

Latex allergen in respirable particulate air pollution

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Objective: Urban air samples contain numerous irregular respirable black particles, which may be airborne tire fragments. A major component of tires is natural latex. Proteins of natural latex can act as adjuvants and as antigens capable of eliciting immediate hypersensitivity, making their presence in particulate air pollution an important clinical issue.

Methods: Particulate air pollutants were collected by volumetric sampling devices and characterized by optical microscopy, chemical solubility tests, and mass spectrometry. Extracts of rubber tire fragments were tested for elutable latex antigens by antibody inhibition assays.

Results: Identification of latex in air samples and milled material from automobile tires was supported by mass spectrometry results and was further confirmed by physical appearance and chemical solubility studies. Competitive immunoassay confirmed the presence of extractable latex antigens from rubber tire fragments.

Conclusions: Latex antigens are extractable from rubber tire fragments, which are abundant in urban air samples. Given the adjuvant and sensitizing effects of latex, these airborne particles could contribute, through direct and indirect mechanisms, to the increase in both latex sensitization and asthma. The impact of these particles should be considered in the issue of morbidity and mortality rates associated with respiratory diseases and air pollution.

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Key words: Latex, rubber tires, air pollution, asthma

Natural latex is used in a wide variety of products that have become part of our everyday environment. The main source of natural latex is the sap of the tropical rubber tree, *Hevea brasiliensis*, and over 7 million metric tons are produced annually.¹ Native latex coagulates by forming polymers of cis-1,4 isoprene several thousand units in length.² Proteins comprise about 2% of the total solids of uncoagulated latex.³ Two of these proteins involved in the polymerization of isoprene units have been implicated in hypersensitivity reactions to latex products.^{4,5}

Sensitivity to latex had not been considered a major clinical problem until recent years. The

marked increase in the use of latex products, particularly in the health care industry, has likely contributed to the increase in latex sensitization.⁶ Clinical reactions vary from skin rashes and mild rhinitis to more severe bronchial asthma and life-threatening anaphylactic reactions.^{7,8} Risk factors identified include frequency of exposure and atopy.⁹ Recent studies indicate that up to 14% of health care workers are affected, as well as 64% of patients with spina bifida who undergo repeated surgery and catheterization.^{10,11} Latex sensitization of nearly 10% has been reported in atopic individuals undergoing routine aeroallergen skin testing.⁹

Relatively low concentrations of respirable particulate matter have been significantly associated with increases in daily mortality rates, acute bronchitis, and hospital visits for treatment of lower respiratory tract symptoms.¹²⁻¹⁵ Both morbidity and mortality rates for respiratory asthma have increased dramatically, particularly in urban areas throughout the world.¹⁶⁻²² Children seem to be at particular risk, and particulate air pollution of 2 to 10 μm has been implicated.²³⁻²⁹

A significant portion of particulate air pollution

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in urban areas may consist of small irregularly shaped black particles. The most likely source of these particles is the abrasion of rubber tires on road surfaces. Tires are made of various mixtures of natural and synthetic rubber along with sulfur, carbon black, and zinc oxide. This results in a flexible yet sturdy material that can withstand heat and friction well.³⁰ However, tire wear releases particles of varying size, which may add to atmospheric pollution burden.

In this study we confirmed that a large number of respirable tire fragments are found in urban air. We investigated the hypothesis that these fragments contain latex proteins. These particles could be partially responsible for the increase in latex sensitization, as well as the respiratory problems associated with air pollution.

METHODS

Physical and chemical characterization of particles

Particulate samples were collected by three different procedures: rotary impaction sampling (Rotorod; Sampling Technologies Inc., Los Angeles, Calif.); high-volume air sampling with a PM₁₀ sampler equipped with an inlet that discriminated against particles larger than 10 μ m (Sierra Instruments, Monterey, Calif.); and passive gravimetric air sampling with glass plates (20 $\times$ 20 cm) coated with silicone grease. The impaction sampler was stationed 7.4 m above ground level, 48 m from a four-lane, moderately travelled road. The PM₁₀ samplers were located at two different Colorado Department of Health sampling stations in the Denver metropolitan area. Rotorod samples were stained with Calberla's solution to facilitate pollen and particulate counting.³¹ The glass plates were exposed at ground level 30 m from roadside air for 6 hours, and samples were harvested by scraping with a flat surgical blade.

The size of the particles was determined with an optical microscope and a 45 $\times$ achromatic lens. The eyepiece (10 $\times$) of the microscope was fitted with a graduated reticle to permit measurement of particle sizes. The reticle was calibrated with a 22 mm glass slide cover. Particle sizes were reported as their orthogonal mean diameters. Particle counts were performed by counting 1000 consecutive particles on five separate samples ($n = 5000$).

Chemical identification of the particles was attempted by both qualitative solubility tests and semiquantitative gas chromatography/mass spectrometric analysis. The solvents used for the solubility tests included 5N HCL, 5N NaOH, 20% sodium lauryl sulfate, 1,3-dichlorobenzene, 1,2-dichlorobenzene, chloroform, and 95% ethanol. Extracts in 1,3-dichlorobenzene of an authentic latex sample derived from latex gloves, a tire dust sample, and a PM₁₀ air sample were analyzed with a Hewlett Packard 5890/5882 gas chromatography/mass spectrometry system

(Hewlett-Packard Co., Palo Alto, Calif.). Extraction of samples was performed with a heated (50° C) ultrasonic bath. The chromatographic analysis was performed with an HP-1 capillary column operated in a temperature-controlled oven, programmed from 120° to 280° C at 10 degrees per minute. The mass spectrometry detector was operated in electron impact mode and maintained at 250° C. The mass range recorded was from mass to charge ratio = 30 to 500.

Protein extraction and antigen studies

A rubber tire (Turanza-QL10, steel-belted radial; Bridgestone Tires, Warren County, Tenn.) with moderate wear was milled with a fine-tooth electric handsaw. Fragments were collected on filter paper (Whatman Qualitative; Whatman PLC, Maidstone, Kent, England). A 100 gm sample was extracted for 30 seconds with 200 ml of distilled water in a high-speed blender (Vitamix, Cleveland, Ohio). The preparation was filtered (Whatman Qualitative), dialyzed in cellulose dialysis tubing against distilled water (Spectropor with a nominal molecular weight cutoff of 1000 kd; Spectrum, Houston, Texas), concentrated fourfold by evaporation at room temperature and lyophilized. The rubber glove extract was prepared according to the method of Kurup et al.³² with powderless latex medical gloves (Aladan Co., Dothan, Ala.). Competitive inhibition assays were performed in duplicate with the Pharmacia CAP system (Kabi Pharmacia, Uppsala, Sweden). Equal volumes of serum and either lyophilized tire extract dissolved in saline solution, latex rubber glove extract dissolved in saline solution, or saline solution alone were incubated overnight at 4° C. Fifty-microliter aliquots of these samples were assayed in duplicate with native latex (*Hevea brasiliensis*) protein extract as the solid-phase allergen source (Pharmacia CAP system). Individual serum samples containing latex-specific IgE from patients with clinical histories of latex reactivity were used. Identical inhibitions were performed with a serum sample containing 5.3 kUa/L *Alternaria*-specific IgE for specificity controls. Inhibition was calculated with the formula:

Percent inhibition

$$= 100 \times (1 - [\text{response sample}/\text{response saline}])$$

RESULTS

The particles observed in the ambient air samples were black, rarely spherical, and typically coarse with ragged edges (Fig. 1). The airborne quantity ranged from 3800 to 6900 particles per cubic meter. Their size varied greatly, but over 90% were between 2.2 and 35.2 μ m in mean orthogonal diameter with a mode of 6.6 μ m (Fig. 2). A birch pollen grain, which is consistently around 35 μ m (in Calberla's solution), was included in the photograph for reference.³¹ A high percentage (58.5%) of the particles were in the

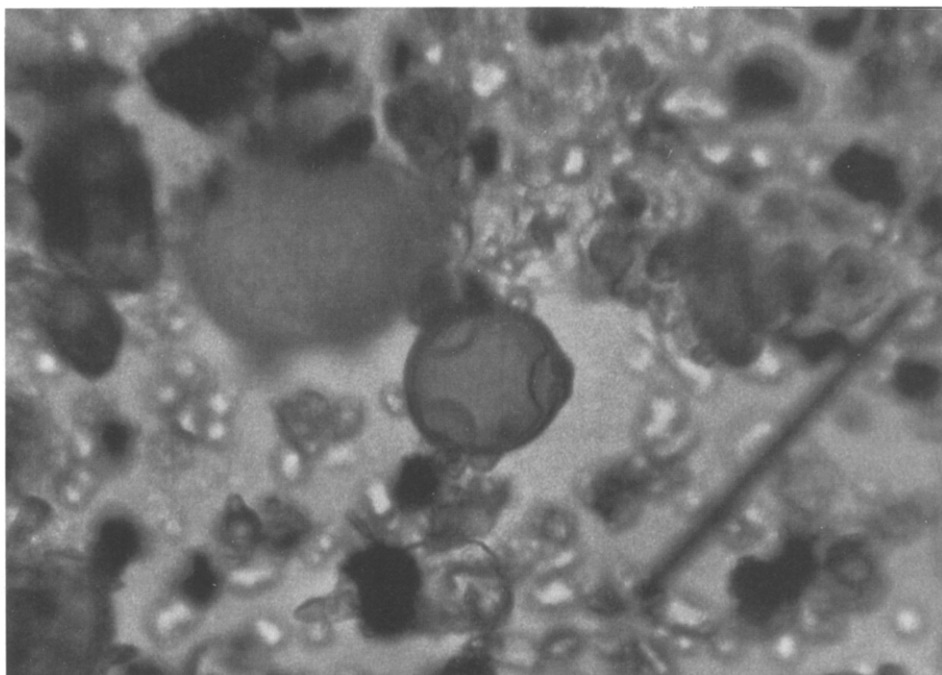


FIG. 1. Photomicrograph of ambient air sample collected on impact sampler. A birch pollen grain (35 μm in diameter) was included for reference. ($\times 450$.)

AIRBORNE TIRE DEBRIS SIZE DISTRIBUTION AMBIENT VOLUMETRIC SAMPLER COLLECTION

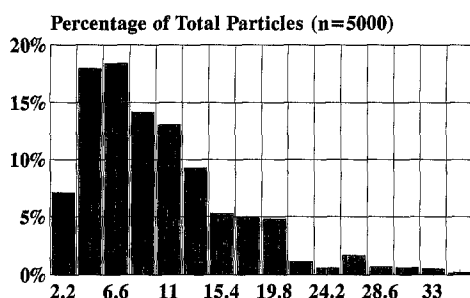


FIG. 2. Distribution of tire debris size from impact sampler ($n = 5000$). Particle sizes were determined with a calibrated reticule with light microscopy. ($\times 450$.)

respirable range of less than 10 μm .³³ There was a sharp drop in the number of particles below 4 μm . Attempts to tease this material apart under the microscope indicated that it was pliable and resilient, regaining its original shape after stretching. In chloroform and the dichlorobenzenes the fragments underwent swelling, as is characteristic of cross-linked hydrophobic polymers. The smaller particles, in the range of 2 μm , seemed more rounded in shape and resembled oil droplets. However, these did not dissolve in any of the solvents, indicating that they were not simple hy-

drocarbons. The fragments produced in the laboratory exhibited similar characteristics and behaved similarly in the solvent tests.

The total ion chromatograms for each of the three samples analyzed with gas chromatography/mass spectrometry are shown in Fig. 3. The broad peak located between 16.5 and 18.5 minutes' retention time in each of the chromatograms is characteristic of a polymeric substance and produced similar mass spectra in each of the three samples. The most abundant ions in the mass spectra were at mass to charge ratio = 75, 149, and 265, which is consistent with spectra observed for latex and cross-linked rubber.³⁴

The results of the inhibition experiments are presented in Table I. All but one of the sera containing latex-specific IgE were inhibited by the rubber tire extract, with varying degrees of inhibition. For each serum sample, the inhibition was generally equivalent to that achieved with a latex glove extract (1 mg of protein per milliliter) but occasionally higher with the rubber tire fragment extract. The specificity of this cross-reactivity was confirmed by demonstrating no inhibition of *Alternaria*-specific IgE by the rubber tire extract.

DISCUSSION

This study supports the hypothesis that latex allergens are present in particulate air pollutants in

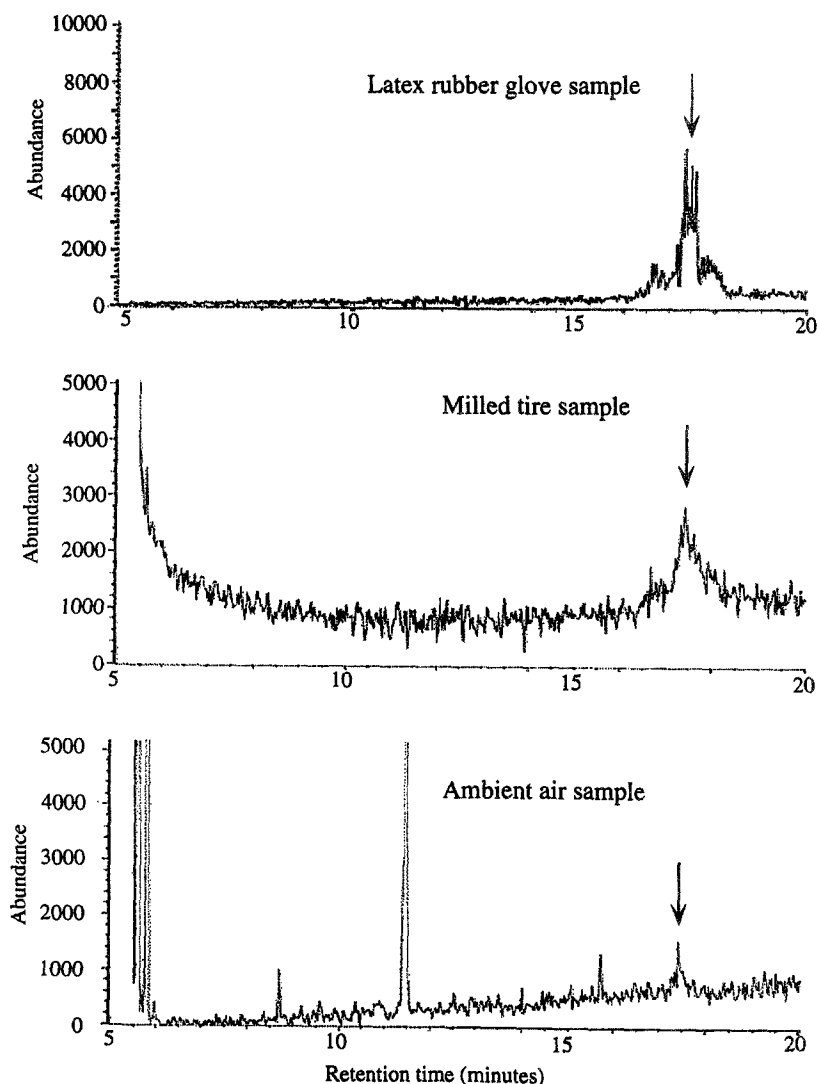


FIG. 3. Total ion chromatograms for each of the three samples extracted in dichlorobenzene. The broad peak observed in each of the samples at 16 to 18 minutes of retention time is indicative of a polymeric structure. The mass spectra obtained for the species in these peaks were similar in each of the samples and were consistent with mass spectra observed for authentic latex samples.

urban areas. The abundance of these black particles at a station 7.4 m above the surface ranged from 3800 to 6900 per cubic meter. The most prevalent size in our samples was 6 to 7 μm mean orthogonal diameter, and over 58.5% were of a size that is fully respirable.³³ Our hypothesis is that these particles represent abraded tire fragments, and it is supported by mass spectroscopic, physical, and chemical data. The mass spectroscopy indicated a similar spectrum for rubber tire fragments, latex gloves, and material collected from ambient air with a PM_{10} sampler. Physically, the particles were resilient, regaining their original shape after they were teased apart; and the inability of a

variety of solvents to dissolve these fragments suggests that they are composed of highly structured polymeric material.

The use of natural latex as a constituent of most tires presents the possibility that tire fragments could be immunologically active. This possibility was verified by demonstrating elutable latex antigen activity by the inhibition assays. Collectively, these data strongly indicate that respirable tire fragments, containing readily elutable latex antigens, are present in large quantities in urban air.

Earlier studies on tire wear characterization failed to detect tire particles in the respirable range.³⁵⁻³⁷ In a series of studies in 1974, Pierson

TABLE I. Inhibition of latex-specific IgE with glove and tire fragment extracts

Sample	Response to saline	Response to GE	% Inhibition glove	Response TE	% Inhibition tire
1	4,378	177	95.96	277	93.67
2	4,762	815	82.88	594	87.53
3	4,853	1,028	78.81	640	86.81
4	6,665	1,345	79.82	1,742	73.86
5	10,180	6,725	33.94	4,899	51.87
6	11,848	10,071	14.99	7,955	32.86
7	14,414	12,058	16.34	14,311	0.71

GE, Glove extract; TE, tire extract.

and Brachaczek³⁸ concluded that although tire wear was a significant pollutant (600,000 metric tons per year in the United States), most of this was in the form of nonsuspendable particles deposited adjacent to roadways. The majority of these data were derived from samples collected at ground level. They concluded that the average airborne amount (50,000 tons/yr) is equivalent to 20% of airborne particulate matter from gasoline engine exhaust, which is a substantial amount of airborne material. Consumption of natural rubber for tires and associated products worldwide has increased since this time and measures approximately 3.9 million metric tons yearly.³⁹ In 1981, an Environmental Protection Agency laboratory study characterized tire wear particulates with the use of a stainless steel wearing surface.⁴⁰ This study failed to demonstrate rubber particles in the 1 to 10 μm range but suggested that the lack of small particles may have resulted from their experimental design. It is possible that freshly worn rubber particles without additional abrasive material would form aggregates, excluding small particles on cascade-type collectors. When cornstarch was added to their system as an abrasive, smaller particles were in fact observed. More recent studies indicate that tire dust of respirable size is a significant contribution to the carbonaceous aerosol of less than 3.5 μm in Los Angeles.⁴¹

Rubber tires are manufactured with varying concentrations of natural latex (cis 1,4-polyisoprene) and synthetic rubber (1,4-styrene polybutadiene).³⁰ Truck tires have higher amounts of natural latex.⁴⁰ The natural latex is desirable because it causes less friction and can withstand higher temperatures but has the propensity to release smaller particles on abrasive wear. Wear of radial, as opposed to bias ply, constructed tires also results in smaller particles.⁴⁰ The increased prevalence of radial tire use over the past 2 decades

could account for the smaller particle sizes seen in our study.

The fact that we were able to extract functionally intact latex antigens from abraded tire fragments was somewhat surprising, considering the high temperatures of vulcanization (130°C) and extensive cross-linking.⁵ This extends other findings that latex allergens are thermally stable.⁸ The serum samples used for these experiments were from patients clinically sensitive to products containing natural latex. All contained high amounts of IgE specific to latex-derived antigens. Our experiments demonstrate essentially equivalent results at maximal inhibition with latex glove antigens and the rubber tire extract in all the serum samples tested. This indicates that a close relationship exists between the specificities of the antibodies being inhibited. Further studies are in progress to define the quantitative relationships on a protein basis.

Chronic exposure to respirable fragments of rubber that contain carbon black, latex antigens, and sulfur would be expected to have a number of health consequences. Respirable particles can act as irritants, inducing nonspecific inflammation. Small particles suspended in polluted air have been significantly linked to hospital admissions for treatment of asthma, particularly in young children.⁴² Furthermore, several studies have linked fine particulate air pollution to increased mortality rates in infants, as well as in the general population in a number of U.S. cities.²³⁻²⁵ It has been demonstrated that respiratory irritants stimulate IgE responses to environmental allergens.^{43, 44} Thus the rubber particles by themselves or in conjunction with other particulates could contribute to allergic responses in respiratory tissues by acting as non-specific adjuvants.

Latex allergens may also act as specific adjuvants for IgE responses. Kurup et al. demonstrated high levels of IgE and blood eosinophilia in mice ex-

posed to latex proteins by intranasal and intraperitoneal routes.⁴⁵ The latex antigen exposed mice developed high levels of interleukins 4 and 5, consistent with the stimulation of CD4⁺ T_{H2} lymphocytes. Preferential stimulation of CD4⁺ T_{H2}-type lymphocytes results in enhanced production and secretion of IgE (interleukin-4 effect) and eosinophil differentiation (interleukin-5 effect).⁴⁶ Thus latex allergens, by acting as an adjuvant for IgE responses, might contribute to allergic responses to unrelated allergens.

Japanese studies have suggested an adjuvant effect of diesel fuel particulates.⁴⁷ These authors demonstrated that enhanced IgE responses occur in animals exposed to diesel fuel exhaust particulates. Experiments with suspended particulate matter from urban districts of Japan have also been shown to have potent adjuvant effects on IgE responses.⁴⁸ A dose of 0.25 µg given intranasally at 3-week intervals was sufficient to obtain an appreciable IgE effect. The air along busy roads had concentrations of 200 to 480 µg/m³ of this material.⁴⁸ Although not addressed by the authors, these samples of ambient polluted air were likely to contain rubber tire fragments, which could have contributed to the adjuvant effects observed.

The interaction of airborne particulate matter with pollen grains has been studied, indicating a direct interaction between pollen surfaces and airborne particulates causing preactivation and altered antigenicity.^{49,50} Such effects were prominent in industrialized regions and near roads with heavy traffic.⁵¹ These interactions, coupled to the adjuvant effects predicted for rubber tire fragments, might explain the elevated incidence of pollinosis in urban areas, as seen in a study that compared the incidence of Japanese red cedar (*Cryptomeria japonica*) pollinosis in urban and rural areas.⁵² Pollen counts were similar in both areas, but an incidence of 13.2% among residents located near intercity roads was seen, whereas the incidence of cedar pollinosis among forest residents (exposed to little or no motorized traffic) was 5.1%. These results support the concept that pollinosis is augmented by air pollution and automobile by-products.

An additional consequence of exposure to latex-containing airborne particles could be direct sensitization to latex antigens. The prevalence of latex sensitization has been increasing at an alarming rate. Recent reports indicate that up to 14% of health care workers and nearly 10% of atopic individuals are sensitized to latex; and the rate of sensitization in atopic individuals who are fre-

quently exposed to latex has reached 36%.⁹ Although increased use of latex gloves and other products has been suggested, an additional risk factor may be breathing urban air polluted with respirable tire fragments containing latex antigens. These fragments could be acting both specifically and nonspecifically as an adjuvant for enhancing IgE responses. For example, a nonspecific irritant effect could enhance sensitization to inhaled antigens, which could include latex itself.

A variety of inhaled particulates have been linked to adverse health effects including declining lung function, shortness of breath, wheezing, asthma attacks, chronic obstructive pulmonary disease, increased rates of hospitalization, and increased mortality rates.¹²⁻²⁹ These may be due to inert physical properties, direct toxic effects, carcinogens, or stimulation of inflammatory reactions. We suggest that respirable rubber tire fragments, not mentioned in these prior studies, may represent a potent stimulus for both specific and nonspecific inflammatory responses, which are not mutually exclusive possibilities. In light of the potential adjuvant and antigenic properties of these fragments, serious consideration must be given to the possible role of these particles in the initiation and perpetuation of respiratory tract diseases such as asthma, allergic rhinitis, and allergic conjunctivitis. The role of these particles in the sensitization to latex revealed by subsequent acute systemic reactions to latex exposure in a medical context must also be considered. These observations permit the organization of systematic epidemiologic and immunologic studies to clarify the role of latex-bearing particulate air pollutants in pulmonary diseases and clinical latex allergy.

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