Some of these data are reviewed below. However, there are limitations in using occupational data on air toxics to better understand community exposure–response relationships, as follows:

- Concentrations of airborne chemicals are often high in occupational settings, particularly for RADS, whereas in community settings lower exposures are expected (e.g., ambient H_2S from pulp mill emissions vs. occupational H_2S exposures linked to asthma).
- Typically, single-causal agents are identified in occupational asthma, whereas complex mixtures are encountered in ambient air, making it more difficult to ascribe causality to any one agent in ambient air.
- Dose–response relationships are often not well enough established in the occupational data to allow an extrapolation to low levels of prolonged ambient exposure.
- There may be no similar exposures in ambient air except for occasional fugitive emissions from industrial sites that could impact asthma and allergic sensitization locally (e.g., TDI) (*34*).
- The importance of allergenic cofactors to effects from air toxics may be less important in occupational asthma compared with nonoccupational asthma, where common allergens may be the predominant and most frequently encountered causal determinant of asthma flares.
- Occupational asthma affects adults, whereas the majority of asthma in the community is pediatric, and there are clinical and probably etiological differences, depending on age of onset (*31*).
- Even limiting comparisons to adults, there is still the problem of the healthy worker effect in occupational studies. This is a form of confounding bias where persons of good health are selected for employment and/or they choose to be selected. Additionally, early in employment, workers will choose to quit when ill, or when work conditions are perceived to cause illnesses such as asthma. This limits the applicability of findings to the general adult population, particularly for negative results.

Despite the above limitations, several agents known to cause occupational asthma should be investigated in relation to nonoccupational asthma. Categories of low molecular weight agents associated with occupational asthma are shown in Table 1 (*22*). One of the aldehydes, formaldehyde, is a compound for which there is epidemiologic evidence for respiratory allergic responses in children (reviewed below). However, many major low molecular weight agents commonly present in ambient air have not been clearly identified as causes of occupational asthma despite potentially high workplace exposures. These include polycyclic aromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene, some petroleum-related volatile organic compounds (VOCs) such as benzene, toluene, and xylenes, and some industrial process-related VOCs such as carbon tetrachloride, chloroform, 1,4-dichlorobenzene, and trichloroethane.

PAH Exposures

PAHs are found in relatively high concentrations in automobile and DE, along with other potentially important chemicals including nitroaromatics, aldehydes, alcohols, ketones, quinones, phenols, and other organic compounds, as well as volatile co-pollutants—oxides of nitrogen and of sulfur, CO, and numerous VOCs such as formaldehyde, benzene, and 1,3-butadiene. Diesel exhaust particles (DEPs) have a submicrometer elemental carbon core coated with organic compounds (including PAHs), nitrites, sulfites, and trace metals. The most common type of PAH compound in DEPs includes the phenanthrenes, followed by fluorenes, fluoranthrenes, naphthalenes, and pyrenes (*35*). However, PAHs are semivolatile, and so much of the PAHs emitted from motor vehicles is not particle bound. Selected indoor home concentrations of various semivolatile PAH compounds for 33 homes in California

Table 1. Low molecular weight agents associated with occupational asthma.[a]

Chemical category	Examples
Diisocyanates	TDI
Acid anhydrides	Phthalic anhydride
Aliphatic amines	Ethylene diamine
Ethanolamines	Monoethanolamine
Heterocyclic and other aromatic amines	Piperazine hydrochloride
Metals	Halogenated platinum salts, chromium, cobalt, nickel, zinc
Aldehydes	Formaldehyde
Drugs	Penicillins, cephalosporins
Reactive dyes	Carmine
Biocides	Chloramine T
Miscellaneous chemicals	Styrene, polyvinyl chloride fumes, aziridine

[a]Data summarized from Bernstein et al. (*22*).

and Ohio ranged from 9.2 to 210 ng/m^3 for phenanthrene, 0.29 to 1100 ng/m^3 for quinoline, 2.40 to 37.4 ng/m^3 for fluoranthrene, and 0.00 to 4.13 ng/m^3 for benzo[*a*]pyrene (*36*). Concentrations were higher in homes with tobacco smoking. Phenanthrene, for example, was 87 ng/m^3 for homes with smoking and gas stove/heat versus 31 ng/m^3 for nonsmoking homes with gas stove/heat. PAH concentrations are also likely to be higher where there is a high density of trucks, such as downtown Los Angeles, California, where DE was found to make up 32.7% of the fine particle mass (*37*).

The following section will examine some of the experimental evidence for the potential causal role of PAHs in asthma, as well as complementary epidemiologic evidence from both the occupational and non-occupational literature.

Overview of Experimental Evidence for PAHs as Proinflammatory Compounds

The experimental evidence that suggests an important mechanistic role for PAHs from DEPs in allergic respiratory illnesses has been extensively reviewed before (*38*), so the present section serves as a brief overview. Takenaka et al. (*39*) showed that IgE production in purified B cells following the addition of IL-4 and CD40 monoclonal antibody was enhanced 20–360% by the addition of an extract of PAH from DEPs. The effect was replicated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, demonstrating that the action of the PAH extract was likely attributable to aromatic hydrocarbons rather than a DEP contaminant, possibly acting through aryl hydrocarbon receptor–mediated effects on nuclear activities. Tsien et al. (*40*) also found *in vitro* enhancement of IgE production in human B cells using a total PAH extract of DEPs, as well as the major PAH component of DEPs, phenanthrene.

Diaz-Sanchez et al. (*41*) found that topical treatment of nasal epithelium with the corticosteroid drug fluticasone inhibited significant increases in cytokine messenger RNA (mRNA) for IL-4 and IL-5 after ragweed challenge, but it did not block a greater cytokine mRNA production after DEP challenge. The authors suggested that fluticasone was unable to inhibit a broad polyclonal activation because of an adjuvantlike activity of DEPs. They cited earlier evidence that intranasal challenges with DEPs leads to significant increases in many cytokines (*42*), whereas allergens such as ragweed predominantly increase IL-5 (*43*). In addition, the increase in allergen-specific IgE with ragweed alone is less than a combined challenge with ragweed plus DEPs (*43,44*). Interestingly, Fujieda et al. (*44*) found that DEPs plus ragweed exposure also drives *in vivo* isotype switching to IgE in nasal lavage cells from humans with ragweed allergy but not either exposure alone.

PAHs from DEPs enhance IgE responses, but does DEP exposure induce initial atopic sensitization? Diaz-Sanchez et al. (*45*) tested this using a neoallergen (keyhole limpet hemocyanin [KLH]) to which subjects could not have been previously exposed. When 10 atopic human volunteers were nasally immunized with KLH, anti-KLH immunoglobulin G and immunoglobulin A were produced after KLH challenge but not IgE. In 15 other subjects, the KLH immunization was preceded by DEP administration 24 hr previously. KLH challenge in 9 of these subjects led to the additional production of anti-KLH–specific IgE.

Clinical relevance of the nasal challenge studies to lower respiratory allergic responses remains to be established. Salvi et al. (*46*) exposed 15 healthy subjects to clean air and DE on different days over 3 weeks and examined lung function, airway lavage, and bronchial biopsies 6 hr after 1-hr exposures (PM_{10}, 300 μg/m^3; NO_2, 1,600 ppb; formaldehyde, 260 μg/m^3). They saw increases in neutrophils and B lymphocytes in lavage fluids. Bronchial biopsies showed increased inflammatory cells (neutrophils, mast cells, $CD4^+$, and $CD8^+$ T lymphocytes) and significant increases in expression of endothelial adhesion molecules and their ligands. Increases in neutrophils and platelets were found in peripheral blood. There were no significant changes in lung function, but the effect on the asthmatic lung remains to be tested.

In summary, PAHs from fossil fuel combustion may contribute to worsening respiratory allergic responses and induction of the initial clinical expression (*38*). Potential targets for PAHs include antigen-presenting cells, macrophages, mast cells, respiratory epithelial cells, and possibly T_H2 cells directly. All of these cells are thought to possibly play a role in the adjuvant effects of DEPs on allergic inflammation (*38*). Experimental findings have shown that whereas DEPs alone have a nonspecific effect in increasing cytokine production, DEPs plus ragweed antigen selects against a T_H1 profile while stimulating a T_H2-type response (*38*). The clinical relevance of these experimental findings remains to be established, especially for asthma. The relevance to public health and to epidemiologic findings of air pollution health effects also remains to be established. The ability of PAHs to exacerbate disease severity among asthmatic individuals has not been directly investigated in an epidemiologic study. The following review of the epidemiologic literature involves complex exposure mixtures that contain relatively high concentrations of PAHs along with other potentially causal pollutants.

Occupational Evidence for Respiratory Effects of DE

Occupational exposures to DEP can be high, thus giving researchers the opportunity to examine associated health effects. Exposures range from 1 to 100 μg/m^3 for 8-hr averages in occupations such as trucking or transportation where mixed automobile and truck exposures are expected. Exposures are much higher for other occupations such as underground mining, which uses diesel equipment operated in enclosed spaces, and range from 100 to 1,700 μg/m^3 (*47*).

A case report of three railroad workers is the only paper linking new-onset asthma to occupational DE exposures (*48*). The workers developed asthma after exposure to locomotive exhaust while riding immediately behind a lead engine. However, all had been working for the railroad for many years, which leaves open a role for chronic exposures. They had no previous history of asthma or other chronic lower respiratory disease and were nonsmokers. One subject had a history of seasonal rhinitis, and one had a family history of asthma and rhinitis, suggesting underlying susceptibility. The diagnosis was confirmed by spirometry, airways hyperreactivity to methacholine, and exercise challenge. Two workers showed reversibility in lung function deficits with an inhaled bronchodilator; the other showed reversibility 3 years later. All three experienced asthma symptoms upon reexposure to locomotive DE, and one showed peak expiratory flow (PEF) rate fall with work exposure. All developed persistent asthma with exacerbations occurring with various triggers including exertion, cold air, and passive smoke. One other paper reported a similar high-exposure event involving 13 railroad workers, two of whom complained of chest tightness and wheezing, but no other diagnostic data were provided (*49*). In addition to the above case report, a number of cross-sectional occupational studies of DE-exposed workers have been conducted.

An early study of 200 coal miners found no association between diesel exposure and respiratory health (*50*). A better-designed study by Reger et al. (*51*) showed adverse effects in 823 miners in diesel coal mines frequency-matched to 823 miners in nondiesel coal mines by age, height, smoking status, and years underground. Persistent cough and phlegm were significantly higher in diesel-exposed workers, but the opposite was found for dyspnea; there was no difference in wheezing. Compared with nondiesel workers, diesel workers also had significant decrements in FVC, FEV_1, and forced expiratory flow rate at 75% and 90% of FVC (FEF_{75} and

FEF_{90}) but no evidence of obstruction using the ratio FEV_1/FVC. Other studies were conducted by some of the same investigators in coal mines. One study of acute effects of DE during an 8-hr work shift in 90 coal miners compared diesel-exposed and unexposed miners (*52*). Investigators found that cross-shift deficits in FEV_1, FVC, and forced expiratory flow rate at 50% of FVC (FEF_{50}) were greater for diesel-exposed subjects, but not significant. The same group conducted a 5-year prospective study of 280 diesel-exposed and 838 unexposed miners in different mines (*53*). They found no significant age-adjusted differences in 5-year changes in FEV_1 or FVC, or in chronic cough, phlegm, or breathlessness. However, diesel-exposed western miners who, unlike the eastern miners, provided the control group, showed a significant deficit in FEF_{50}. An internal analysis of diesel-exposed workers based on cumulative years of diesel exposure was negative.

A study by Gamble et al. (*54*) of 283 diesel bus garage workers compared with blue-collar controls, showed garage workers had a significantly higher incidence of cough, phlegm, and wheezing adjusted for age, race, and smoking. However, pulmonary function was, on average, higher in garage workers than the controls by all race and smoking status categories adjusted for age and height. An internal comparison based on tenure showed progressively decreasing FEV_1, FVC, and FEF_{50} adjusted for age, height, race, and smoking status. The internal comparison also showed a consistent increase in prevalence of dyspnea, wheeze, and cough with tenure. The same research group studied 259 salt miners in five mines with different diesel exposures (2 with extensive diesel use, 2 with limited use, 1 with none) (*55*). There was a nonsignificant increased trend in cough and dyspnea and a significant trend in phlegm by years of tenure in diesel-exposed jobs but no association with lung function adjusted for smoking, age, and height. The adjusted prevalence of cough and phlegm was also higher than that of a blue-collar comparison group, but lung function did not differ.

None of the above papers compared groups based on any actual pollutant measurements. However, the same 259 salt miners discussed above were studied with personal samples of NO_2 and respirable particles (cyclone sampler). The personal samples were used to estimate cumulative exposure by tenure, with NO_2 as a surrogate measure of diesel exposure (*56*). Cough, dyspnea, and pulmonary function (FVC, FEV_1, peak flow, FEF_{50}, FEF_{75}) were not associated with estimated cumulative NO_2 (mean 200–2,500 ppb) or respirable particle exposure (mean 200–700 μg/m^3). Only phlegm was associated with the exposures. Gamble et al. (*57*) also used personal samples of NO_2 and respirable particles to assess acute effects in 232 of the 283 diesel bus garage workers in their previous paper discussed above. Both NO_2 (mean 230 ppb) and respirable particles (mean 240 μg/m^3) exposures were associated with increased postwork shift symptoms of cough, difficult or labored breathing, chest tightness, and wheeze but not lung function. Attfield et al. (*58*) studied 630 miners in six potash mines in New Mexico with different exposures and exposure durations to underground DE. They also used personal passive samples of NO_2 (range 100–3,300 ppb). Internal analysis showed average percent predicted FEV_1 and FVC were not associated with particular mines in nonsmokers or smokers (adjusted for pack years). Lung function and symptoms were not associated with predicted cumulative NO_2 exposure. However, when years of exposure were examined, lung function actually improved and there was no trend in symptoms (cough, phlegm, dyspnea), suggesting a harvesting effect that selected against workers with adverse pulmonary responses. Robertson et al. (*59*) studied 44 matched pairs of coal miners differently exposed to NO_2 and found no difference in respiratory symptoms or FEV_1. Purdham et al. (*60*) found that work shift changes in FEV_1 among 17 stevedores employed in ferry operations did not differ from those of 11 office controls. Area measurements of NO_2, formaldehyde, and acetaldehyde were also not different, but poor precision was possible.

Other occupational studies have examined workers exposed to automobile exhaust, which can include diesel fumes as well. Studies by Speizer and Ferris (*61,62*) compared two groups of policemen with different exposure levels to auto exhaust and found no significant differences in symptoms or pulmonary function. Ayres et al. (*63*) showed tunnel workers had worse pulmonary function and more respiratory symptoms than bridge workers with lower exposures. Ulvestad et al. (*64*) compared 221 tunnel workers with 205 heavy-construction workers. They found tunnel workers, but not heavy-construction workers, had significant decreases in percent predicted FVC and FEV_1 with tenure, adjusted for smoking and atopy by radioimmunoassay test (RAST). Tunnel workers reported significantly more respiratory symptoms than referent workers, and prevalence of chronic obstructive pulmonary disease was also higher. However, in an earlier study there were no differences in the prevalence of respiratory symptoms between tunnel and turnpike workers, although both may have been highly exposed (*65*). A small study of 89 workers on roll-on roll-off ships, car ferries, and a bus garage showed significant FEV_1 and FVC decrements during workdays after several days with no exposure (*66*).

The above occupational studies, most of which are cross-sectional in design, reveal a mixed picture of adverse and null effects. Other pollutant exposures such as coal dust could have been responsible for positive associations in internal comparisons, as well as for positive and negative findings in between-group comparisons because both groups were usually in occupational groups exposed to airborne pollutants. Control for adverse smoking effects, which were generally strong, may also have been inadequate or subject to undetected multicollinearity or interaction. However, it is likely that the healthy worker effect strongly influenced findings. Therefore, the limited findings of adverse effects in working men supports the expectation of stronger associations in susceptible individuals in the general population, including people with current asthma, children, and the elderly. Evidence for a healthy worker effect is that in many of the studies, workers had higher baseline FEV_1 values compared with those of control groups or with advancing tenure (*50,51,53,54,58,60*). There is other evidence in the occupational literature on diagnosed occupational asthma in bakers, and on allergic sensitization to platinum salts and to TDI, that risk is greatest in the initial 1- to 2-year period of employment (*67*). Except for the case report of "diesel asthma" (*48*), none of the occupational studies reviewed above performed standard spirometric tests to diagnose asthma, and none followed workers prospectively from the start of employment.

Epidemiologic Evidence for Pollutant Mixtures Containing PAHs: Environmental Tobacco Smoke

One common indoor air pollutant high in PAHs is environmental tobacco smoke (ETS). ETS also contains other toxic air pollutants, including 29 air toxics of 49 major components (*68*), making it difficult to ascribe effects to any one pollutant. Serum IgE is higher in smokers than in nonsmokers (*69–72*) and is possibly higher in ETS-exposed subjects (*72,73*). This suggests an acute enhancement of IgE responses is possible, but whether the initial expression of allergic sensitization is enhanced by ETS is in dispute. A quantitative meta-analysis of studies up to April 1997 showed no association between parental smoking during pregnancy or infancy and atopic sensitization by skin prick tests (SPTs) in children without asthma or wheezing disorders (*73*). There was considerable inconsistency across studies (*73*). Other more-recent reviews have concluded that the relationship between ETS exposure

in school-age children and the development of both asthma and allergy is poorly understood (*74,75*). A recent study of 5,762 school-age children had sufficient power to find a significant association between *in utero* exposure to maternal smoking without subsequent ETS exposure and history of physician-diagnosed asthma, current asthma, and asthma requiring medication (*76*). The same study showed that although current or past ETS exposure occurring only after birth was associated with reports of wheezing, it was not associated with asthma prevalence. Furthermore, combined *in utero* plus postnatal exposures did not increase risk of asthma beyond *in utero* exposures alone. The finding that maternal smoking during pregnancy has a stronger relationship to asthma onset than later ETS exposures was supported by several other studies that separated maternal *in utero* exposures from postnatal exposures (*77–82*). It is conceivable that *in utero* exposures to ETS shifts the immune response toward a T_H2-type pattern as a result of the adjuvant action of PAH components interacting with *in utero* allergen exposures, which are now believed to lead to atopic sensitization before birth (*83,84*). It is plausible that postnatal coexposures would do the same, but the epidemiologic data are inconsistent for the relationship between ETS exposure and childhood asthma incidence.

On the other hand, there is a preponderance of evidence linking ETS to acute exacerbations of asthma in asthmatic children. A recent meta-analysis concluded that studies showed an excess incidence of wheezing in smoking households, particularly in nonatopic children, suggesting a "wheezy bronchitis" pattern; however, in children with diagnosed asthma, parental smoking was associated with greater severity rather than incidence (*78*). A quantitative meta-analysis of studies up to April 1997 for 25 studies of asthma prevalence showed a pooled odds ratio (OR) for asthma of 1.21 (95% confidence interval [CI], 1.10–1.34) if either parent smoked (*85*). Well-conducted panel studies are still needed to evaluate acute exposure–response relationships using repeated measures methods. A recent daily panel study over 3 months in 74 asthmatic children showed that acute asthma symptom severity, PEF, and bronchodilator use was associated with ETS exposure (*86*).

There is less information about adult-onset asthma. A cohort study of 451 nonsmoking asthmatic adults found that acute asthma severity, asthma-specific quality of life, and health status were associated with self-reported ETS exposure (*87*). Cohort studies have also shown increased risk of developing adult asthma from ETS (*88*), including occupational exposures (*89*). Among 3,914 nonsmoking adults followed 10 years, the relative risk for asthma onset from 10 years of working with a smoker was 1.45 (95% CI 1.21, 1.75) (*85*). A large survey of 4,197 never-smoking adults showed an elevated risk of physician-diagnosed asthma from any ETS exposure [OR 1.39 (95% CI 1.04–1.86)] but no increased risk of allergic rhinitis (*90*). Reviews that have included other epidemiologic studies have concluded that although ETS is consistently associated with adult asthma onset, the number of studies is limited and the magnitude of effects are small, with limited dose–response information (*91,92*). One question that remains to be answered is what are the chemical determinants of associations between asthma and ETS, which is a complex mixture of particle and gas-phase components? Do PAHs play a major role in these associations?

Epidemiologic Evidence for Pollutant Mixtures Containing PAHs: Automobile and Truck Exhaust

The urban exposure most relevant to the potential importance of PAHs to asthma is exposure to automobile and truck traffic. An earlier descriptive study spurred interest in potential adjuvant effects of DEP on IgE-mediated respiratory allergic responses (*93*). This was a cross-sectional study of 3,133 Japanese persons that showed the prevalence of cedar pollen allergy was higher near busy highways despite equivalent local exposure to cedar pollen in less-busy areas.

No epidemiologic studies have used quantitative exposure estimates of either DEP or ambient PAHs. However, European research has had access to black smoke measurements. A panel study of 61 (77% on asthma medications) children in the summer showed stronger associations for black smoke than for PM_{10} in relation to PEF, respiratory symptoms, and bronchodilator use (*94*). The authors hypothesized that black smoke may be a better surrogate for fine particles emitted by diesel engines or for other chemicals that may be the causal components in DE. Ambient NO_2 could additionally serve as a marker for traffic exposure. Studnicka et al. (*95*) explicitly used outdoor NO_2 as a surrogate to show "traffic-related pollution" was associated with asthma prevalence among 843 children living in areas of lower Austria without local industrial emissions of air pollution.

Numerous epidemiologic studies have shown associations between traffic density and asthma prevalence or morbidity. All but one were conducted in Europe and Asia (Table 2). Fifteen of these have been in children (*96–110*), four in adults (*111–114*), and one study in both children and adults (*115*). All but seven have been purely cross-sectional studies. Krämer et al. (*109*) conducted a cross-sectional study of atopic sensitization and asthma diagnosis but had a prospective outcome assessment of atopic symptoms for 1 year along with seasonal NO_2 measurements. Other designs include three case–control studies of hospital admissions (*97,99,108*), and one case–control study of California Medicaid claims for asthma (*105*). Another study was a mixture of cross-sectional, survey-nested case–control, and historical cohort (*110*). One study of adult Japanese women was cross-sectional for symptom prevalence and also tested longitudinal models for 10 seasonal repeated measures for lung function in a subsample (*112*). Eleven looked at traffic density, but no air pollution measurements were used in effect estimates or as confirmation of exposure gradients (*96–98,100,101, 104,105,108,110,113,114*); four had traffic density, black smoke and/or NO_2 (*102,103, 111,112*); and five used combustion-related air pollution measurements near the home (CO, benzene, and/or NO_2) as modeled surrogates for traffic exposures (*99,106,107, 109,115*). Hirsch et al. (*107*) briefly mentioned results for truck traffic, focusing instead on predicted home exposures from one hundred eighty-two 1-km^2 grid measurements of CO, benzene, NO_2, SO_2, and O_3. Pershagen et al. (*99*) used predicted NO_2 from models involving traffic data near the home and background ambient NO_2 data, with home residence time as a weighting factor. Oosterlee et al. (*115*) investigated respiratory symptom prevalence and asthma in relation to busy and quiet streets predicted with model calculations of NO_2 concentrations using the Dutch CAR (Calculation of Air Pollution from Road traffic) model (*117*). Only four studies have separately assessed exposures from truck versus automobile traffic (*102–104,113*), two of which examined the same children in South Holland using actual 1-year measurements of traffic density in relation to lung function (*102*) and symptoms (*103*). Another study in Germany had only self-reported truck traffic density in relation to symptoms (*98*). Except for one study (*113*), all of the above studies examining truck traffic showed increased risks in respiratory symptoms including wheeze from higher truck traffic density near the home (*98,103,104*). The Holland studies showed greater increased risks in respiratory symptoms including wheeze (*103*) and lung function deficits (*102*) from higher truck traffic than from automobile density near the home. Both Holland studies confirmed the possible relevance of DE by finding that black smoke measurements at the children's schools were also associated with increased symptoms (*103*) and lung function deficits (*102*). A

Table 2. Epidemiologic studies of the relationship between asthma prevalence or morbidity and traffic-related exposures.

Reference ciitation	Design and location of study. Subject ages (yr) and characteristics	Exposures	Health outcomes	Results
Wjst et al. (*96*)	Cross-sectional. Munich, Germany. In school districts with multiple large roadways; 7,000–153,000 vehicles/day. Children: 9–11 yr, living in the same residence 5 years (n = 4,320 pulmonary function; 4,678 questionnaires).	Traffic density: traffic on the road with the highest traffic volume passing through the school district but no information relating to distance from home or school.	Lung function: FEV_1, FEV_1/FVC, PEF, FVC, PEFR, MEF_{25}, MEF_{50}, MEF_{75}, and MEF_{50}/FVC. Respiratory conditions: Respiratory tract infections (>10 in past year); common cold (symptoms present at exam); coughing, and recurrent conditions (bronchitis, wheezing, or dyspnea) Physician-diagnosed illness: asthma, croup, allergic rhinitis (self-reported).	Regressions controlled for parental history of asthma, parental education, passive smoking in home, number of home residents, gas or coal for cooking or heating, month of survey, and questionnaire respondent (for symptoms). Lung function models also adjusted for test compliance, height, and weight. Percent difference in lung function per 25,000 cars was significant or borderline significant ($p < 0.1$) but small (<1%) for FEV_1, PEFR, MEF_{25}, MEF_{50}, MEF_{50}/FVC. No association with MEF_{75} and FVC ($p > 0.4$). Respiratory tract infections and recurrent bronchitis were not significantly associated with traffic. Small significant associations were found for recurrent wheezing [OR/25,000 cars 1.08 (95% CI 1.01, 1.16)] and recurrent dyspnea [OR 1.10 (95% CI 1.00, 1.20)], borderline associations were found for cough [OR 1.06 (95% CI 0.99, 1.13)]. Significant association for common cold at exam suggests possible confounding of lung function. Significant small OR/25,000 cars were found for lifetime croup [OR 1.09 (95% CI 1.00, 1.18)], but asthma and allergic rhinitis were not significantly associated with traffic.
Edwards et al. (*97*)	Case–control. Birmingham, West Midlands, UK. Homes near many busy roads with traffic congestion. Children: cases 0–4 yr admitted to hospital for asthma (n = 715), versus community controls (n = 736), and versus nonrespiratory hospital controls (n = 722).	Traffic density: major roadway on or near home. Binary classification: <24,000 versus >24,000/day Ordinal classification: > 35,000; 28,000–35,000; 24,000–27,000; 20,000–23,000; 14,000–19,000; <14,000/day. Distance to roadway home within 0–200 m; 201–500 m; >500 m.	Cases admitted to hospital with asthma.	Only unadjusted results were given. Cases lived more often near roads with high traffic density than community controls [OR 1.40 (95% CI 1.13, 1.74)] and hospital controls [OR 1.29 (95% CI 1.04, 1.50)]. Ordinal traffic density showed a significant trend for subjects living < 500 m from a major road (p-value for trend <0.006). Cases were more likely to live 0–200 versus >200 m than community controls [OR 1.52 (95% CI 1.22, 1.90)], but not hospital controls [OR 1.16 (95% CI 0.94, 1.44)].
Weiland et al. (*98*)	Cross-sectional. Bocham, Germany. Children: 12–15 yr (n = 2,050) from 13 randomly selected schools.	Truck traffic density: subject self-reported frequency of truck traffic (never, seldom, frequent, and constant).	Respiratory symptoms (recalled for last year): Wheezing—written and video questionnaires (ISAAC). Allergic rhinitis symptoms—written questionnaires.	Logistic regressions controlled for age, gender, nationality, parental history of asthma, parental education, passive smoking in home, active smoking, number of siblings, single bedroom, pets, and bedroom carpets. Increased prevalence of wheezing by video questionnaire for more truck traffic: frequent versus never [OR 1.58 (95% CI 1.13, 2.20)], constant versus never [OR 1.94 (95% CI 1.26, 2.99)], consistent with ORs using written questionnaire. Increased prevalence of allergic rhinitis for frequent versus never [OR 1.67 (95% CI 1.17, 2.38)], constant versus never [OR 1.54 (95% CI 0.97, 2.44)].
Pershagen et al. (*99*)	Case–control. Stockholm, Sweden. St. Goran's Children Hospital. Children: 4–48 months (n = 197) admitted to hospital for breathing difficulties with wheezing versus 350 controls 4–48 months of age recruited from hospital catchment area; frequency matched for age.	Ambient air pollution: NO_2 (μg/m^3: <35, 35–45, 46–70, >70) predicted from dispersion models involving traffic data near the home and day care center, background ambient NO_2, and time in months at home and day care addresses.	Cases diagnosed with wheezing bronchitis (from administrative data).	Logistic regressions controlled for parental asthma and maternal smoking.Cases had higher predicted NO_2 exposures than controls, restricted to girls only: Ordinal p for trend <0.02; OR for >70 versus <35 μg/m^3 NO_2: 2.7 (95% CI 1.1, 6.8).
Waldron et al. (*100*)	Cross-sectional. East Surrey, Great Britain. Rural and urban wards with and without motorways. Children: 13–14 yr (n = 2,324).	Traffic density: Binary classification of wards: motorway versus nonmotorway. There was no definition of motorway, and a ward was classified as motorway if any part of the motorway passed through it.	Respiratory symptoms: Ever wheezing; in past year: wheezing, sleep disturbance from wheeze, speech limitation from wheeze, wheeze after exercise, dry cough at night, and ≥4 wheezing attacks. Physician-diagnosed asthma (self-reported).	Unadjusted comparisons only with chi-square tests showed no associations in relation to wards having versus not having a motorway.
Duhme et al. (*101*)	Cross-sectional. Münster, NW Germany. Administrative city with few industrial areas; urban and rural settings sampled with various traffic densities. Children: 12–15 yr (n = 3,703).	Traffic density: self-reported frequency of truck traffic near home (never, seldom, frequent, and constant). Traffic noise: self-reported frequency of intense traffic noise near home (never, seldom, frequent, and constant).	Respiratory symptoms (recalled for last year): Wheezing—written and video questionnaires (ISAAC). Allergic rhinitis symptoms—written questionnaires.	Logistic regressions controlled for age, gender, parental history of asthma, passive smoking at home, and active smoking. Found increased prevalence of wheezing by video questionnaire for more truck traffic: frequent versus never [OR 1.35 (95% CI 1.04, 1.77)], constant versus never [OR 1.94 (95% CI 1.33, 2.84)]. Effects using written questionnaire responses were consistent. Consistent significant trends with ordinal intense traffic noise. Found increased age- and gender-adjusted prevalence of allergic rhinitis for children; frequent versus never [OR 1.71 (95% CI 1.36, 2.15)], constant versus never [OR 1.96 (95% CI 1.40, 2.76)]. Consistent significant trends with ordinal intense traffic noise. Effect modification of allergic rhinitis risk seen for duration: association only found for subpopulation >5 yr in present home

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Table 2. *Continued.*

Reference citation	Design and location of study. Subject ages (yr) and characteristics	Exposures	Health outcomes	Results
Brunekreef et al. (*102*)	Cross-sectional. Netherlands, Province of South Holland. Six residential areas with homes near major freeways; 80,000–152,000 vehicles/day. Children: 7–12 yr, lived within 1,000 m of freeway assessed in 1995 (n = 778), [subset of van Vliet et al. (*103*) below]; 85% lived at current residence for 3 or more years.	Annual (1993) truck traffic density per region and school. Annual (1993) auto traffic density per region and school. Distance home to freeway: ≤100 m versus >100 m. Indoor school air pollution: NO_2, black smoke.	Lung function: FEV_1, PEF, FVC, and $FEV_{25–75\%}$.	Regressions controlled for age, gender, smoking in home, pets, home dampness or mold, ethnicity, number of home residents, gas cooking, gas unvented water heaters, and parental education. Home within 100 m versus >100 m of freeway not significant. Deficits found for truck (not auto) traffic density, and deficits larger for children living within 300 m of freeway: for 10,000 trucks/day FEV_1, –4.1 (95% CI –7.9, 0.1); FVC, –3.6 (95% CI –7.4, 0.3). Pollutant-related deficits larger for children living within 300 m of freeway, and significant deficits for black smoke: per 10 μg/m^3, FEV_1, –3.7 (95% CI –7.7, –0.2); FVC, –2.7 (95% CI –6.1, 0.9); $FEV_{25–75\%}$, –6.3 (95% CI –13.2, 1.2). Similar deficits for PEF. NO_2 significant only for $FEV_{25–75\%}$ per 10 μg/m^3: –3.6 (95% CI –7.1, –0.1). Deficits larger in girls than boys; for 10,000 trucks/day FEV_1 for boys: –1.8 (95% CI –7.5, 4.2); girls, –8.3 (95% CI –13.0, –3.4).
van Vliet et al. (*103*)	Cross-sectional. Netherlands, Province of South Holland. Six residential regions with homes near major freeways: 80,000–152,000 vehicles/day. Children: 7–12 yr, lived within 1,000 m of freeway assessed in 1995 (n = 878). 85% lived at current residence for 3 or more years.	Annual (1993) truck traffic density per region and school. Annual (1993) auto traffic density per region and school. Distance home to freeway: ≤100 m versus >100 m. Indoor school air pollution: NO_2, black smoke.	Respiratory symptoms: chronic cough, wheezing, asthma attacks, rhinitis. Physician-diagnosed illness: asthma, bronchitis (self-reported). Physician diagnosed allergy to pets, dust mites, pollen (self-reported).	Logistic regressions controlled for age, gender, smoking in home, pets, home dampness or mold, ethnicity, number of home residents, gas cooking, gas unvented water heaters, and parental education. Associations found in girls not boys: For truck (not auto) traffic density (per 9,482 vehicles/day) and wheeze [OR 3.42 (95% CI 0.98, 11.9)] and asthma attacks [OR 4.34 (95% CI 1.12, 16.8)]. Home within 100 m of freeway and chronic cough [OR 2.45; 95% CI 1.16, 5.16), wheeze [OR 3.05 (95% CI 1.11, 8.41)], and rhinitis [OR 2.30 (95% CI 0.96, 5.52)]. Black smoke and chronic cough [OR 2.94 (95% CI 0.98, 8.83)], and rhinitis [OR 3.06 (95% CI 0.87, 10.8)]. NO_2 not significant. Physician-diagnosed asthma was not associated with increased exposure, but fewer persons with asthma lived near high traffic density freeways. Physician-diagnosed allergy was inversely associated with NO_2 and black smoke.
Ciccone et al. (*104*)	Cross-sectional. Ten sites in northern and central Italy with rural and urban settings, including three large cities: Torino, Milan, and Rome. Children: 6–7 yr (n = 18,737); 13–14 yr (n = 21,067). 53.3% of subjects had never moved from home since birth.	Traffic density: self-reported frequency of traffic near home (absent, low, moderate, and high). Self-reported number of bus routes near home (0, 1, and ≥2). Self-reported truck transit near home (never or seldom, sometimes, and often).	Respiratory disease (first 2 years of life): bronchitis (>three episodes), pneumonia, bronchiolitis, spastic laryngitis, wheezing bronchitis (>three episodes), none of the diseases listed (reference group). Respiratory symptoms (past year): wheeze, severe cough, dyspnea + wheeze, morning chest tightness, conditions apart from colds (nocturnal dry coughs, persistent cough, persistent cough > 2 months, persistent phlegm > 2 months), none of the conditions listed (reference group). Physician-diagnosed illness: current asthma, asthma attack that resulted in hospitalization (self-reported).	Logistic regressions controlled for age, gender, study center, change of residence, parental history of asthma, parental education, smoking (self, mother, father, others), number of home residents, gas cooking, heating system, month of survey, maternal smoking, bedroom (dampness, mold, bedding), floor level. No significant associations for overall traffic density. Significant positive associations found for metropolitan areas for combined respiratory diseases first 2 yr of life with bus routes and truck transit: OR for often versus never truck traffic 1.39 (95% CI 1.19, 1.62); consistently positive associations across individual respiratory diseases. Positive associations found for combined respiratory symptoms the last year plus illnesses and bus routes and truck transit: OR for often versus never truck traffic 1.29 (95% CI 1.15, 1.45); consistently positive associations across individual current respiratory conditions. OR for current asthma and truck traffic, often versus never: 1.25 (95% CI 0.99, 1.59), which was higher in children with persistent cough and phlegm for 2 months [OR 1.70 (95% CI 1.11, 2.61)]. Asthma hospitalizations (n = 36) were not associated with exposure.
English et al. (*105*)	Case–control. San Diego, Califonia, USA. Children: ≤14 yr; 5,996 cases diagnosed with *ICD-9* code for asthma in the 1993 California Medicaid claims database, including pharmacy visits; 2,284 random nonrespiratory control claims.	Traffic density: average weekday traffic density within a 550-ft radius around home using GIS on the street with highest volume, the closest street, and the sum of all streets weighted using dispersion models without wind data.	Cases diagnosed with asthma on Medicaid claims. Case-based analysis: cases with ≥2 versus 1 medical visit per year of study.	Logistic regressions controlled for race, medical visit type, and urban/rural residence. Case–control: there were no significant associations and all ORs were close to 1.00 with wide confidence intervals. No differences were found in separate models by gender or excluding accident controls. Case-based: there were elevated ORs for each quintile of traffic flow on the nearest street; no evidence of dose-response. OR for case having two or more visits versus one with traffic flows > 41,000 cars/day (95th percentile): 2.91 (95% CI 1.23, 6.91).

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Table 2. *Continued.*

Reference citation	Design and location of study Subject ages (yr) and characteristics	Exposures	Health outcomes	Results
Guo et al. (*106*)	Cross-sectional. Taiwan. Children: middle school students attending schools located within 2 km of 55 air pollution monitoring stations (n = 331,686). Excluded active smokers.	Ambient air pollution: annual mean from 55 monitoring sites. Principal component analysis factors: Factor 1: positively associated with CO and NO_x, negatively associated with O_3 - "traffic related." Factor 2: positively associated with SO_2, and PM_{10} - "industry, power plants, domestic fuel." Weather: annual mean temperature and RH.	Physician-diagnosed asthma (self-reported). Questionnaire-determined asthma from student video questionnaire (ISAAC)[a] report of dyspnea and nocturnal dyspnea associated with wheezing, or parent-reported attacks of dyspnea with wheezing, or parent-reported physician-diagnosed asthma.	Two-stage logistic regression. First stage: site-specific asthma prevalences were adjusted for age, history of atopic eczema, and parental education in each of 55 monitoring catchments sites. Second stage: site-specific asthma prevalences rates were adjusted for temperature and relative humidity to assess effects of air pollutant factor scores. Factor 1 was positively associated with physician-diagnosed asthma in boys and girls ($p < 0.001$) and with questionnaire-determined asthma in boys and girls ($p < 0.01$). For an interquartile increase in CO (326 ppb) and in NO_x (17.3 ppb), the prevalence of either physician-diagnosed or questionnaire-based asthma increased around 1% for both boys and girls Parameters for factor 2 were negative for all models.
Hirsch et al (*107*)	Cross-sectional. Dresden, SE Germany. Children: 5–7 yr (n = 2,796) 9–11 yr (n = 2,625), who lived in Dresden 12 or more months. Random subsamples of 5- to 7-yr olds and all 9- to 11-yr olds were used for SPT (n = 1,138 and 2,050, respectively) and serum IgE (n = 870 and 1,887, respectively). Random subsamples of 9- to 11-yr olds were used for lung function (n = 1,137) and BHR (n = 956).	Ambient air pollution: SO_2, NO_2, CO, benzene, O_3 measured for 1 yr in 182 1-km^2 grids across urban Dresden and geocoded and weighted to the subject's school and home addresses. Traffic density: parent-reported frequency of truck traffic near home.	Respiratory symptoms: wheezing, morning cough last year. Atopic symptoms: Rhinoconjunctivitis, symptoms of atopic eczema. Physician-diagnosed illness: Asthma, bronchitis (self-reported). Atopic sensitization: SPT, specific IgE antibodies. Lung function: FEV_1, $FEF_{25–75\%}$. BHR	Logistic regressions controlled for age group, birth weight, central heating, maternal smoking, pets, home dampness, carpets, floor level, parental education. Wheeze last 12 months was not associated with exposures. Morning cough was positively associated with SO_2, NO_2, CO, and benzene inversely with O_3. Per 1 $\mu g/m^3$ benzene at home plus school OR 1.21 (95% CI 1.04, 1.40). OR from constant truck traffic versus none: for cough, 1.60 (95% CI 1.06, 2.42), for wheeze, 2.09 (95% CI 1.24, 3.53). Tendency for increased prevalence of asthma, but significant only for benzene: OR 1.21 (95% CI 1.01, 1.45). However, in subgroup models, effects on asthma prevalence were significant for nonatopic, children from SO_2, NO_2, CO, and benzene (lower 95% CI ≥ 1.00; ORs 1.29–1.49). Significant increase in prevalence of bronchitis for NO_2, CO, and benzene (ORs 1.16–1.27). No association with prevalence of atopic symptoms, atopic sensitization lung function, or BHR.
Wilkinson et al. (*108*)	Case–control. North Thames (West), UK. Children: 5–14 yr 1,380 cases with Emergency admissions for *ICD-9* code for asthma; 2,131 cases all *ICD-9* respiratory admissions including asthma; 5,703 controls with nonrespiratory admissions excluding accident.	Traffic density: modeled vehicle meters/hr along roads within 150 m of the postcode centroid of home, linked by GIS. Distance: from postcode centroid of home to nearest main road (>150 m versus. ≤ 150 m); and to nearest road with modeled peak > 1,000 vehicle-meters/hr.	Cases admitted to hospital with asthma (from administrative data). Cases admitted to hospital with any respiratory illness (from administrative data).	Logistic regressions controlled for age, gender, hospital, and average census tract SES. For both asthma and all respiratory admissions there was no significant difference for traffic density or distance to nearest main road. For asthma, a borderline ($p < 0.06$) decreasing risk with increasing traffic was seen. No differences were found in separate models by gender.
Krämer et al. (*109*)	Cross-sectional, as well as, prospective outcome assessment of atopic symptoms for 1 yr along with NO_2. Dusseldorf, W. Germany. Two urban areas near major roads and one suburban area. Children: 9 yr (n = 306); urban = 204; suburban = 102; lived 2 or more yr at same home.	Ambient air pollution. Palmes tubes passively sampled NO_2 at 158 locations for 1 week in each of 4 seasons. Palmes tubes were used for other NO_2 samples in March and September 1996. Analytic variables are interpolated outdoor NO_2 from 158 sites and predicted personal NO_2 from actual personal and micro-environmental NO_2.	Respiratory symptoms: wheezing and allergic rhinitis symptoms reported weekly in diaries over 1 yr. Physician-diagnosed illness: asthma, hay fever, eczema (self-reported). Atopic sensitization: SPT (pollen, dust mites/cats, and milk or eggs); serum (IgE antibodies).	Logistic regressions controlled for older siblings, gender, and education of parents. Associations were dominated by urban subgroup as follows: Outdoor NO_2, but not personal NO_2, was significantly associated with reports of at least 1 week with symptoms of wheezing [OR for 10-$\mu g/m^3$ increase: 14.9 (95% CI 2.59, 86.4)] and with symptoms of allergic rhinitis [OR 1.81 (95% CI 1.02, 3.21)], which in pollen season increased to OR 3.09 (95% CI 1.38, 6.92). An ever diagnosis of hay fever was associated with outdoor NO_2 [OR 4.24 (95% CI 1.01, 17.8)]; asthma was not [OR 1.82 (95% CI 0.36, 9.36)]. Atopic sensitization to pollen, house dust mite or cat, and milk or egg were each significantly associated with outdoor NO_2 (ORs ranged from 3.5 to 5.0), but not personal NO_2. (See text and Figure 2.)
Venn et al. (*110*)	Cross-sectional. Case–control selected within initial survey. A cohort subset was taken from historical data on wheeze 7 years previously. Nottingham area, United Kingdom. Children: Survey: 4–11 yr (n = 22,986) 11–16 yr (n = 27,826). Case–control: 2,648 cases of all children reporting wheeze, versus random sample of 3,928 controls without recent wheeze. Cohort: 765 adolescents in both old and new survey.	Traffic density (24 hr): TAI (meters traveled/day/km^2) for 1 km^2 around subject's school; no information relating to distance from home. TAI tertile (in millions): low ≤ 22; medium 23–31; high ≥ 32.	Respiratory symptoms: past year attacks of wheeze and presence of troublesome cough (especially at night) apart from cold or chest infection. Physician-diagnosed illness: asthma (self-reported).	Prevalence of wheeze adjusted for age and sex in subjects 4–11 yr was not associated with continuous TAI, but was associated with middle and upper versus lower tertile [OR 1.11 (95% CI 1.02, 1.22) and 1.13 (95% CI 1.03, 1.24), respectively]. Prevalence of cough adjusted for age and sex in subjects 4–11 yr was also nonlinearly associated with the middle and upper versus lower tertile TAI [OR 1.21 (95% CI 1.02, 1.44) and 1.22 (95% CI 1.02, 1.45), respectively]. Prevalence of asthma adjusted for age and sex in subjects 4–11 yr was also nonlinearly associated with the middle and upper versus lower tertile TAI [OR 1.16 (95% CI 1.02, 1.31) and 1.16 (95% CI 1.02, 1.32), respectively]. In subjects 11–16 yr there was no association of wheeze, cough, or asthma with either continuous TAI or tertiles. ORs for wheeze, cough, and asthma in case–control sample adjusted for age, sex, social class, and maternal smoking were positive but not significant. Weak linear relationship of persistent wheeze in cohort sample with TAI (p = 0.06); OR 1.05 (95% CI 1.00, 1.11) per 10 million TAI units.

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Table 2. *Continued.*

Reference citation	Design and location of study. Subject ages (yr) and characteristics	Exposures	Health outcomes	Results
Oosterlee et al. (*115*)	Cross-sectional. Haarlem, Netherlands. Children: 106 children (0–15 yr) living along busy traffic streets (72% born in same house) compared with 185 control children living along streets with little traffic, same neighborhoods, same housing type (66% born in same house). Adults: 673 adults living along busy traffic streets compared with 812 controls as above.	Traffic classification: binary; busy streets versus quiet streets predicted with model calculations of NO_2 concentrations based on detailed traffic data including traffic density (CAR model) (*117*); estimated traffic density on busy streets 10,000–30,000 vehicles/day.	Respiratory symptoms: chronic cough, cough with phlegm, dyspnea (ever/in past year), wheeze (ever/in past year), dyspnea with wheeze (ever/in past year). Medication: asthma medication currently; respiratory medication ever. Physician-diagnosed illness: asthma, allergy (self-reported).	Logistic regressions controlled for age, sex, education of mother, change of residence, parental history of asthma, passive smoking, presence of an unvented gas hot water heater, number of home residents, gas cooking, type of heating system, pets, and home humidity. Children: too few with asthma, chronic cough, or cough with phlegm to analyze. Seven of 9 other ORs ranged from 1.5 to 4.8; only ever respiratory medication was significant, and ever wheezing was $p < 0.06$. Effects were dominant in girls and most significant: wheeze in past year [OR 5.3 (95% CI 1.1, 25.0)], attacks of dyspnea with wheeze in past year [OR 15.8 (95% CI 1.4, 174)]. Physician-diagnosed allergy not associated with traffic. Adults: only dyspnea while walking significant: OR 1.8 (95% CI 1.1, 3.0).
Nitta et al. (*111*)	Cross-sectional, three surveys. Western suburbs of Tokyo, Japan. Three areas with homes near major roadways; 30,000–53,000 vehicles/12-hr day. Adults: Women only, 40 yr of age or older: 1979 ($n = 1,517$), 1982 ($n = 2,413$), and 1983 ($n = 2,389$). Lived 3 or more yr at same home.	Distance to major roadway: <20 m versus 20–150 m for 1979 and 1983; <20 m versus 20–50 m, and versus 50–150 m for 1982. Confirmed gradient difference with 2–7/day average. NO and NO_2.	Respiratory symptoms: chronic wheeze most days or nights apart from colds, chronic cough or chronic phlegm 3 or more months last year, dyspnea with walking, off work with chest illness with phlegm in last 3 yr.	Logistic regressions controlled for age, smoking status, years at residence, education, occupation, and type of home heating. 1979: all five ORs >1.0, ranging from 1.35 to 2.75, and all but one symptom (dyspnea) was significant. 1982: four of five ORs >1.0, ranging from 1.13 to 1.87; only (OR 1.87) was significant for <20 m versus 20–50 m, and only chronic cough (OR 1.78) and phlegm (OR 1.85) were significant for <20 m versus 50–150 m. 1983: Three of five ORs > 1.0, ranging from 1.26 to 1.66; only dyspnea was significant (OR 1.66).
Nakai et al. (*112*)	Cross-sectional. Repeated measures for lung function. Tokyo, Japan. Areas within varying distances from roads with heavy traffic: 30,000–34,000 vehicles/12-hr day (<21% diesel powered), versus referent area away from roads with heavy traffic. Adults: women only, 39–59 yr ($n = 1,986$). Lived 3 or more yr at same home.	Distance home to major roadway: Zone A = 0–20 m; B = 20–150 m; C = reference zone in suburbs. Confirmed gradient difference with NO_2 (passive indoor, personal, and outdoor at 0, 20, and 150 m from roadside) 2 days each in 10 seasons, fall 1987 to winter 1990. Personal NO_2 exposures were primarily attributable to traffic if no gas stoves in the home, as reported in Nakai et al. (*116*).	Respiratory symptoms: Chronic wheeze most days or nights apart from colds, chronic cough or chronic phlegm 3 or more months last year, dyspnea with walking. Lung function: age-and height adjusted FEV_1, FVC in subsample of 200 nonsmoking women without history of respiratory disease; repeated measurements each of 10 seasons.	Logistic regressions controlled for age, smoking status, years at residence, occupation, and type of home heating. Prevalence of chronic cough and chronic phlegm were higher in zone A than C [OR 2.18 (95% CI 1.08, 4.42) and OR 1.79 (95% CI 1.07, 3.01), respectively]. Chronic cough was higher in zone A than B [OR 1.87 (95% CI 1.02, 3.42)]. Zone B did not differ from C. There were no consistent differences for wheeze or dyspnea. Longitudinal mixed regression models for lung function decline showed no consistent differences by zone.
Montnémery et al. (*114*)	Cross-sectional. Malmöhus and Skåne counties, Sweden. Adults: random sample by age deciles 20–59 yr.	Traffic classification: Binary. "Yes" versus "no" to question "Do you live close to a road with heavy traffic?"	Respiratory symptoms: Asthma symptoms last 12 months including dyspnea with or without cough or wheeze; long-standing cough last year. Physician-diagnosed illness: asthma (self-reported).	Symptom prevalence rates were adjusted for age and gender by direct standardization to county. Comparing subjects living close versus those not to living close to heavy traffic, asthma symptoms were more prevalent (10.5 vs. 8.4%, respectively; $p = 0.001$) and long-standing cough was also more prevalent (15.9 vs. 10.5%, respectively; $p = 0.001$). Logistic regressions on asthma diagnosis controlled for age, gender, and smoking behavior. Asthma diagnosis was significantly associated with living close to heavy traffic [OR 1.29 (95% CI 1.02, 1.62)].
Wyler et al. (*113*)	Cross-sectional. Basel-Stadt, NW Switzerland. Traffic "decimals" ranged from 24 to 32,504 vehicles/day. Adults: 18–60 yr (mean 41.1); $n = 820$. Known residence time at same address incorporated into analysis: 1–9 yr versus ≥10 yr	Traffic density on street of home address: Cars per 24 hr: 24–710; 711–1,620; 1,621–5,250; 5,251–32,504 Trucks per 24 hr: 0–20, 21–100, 101–360, 361–4,744.	Respiratory symptoms: hay fever past 2 yr; ever symptoms of seasonal rhinitis or conjunctivitis when exposed to pollen; ever seasonal asthma symptoms of cough or wheeze or chest tightness or dyspnea when exposed to pollen. Atopic sensitization: SPT for local pollen (timothy grass, birch, pellitory-of-the-wall), dust mite, cat, dog, fungi (cladosporium, alternaria).	Logistic regressions controlled for age, gender, smoking behavior, education, number of siblings, and family history of atopy. There were no associations between any respiratory symptoms and traffic density. Sensitization to pollen: ordinal comparisons to lowest car density showed a significant trend, with larger effects for resident living in same home ≥10 yr: OR 1.99 (95% CI 0.91, 4.38), OR 2.47 (95% CI 1.06, 5.73), OR 2.83 (95% CI 1.26, 6.31). Effects were similar for truck traffic. Effects were larger for women than men. Sensitization to indoor allergens (dust mite, cat, dog): no significant trends were found.

Abbreviations: BHR, bronchial hyperresponsiveness; *ICD-9, International Classification of Diseases, 9th Revision*; ISAAC: International Study of Asthma and Allergies in Childhood; MEF, maximal expiratory flow rates when, as indicated by subscripts, 25%, 50%, or 75% of forced vital capacity has expired; PEFR, peak expiratory flow rate; SPT, skin prick test; TAI, traffic activity index.

study in Italy also found increased prevalence of asthma and symptoms from truck and bus traffic but not overall traffic (*104*). Only the study by Wyler et al. (*113*) failed to show any difference between truck and car traffic in strengths of association; positive associations were limited to atopic sensitization.

Although most of the traffic studies did not report associations by gender, four did find adverse effects of traffic-related exposures in children to be stronger in girls than in boys (*99,102,103,115*), while two other showed null results for both genders (*105,108*). In the study by Wyler et al. (*113*) in adults, associations between pollen sensitization and home traffic density were larger for women than men. These gender differences are unexplained. Although differences in the perception of symptoms or reporting bias are possible, this does not explain the considerably larger lung function deficits in girls reported by Brunekreef et al. (*102*).

Negative results in the studies of traffic-related exposures may be due to weaknesses that lead to exposure and outcome misclassification, which generally, but not always, lead to bias toward the null hypothesis if the misclassification is independent of systematic errors (*118*). This bias was possible in studies that used areawide exposure estimates without assessments of microenvironmental exposures or traffic near the home and school (*96,100,106,110*), or that relied entirely or partly on self-reported exposures (*98,101, 104,107,114*). Nevertheless, most of these studies still showed positive associations between traffic and respiratory outcomes. Except for pulmonary function tests (*96,102,107,112*) and tests for atopic sensitization (*107,109,113*), respiratory outcomes, including physician-diagnosed illnesses, were either abstracted from administrative databases (*97,99,105,108*) or self-reported for the remaining studies. All but a subsample of two studies (*110,112*) were subject to cross-sectional or case–control biases. One of these biases stems from the use of current exposure. Current exposure may not be a good surrogate for exposure during past times that are more temporally relevant to current disease status. This is because outcomes may have an onset in the past, or because outcomes were previous illnesses or exacerbations of disease recalled in survey questionnaires. An important assumption is that current residence near traffic is a proxy for past exposures, and some, but not all, of the studies screened for residence times (*96,99,102,103,107,109*). One resultant systematic bias that could lead to null results is differential migration away from busy streets by symptomatic subjects. This is supported by the finding of Oosterlee et al. (*115*) that parents with children having respiratory symptoms live an average of 2.6 years shorter at the present address than those of asymptomatic children. A positive bias, on the other hand, could have occurred from socioeconomic status (SES), which was not always controlled for. This is important because people living on busy streets may be poorer. Clearly, well-designed prospective cohort studies and repeated measures panel studies are needed to assess the question of whether exposure to primary pollutants from traffic, which include air toxics, are risk factors for the onset or exacerbation of asthma and other respiratory allergic illnesses in children and adults.

One epidemiologic approach that may prove useful to define source-specific air pollutant exposures such as traffic-related exposures is the use of principal component factor analysis with varimax rotation using available criteria pollutant data. One large survey study used this approach in Taiwan (*106*). They recruited 331,686 middle school children who were nonsmokers and were enrolled in schools within 2 km of 1 of 55 monitoring stations. They compared asthma prevalence rates with air pollution concentrations and found positive associations with asthma prevalence for NO_x and CO. These gases had factor loadings (correlation of a variable with a factor, which is a latent, unobserved variable) over 0.91, along with inverse loadings for O_3 of –0.92, likely from scavenging of O_3 by NO_x (Table 2). For an interquartile increase in CO (326 ppb) and in NO_x (17.3 ppb), the prevalence of either physician-diagnosed or questionnaire-based asthma increased around 1% for both boys and girls. Asthma was not associated with PM_{10} or SO_2, except for an unexpected inverse association in boys for PM_{10}. The association of acute asthma with CO is supported in a Seattle panel study of 133 asthmatic children and is likely explained by more causal components of vehicle exhaust and other combustion byproducts (*119*).

It is possible that associations between allergic respiratory illnesses and traffic density are due to NAAQS criteria air pollutants, particularly NO_2, which is directly related to local traffic density (*120*). Krämer et al. (*109*) assessed this possibility in a study of 306 children 9 years of age living at least 2 years in a home near major roads in Germany (Table 2). Using passive samples with Palmes tubes, weekly average concentrations were measured for personal NO_2 in March and September, and for outdoor home or near-home NO_2 at 158 locations in each of four seasons (levels at home addresses were interpolated). Investigators showed that outdoor NO_2 was a good predictor of home traffic density (Pearson *r*, 0.70) but a poor predictor for personal NO_2 exposure (*r*, 0.37) reflecting the known importance of indoor NO_2 sources. They followed the children with weekly parental questionnaires for atopic symptoms for 1 year. In suburban areas there was little variation in outdoor NO_2, (range 43–46 μg/m^3) and inclusion of suburban subjects (n = 104) in regression models decreased parameter estimates and increased standard errors. For urban areas (n = 202), they found that atopic sensitizations to pollen, to house dust mite or cat, and to milk or egg (by SPTs or RAST) were each significantly associated with outdoor NO_2 (ORs ranged from 3.5 to 5.0) but not predicted personal NO_2. They also found that outdoor NO_2, but not predicted personal NO_2, was significantly associated with reports of at least 1 week with symptoms of wheezing and of allergic rhinitis. Relationships for atopy and rhinitis symptoms by quartile of outdoor NO_2 suggested a dose–response relationship (Figure 2). Although an ever diagnosis of hay fever (n = 35) was associated with outdoor NO_2, diagnosed asthma was not (n = 25). The maximum outdoor NO_2 of the urban sites was 36 ppb (67.5 μg/m^3), which is far less than the U.S. EPA NAAQS of 53 ppb annual mean (100 μg/m^3). The overall results suggest that outdoor NO_2 was serving as a marker for more causal airborne agents rather than a direct effect of NO_2.

High personal exposures to PAHs near busy streets were possible in the study by Krämer et al. (*109*), as well as other studies in Table 2 for high traffic density. Dubowsky et al. (*121*) measured total real-time, particle-bound PAHs from three nonsmoking indoor sites with different traffic densities characteristic of urban, semiurban, and suburban residencies. Diaries were used to detect effects of cooking and indoor combustion events (e.g., candles). A significant contribution of traffic-related PAHs to indoor PAHs was detected. Indoor peaks occurred during morning rush hour on weekdays only (max = 65 ng/m^3 for urban locations). The geometric means of PAHs corrected for indoor sources were urban, 31 ng/m^3; semiurban, 19 ng/m^3; and suburban, 8 ng/m^3.

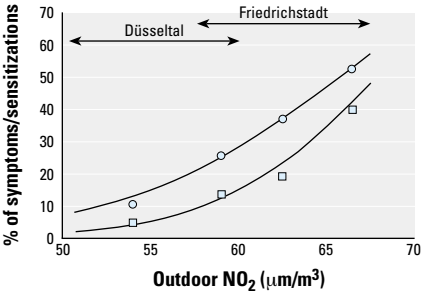

Figure 2. Relationship of symptoms of allergic rhinitis (□) and of atopic sensitization against pollen (○) to quartiles of exposure to outdoor home NO_2 in 202 children 9 years of age living in urban areas of Germany. Adapted from Krämer et al. (*109*).

Despite the suggestion that NO_2 may be acting as a surrogate pollutant, the respiratory effects of NO_2 are still important. However, the magnitudes of effects of NO_2 on asthma are not entirely clear, and there are considerable inconsistencies in the experimental literature. Some studies have shown alterations in lung function, airway responsiveness, or symptoms, whereas others have not, even at high concentrations [reviewed by Bascom et al. (*5*)]. Data that support the traffic density studies come from a clinical crossover study that used ambient exposures of 20 mild pollen-allergic adult asthmatic individuals (*122*). Subjects showed early- and late-phase bronchospastic reactions to pollen allergen challenge that were greater 4 hr after a 30-min exposure in a car parked in a road tunnel (30-min median NO_2, 157 ppb; median $PM_{2.5}$, 95 μg/m^3) compared with a low control exposure in a suburban hotel (24-hr badge NO_2, 22 ppb). Specific airway resistance 15 min after allergen challenge increased 44% in 12 subjects exposed to road tunnel NO_2 > 159 ppb compared with 24% for their control exposures ($p < 0.05$). The higher NO_2 tunnel exposures were associated with significantly more symptoms and beta-agonist inhaler use 18 hr after allergen challenge. In addition, FEV_1 decreased significantly more than with control exposures 3–10 hr after allergen challenge (8.5 vs. 6.8%). Effects were smaller using PM_{10} or $PM_{2.5}$ as the exposure metric. The authors compared their results with those from earlier chamber studies using 265 ppb NO_2 before allergen challenge. They concluded that although those results also showed an enhancement of early- and late-phase asthmatic reactions (*123,124*), effects were greater for lower NO_2 exposures in the tunnel, suggesting other pollutants were important.

Other agents aside from either NAAQS criteria air pollutants or air toxics could explain some part of the association of asthma and allergy outcomes with traffic density. Latex allergen found on respirable rubber tire particles is likely common in urban air (*125,126*) and could lead to sensitization and respiratory symptoms. In addition, the physical action of motor vehicles on road dust, which is known to contain pollen grains, could lead to the production and resuspension of smaller respirable pollen fragments (*37*). Other allergenic bioaerosols such as fungal spores could be fragmented and resuspended as well. Interactions between pollutants and allergens could also influence effects. Allergenic molecules could be delivered to target sites in the airways on diesel carbon particles. as evidenced *in vitro* using the rye grass pollen allergen Lol p1 (*127*). Another study using immunogold labeling techniques found that indoor home soot particles, primarily in the submicrometer size range, had bound antigens of cat (*Fel* d 1), dog (*Can* f 1), and birch pollen (Bet v 1), and this adsorption was replicated *in vitro* with DEP particles (*128*). Other biologic interactions between pollutants and allergens on airways that favor inflammatory reactions have been hypothesized (*129*), including enhancement of allergen sensitization in asthmatic children with ETS exposure (*130*) and pollutant-induced enhancements of the antigenicity of allergens (*131,132*).

Summary of the Potential Role of PAHs in Asthma

Experimental evidence supports the biologic plausibility of a role for PAHs from fossil fuel combustion products in the onset and exacerbation of asthma. However, the occupational data on DE and asthma onset are limited to one three-case series. In addition, despite high exposures, overall inconsistency is found in occupational studies of respiratory symptoms or lung function and diesel/gas exhaust exposures. Bias from the healthy worker effect is likely given the expectation of avoidance behavior among individuals with respiratory sensitivity to inhaled irritants, including asthmatics. This behavior has been hypothesized to result from a toxicant-induced loss of tolerance (*133*). The inconsistent and weak occupational evidence does not rule out different dose–response relationships for asthma in nonoccupational settings. Epidemiologic results showing associations between childhood asthma and ETS may be explained, in part, by PAHs. Positive results in epidemiologic studies of asthma and traffic-related exposures also may be explained, in part, by PAHs. The question that remains is, what are the determinants of asthma associations with complex mixtures of ETS-related and traffic-related particle components and gases?

Coherence with Traffic Studies by Trends in Asthma and Urbanization

The above review gives the overall impression that asthma, related respiratory symptoms, lung function deficits, and atopy are higher among people living near busy traffic. Some data coherent with this view are found in studies showing a higher prevalence of asthma and atopic conditions in more developed Westernized countries and in urban compared with rural areas [reviewed by Beasley et al. (*134*) and Weinberg (*135*)]. For instance, studies in Africa have shown that pediatric asthma is rare in rural regions, whereas African children living in urban areas have experienced an increasing incidence of asthma (*135*). The urban-rural differences have tended to narrow as rural Africans became more Westernized (*135*). This suggests that the increase of asthma seen in developed countries may be attributable to some component(s) of urbanization, including automobile and truck traffic. However, this urbanization gradient is not a consistent finding across the literature (*136*). For instance, in the traffic exposure–response study by Montnémery et al. (*114*) (Table 2), although there were significant associations of asthma symptoms and diagnosis to traffic density, there were no urban-rural differences. In addition, some recent studies that specifically examined farming environments, found a decreased risk of asthma and atopy among children living on farms (*137,138*), particularly where there is regular contact with farm animals. This prompted these investigators to hypothesize that a "protective farm factor" may reflect the influence of microbial agents on T_H1 versus T_H2 cell development or reflect the development of immunotolerance (*137,138*). This possibility, in addition to potentially high levels of confounding by uncontrolled factors that vary by geography, makes it difficult to clearly interpret the cross-sectional studies on urban versus rural areas or ecologic studies of international differences.

Formaldehyde, Asthma, and Atopy in Children

The following section will examine the epidemiologic literature on the relationship of asthma and atopy in children to formaldehyde. This serves to exemplify one of the few low molecular weight agents associated with asthma in both the occupational (*22*) and nonoccupational literature, and to exemplify an air toxic that has effects from low to high exposure levels. However, there are little available nonoccupational data on the risk of asthma onset from formaldehyde.

One study passively measured formaldehyde over 2 weeks in the homes of 298 children and 613 adults (*139*). In log-linear models controlling for SES variables and ethnicity, the study found a significantly higher prevalence of physician-diagnosed asthma and chronic bronchitis in children 6–15 years of age living in homes with higher formaldehyde concentrations over 41 ppb (six asthma and six bronchitis cases). However, the room-specific measurements revealed that the association was attributable to high formaldehyde concentrations (>60 ppb) in kitchens, particularly those homes with ETS exposures (five asthma cases, five bronchitis cases), suggesting possible confounding by other factors not measured. In random effects models controlling for SES and ETS, they found significant inverse associations between morning PEF rates and average formaldehyde from the bedroom, and between evening PEF and household average formaldehyde. There was no

apparent threshold level. The PEF finding was independent of ETS, but the effects of age or of anthropomorphic factors were not mentioned. Symptoms of chronic cough and wheeze were higher, and PEF lower, in adults living in houses with higher formaldehyde levels. There was a significant interaction between formaldehyde and tobacco smoking in relation to cough in adults. Passive measurements of NO_2 did not confound the associations in children or adults.

Other nonoccupational data on formaldehyde relate indirectly to asthma. Wantke et al. (*140*) evaluated levels of specific IgE to formaldehyde using RAST in 62 eight-year-old children attending (for 2.5 years) one school with particleboard paneling and urea foam window framing. The children were transferred to a brick building (23–29 ppb formaldehyde) because of elevated formaldehyde levels in particleboard classrooms (43–75 ppb) and complaints of headache, cough, rhinitis, and nosebleeds. Symptoms and specific IgE were examined before and 3 months after cessation of exposure. At baseline, three children had RAST classes ≥ 2 (positive) and 21 had classes ≥ 1.3 (elevated), whereas all 19 control children attending another school had classes < 1.3. After transfer, the RAST classes significantly decreased from 1.7 ± 0.5 to 1.2 ± 0.2 ($p < 0.002$), and symptoms decreased. However, IgE levels did not correlate with symptoms. None of the children had asthma.

Garrett et al. (*141*) hypothesized that formaldehyde may adversely affect the lower respiratory tract by increasing the risk of allergic sensitization to common allergens. They studied 43 homes with at least one asthmatic child (53 asthmatic, 30 nonasthmatic) and 37 homes with only nonasthmatic children (n = 65). Atopy was evaluated in the children (7–14 years of age) with SPTs for allergy to 12 common animal, fungal, and pollen allergens. Formaldehyde was measured passively throughout the homes over 4 days in four different times of 1 year. Atopic sensitization by SPT was associated with formaldehyde levels [OR for 20 μg/m^3 increase, 1.42 (95% CI 0.99–2.04)]. Across three formaldehyde exposure categories, there was also a significant increase in the number of positive SPTs and in the wheal ratio of allergen SPT over histamine SPT. Mean respiratory symptom scores were significantly and positively associated across the three categories. There was a significant positive association between parent-reported, physician-diagnosed asthma and formaldehyde, but this was confounded by history of parental asthma and parental allergy. It is unclear why these familial determinants were treated as confounders rather than effect modifiers, although knowledge of asthma by parents may lead to bias in the assessment of asthma in their children.

Several other studies of nonasthmatic subjects have examined health outcomes and biomarkers that are relevant to asthma. Franklin et al. (*142*) studied 224 children 6–13 years of age with no history of upper or lower respiratory tract diseases, using expired nitric oxide (eNO) as a marker for lower airway inflammation (*143*). Formaldehyde was passively monitored in the children's homes for 3–4 days. Maximum end expiratory eNO was measured in each child with a fast-response chemiluminescence analyzer. They found no effect of formaldehyde on lung function. However, controlling for age and atopy (by SPT), eNO was significantly elevated to 15.5 ppb (95% CI 10.5, 22.9) in homes with ≥ 50 ppb formaldehyde compared with 8.7 ppb eNO (95% CI 7.9, 9.6) in homes with < 50 ppb formaldehyde. Authors did not report the cross-sectional risk of atopy to common allergens from exposure to formaldehyde. They hypothesized that formaldehyde causes inflammation and the release of cytokines, which leads to the upregulation of inducible NO synthetase. This view was supported by another study that found intranasal exposure to 400 ppb formaldehyde in healthy subjects caused eosinophilia in the nasal epithelium (*144*).

Given that a key marker of the asthmogenic effects of formaldehyde may be specific IgE to formaldehyde-albumin, other air toxics could be similarly screened to evaluate their potential influence on atopic responses.

Experimental Evidence for VOC Mixtures

Some experimental evidence in controlled human exposure studies supports an respiratory irritant mechanism for VOCs (*145,146*), but the human experimental research on lower respiratory or pulmonary immunologic effects of VOCs is scarce apart from studies of agents associated with occupational asthma (e.g., TDI, formaldehyde).

Koren et al. (*146*) conducted a randomized crossover chamber study of 14 healthy nonsmoking young adult men. Subjects were exposed for 4 hr 1 week apart to clean air and 25 μg/m^3 of a VOC mixture typical of indoor nonindustrial microenvironments. Nasal lavage performed immediately after exposure and 18 hr later showed significant increases in neutrophils at both time points. Harving et al. (*147*) conducted a randomized crossover chamber study of 11 asthmatic individuals who were hyperreactive to histamine. Subjects were exposed for 90 min, 1 week apart to clean air and VOC mixtures at 2.5 and 25 μg/m^3. Investigators found FEV_1 decreased to 91% of baseline with 25 μg/m^3, but this was not significantly different from sham exposure, and there was no change in histamine reactivity. It is possible that the null results do not reflect inflammatory changes that influence small airways, which could be missed with FEV_1 measurements. What may be occurring in natural environments is another story, with mixed exposures possibly interacting under a wide range of exposure–dose conditions. This is best investigated with epidemiologic designs.

Epidemiologic Evidence for VOC Mixtures

Indirect evidence of a role for ambient VOCs in asthma comes from research linking a buildup of indoor irritants including VOCs and bioaerosols in office buildings to a nonspecific cluster of symptoms called the "sick building syndrome," which includes upper and lower respiratory tract symptoms, eye irritation, headache, and fatigue. Other studies have also found new-onset asthma occurring in relation to particular nonresidential indoor environments, especially where problems with ventilation systems or dampness have been found (*75*). It is possible that fungal spores or other aeroallergens, mycotoxins, and endotoxins could increase in parallel with VOCs under conditions of inadequate air exchange at work, and be responsible for some of these findings.

Epidemiologic evidence linking indoor home VOCs with asthma or related respiratory outcomes come largely from cross-sectional studies. A survey of 627 students 13–14 years of age attending 11 schools in Uppsala, Sweden, showed self-reported asthma prevalence (n = 40) was higher in schools with higher VOCs (*148*). Other risk factors (e.g., aeroallergens) were not controlled for in this association. In addition, passive, not active, VOC measurements were associated with asthma.

Norbäck et al. (*149*), using a survey sample of 600 adults 20–44 years of age in Uppsala, Sweden, selected a nonrandom subsample of 47 subjects reporting asthma attacks or nocturnal breathlessness the last 12 months or reporting current use of asthma medications. A random subsample of 41 other subjects was selected from the survey pool with negative responses. Logistic regression models adjusted for age, sex, smoking, carpeting, and house dust mites, but not dampness, which was significant. There were no effects on daytime breathlessness from concentrations of 2-hr active VOC samples in the homes. Nocturnal breathlessness was associated with toluene, C8-aromatics, terpenes, and formaldehyde in adjusted models. Bronchial hyperresponsiveness was correlated only with limonene. PEF variability was correlated only with terpenes.

Wieslander et al. (*150*) aimed to examine respiratory symptoms and asthma outcomes in relation to indoor paint exposures in the

last year. They selected an enriched random sample of 562 adult subjects, including asymptomatic responders along with all reporting asthma or nocturnal dyspnea (216 subjects), using the same survey source population as Norbäck et al. (*149*) in Uppsala. Asthma was defined as positive bronchial hyperresponsiveness to methacholine plus asthma symptoms (99 subjects). Thirty-two percent of homes and 23% of workplaces were painted within the last year. Total VOC was elevated by 100 μg/m^3 in 62 newly painted homes. Logistic regression models adjusted for age, sex, and current smoking but not ETS. Asthma prevalence was greater for newly painted homes [OR 1.5 (95% CI 1.0–2.4)], consistent with greater differences in VOCs (especially 2,2,4-trimethyl 1,3-pentanediol diisobutyrate and formaldehyde). Blood eosinophil concentrations were also elevated in newly painted homes. In newly painted workplaces, asthmalike symptoms were significantly increased (wheeze, dyspnea), but there was no association with bronchial hyperresponsiveness or eosinophils. There were no associations for newly painted homes or workplaces and atopy (SPT), serum eosinophilic cationic protein, serum IgE, PEF variability (1 week, self-administered, twice daily), or in-clinic FEV_1. Biases in the above cross-sectional studies in Uppsala include potential selection bias and the possibility that health outcomes preceded exposures.

Diez et al. (*151*) studied 266 newborn children born with birth weight of 1,500–2,500 g, or with elevated IgE in cord blood, or with a positive primary family history of atopic disease. Concentrations of 25 VOCs were monitored indoors during the first 4 weeks of life. Parents filled out questionnaires after 6 weeks and 1 year of age. Postnatal respiratory infections were associated with benzene > 5.6 μg/m^3 [OR 2.4 (95% CI 1.3, 4.5)] and styrene > 2.0 μg/m^3 [OR 2.1 (95% CI 1.1, 4.2)]. Wheezing was associated with reports of restoration (including painting and installation of carpeting) during the first year of life, but not with total or specific IgE at the age of 1 year. These models controlled for heating, gas cooking, home size, new furniture, and animals but did not control for significant effects of ETS, which was correlated with benzene.

All of the above studies of indoor VOCs may be subject to unmeasured confounding by other causal agents that increase indoors under low ventilation conditions, including aeroallergens, or that are correlated with VOCs for other reasons. Most, but not all, of the studies controlled for ETS. The research to date is too sparse to evaluate causality from indoor home VOCs, but there is even less information to evaluate the public health impact on respiratory health from outdoor VOCs, which include some of the same compounds found indoors.

Ware et al. (*152*) conducted a study in a large chemical manufacturing center in the Kanawha Valley, West Virginia. They surveyed 74 elementary schools with interviews of 8,549 children in and out of the valley and measured passive 8-week samples of 5 petroleum-related VOCs (toluene, *m,p*-xylene, benzene, *o*-xylene, decane) and 10 process-related VOCs (1,1,1-trichloroethane, carbon tetrachloride, 1-butanol, chloroform, perchloroethylene, methyl isobutyl ketone, 1,2-dichloroethane, styrene, mesityl oxide, 2-ethoxyethyl acetate). Higher VOC concentrations were found in the valley. Cross-sectional results showed children in the valley had higher rates of physician-diagnosed asthma [OR 1.27 (95% CI 1.09, 1.48)]. Composite indicators for lower respiratory symptoms in the last year were weakly positively associated with petroleum-related VOC levels [OR per 10 μg/m^3, 1.05 (95% CI 1.02, 1.07)] and process-related VOCs levels [OR per 2 μg/m^3, 1.08 (95% CI 1.02, 1.14)]. Asthma diagnoses were weakly positively associated with petroleum-related VOCs [OR 1.05 (95% CI 1.02, 1.08)] but not process-related VOCs (OR 0.99). One school with high petroleum-related VOCs strongly influenced the model. The average concentrations measured in the Kanawha study do not differ greatly from average levels in large urban areas (*68*). For the Kanawha study compared with a Los Angeles ambient exposure study, for example, average toluene was 9.7 μg/m^3 versus 13 μg/m^3, respectively, and for benzene, 3.2 μg/m^3 versus 3.5 μg/m^3, respectively (*153*). In a study of 51 residents of Los Angeles, personal and indoor air concentrations of all prevalent VOCs except carbon tetrachloride were higher than outdoor ambient concentrations (*154*). Also, personal real-time exposures can be even higher, particularly while in cars (*155*). For example, measurements of toluene taken inside cars in New York City ranged from 26 to 56 μg/m^3 and for benzene ranged from 9 to 11 μg/m^3 (*156*).

Conclusions

Considerable progress has been made in identifying risks to asthma morbidity from the major criteria air pollutants such as ambient O_3 and particle mass, as well as from major types of air pollutant mixtures, particularly ETS. Like ambient particle mass though, the causal components of ETS are poorly understood. Less is known about asthma risks from primary emissions linked to car and truck traffic, which compared with ETS may be an equally important mixed-pollutant exposure. Both ETS and traffic exhaust pollutants contain some of the same toxic air pollutants, including PAHs. Experimental data support the biologic plausibility of a role of PAHs in allergic respiratory responses. However, the occupational epidemiology literature on respiratory outcomes and exposures to diesel and automobile emissions is inconsistent, likely due to major methodologic flaws. The nonoccupational epidemiology literature on traffic-related exposures, on the other hand, is more consistent, particularly when better-designed studies are considered. These studies commonly showed an increase in the prevalence of asthma, atopy, upper and lower respiratory symptoms, and lung function deficits in relation to higher exposures to traffic (Table 2). Other air toxics commonly encountered in both indoor and outdoor ambient air include a large number of VOCs, including a known occupational asthmogen, formaldehyde. At present, however, both the human experimental and epidemiologic literature is limited to a few studies. What is needed now is to advance epidemiologic research on relationships of asthma onset and exacerbation to air toxics exposures. It will be important to disentangle effects of air toxics from major air pollutants regularly monitored by governments such as particle mass, black smoke, or NO_2. Studies could focus on air toxics identified as asthmogenic in occupational studies (e.g., certain metal compounds) and on other air toxics expected to have adverse respiratory effects based on biologic mechanisms (e.g., PAHs). Studies most likely to yield clear and valuable information include well-designed prospective cohort studies to ascertain the relevance of air toxics to asthma onset and chronicity, and repeated measures studies to evaluate acute exposure-dose–response relationships in susceptible individuals. Key design issues that have been only partly addressed to date include accurate exposure assessments, including personal and microenvironmental components, and accurate outcome assessments, including validated and objective physiologic measurements of acute and chronic ill health outcomes. Despite limitations in the current state of knowledge about air toxics and asthma, this review gives sufficient evidence to justify more intensive investigation.

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