September 24, 2012

Doug Haines
P.O. Box 93596
Los Angeles, CA 90093-0596

Los Angeles City Council
c/o Los Angeles City Clerk
City Hall, 3rd Floor
200 N. Spring Street
Los Angeles, CA 90012

Re: Council File 12-0967
ENV-2007-365-MND; 5241-5247 Santa Monica Blvd. & 5238-5246 Virginia Ave.

Honorable President Wesson and Council members:

The Los Angeles City Council will consider an appeal by Seta Panosian at its Tuesday, September 25 meeting. This appeal regards the City Planning Commission's April 12, 2012 approval of a Mitigated Negative Declaration ("MND") for a proposed 82,041 sq. ft. development at 5241-5247 Santa Monica Blvd. & 5238-5246 Virginia Ave. in East Hollywood. The appeal, listed on the Council agenda as item #17, argues that an Environmental Impact Report ("EIR") is required for the project under the California Environmental Quality Act ("CEQA"). The Planning and Land Use Management Committee ("PLUM") recommended at its September 11, 2012 meeting that the City Council deny the appeal and approve the MND. This letter addresses written comments submitted by the applicant's representative dated September 10, 2012 and in public testimony. I also ask for your support of our community by upholding Ms. Panosian's appeal.

As approved by the City Planning Commission at its April 12, 2012 hearing, the proposed project is a 49-unit, 5-story, 60-foot tall, 82,041 sq. ft. mixed-use project located immediately adjacent to both Kingsley Elementary School and low-level, restricted density housing (the "Project"). The 45,301 square foot project site consists of five parcels on a vacant lot immediately adjacent to Kingsley Elementary School's playfield to the east, and restricted density housing to the west and north.

At the Sept. 11, 2012 Planning and Land Use Management Committee hearing, committee members and Planning Staff disregarded objections by impacted neighbors and instead voted to recommend that the City Council approve the Project MND. The PLUM Committee did so despite acknowledging that the Project was approved with 17,272 sq. ft of "undefined" space, and that the applicant has no intention of constructing the approved development. The applicant has instead reapplied for an expanded project.

As noted during the PLUM hearing, the developer has filed a new application to construct a five-story, 84-unit project with 15,000 sq. ft. of commercial/retail that would be 30,000 sq. ft. larger than the project being appealed. If developed as outlined in the architect's 1/05/12 construction documents, this new project would have a total square footage of 112,475 sq. ft. with 181 parking spaces, and consist of two buildings on the lot's five parcels. According to the architect's documents, the buildings -- which would be connected by a two-level subterranean garage covering the entire project site -- consist of:

1). A 5-story, 66' 10" -tall structure of 74 dwelling units (Note: the May 18, 2012 Addendum on page 2 instead identifies the Santa Monica building as having 68 units with a maximum 60' height) comprising 75,035 square feet of residential floor area with 17,650 square feet of commercial space;

2). A two-story second building fronting Virginia Avenue, with 10 residential units (Note: the May 18, 2012 Addendum on page 2 identifies the Virginia building as having 16 units) and recreational facilities within 19,790 sq. ft. of floor area.

Project Version	HEIGHT	SQUARE FT.	APARTMENTS
Approved 4/12	60 feet	82,041 sq, ft.	49
New Proposed	66 feet, 10 inches	112,475 sq. ft.	84

According to Planning Staff, however, this revised project description is being changed once again, with the applicant seeking to increase the project's commercial component in response to changes in the site's allowable Floor Area Ratio ("FAR") as approved under the new Hollywood Community Plan. At every stage, therefore, the Project has and continues to be ambiguous, ever changing and undefined, with the MND recirculated in both February and June of this year with major alterations to the Project descriptions yet without any changes to the MND's analysis.

A finite project description is a clear CEQA requirement. Guidelines §§ 15120(c), 15124(b). "An accurate, stable and finite project description is the *sine qua non* of an informative and legally sufficient " environmental analysis. County of Inyo v. City of Los Angeles (1977) 71 Cal.App.3d 185, 199. In contrast, a "curtailed, enigmatic or unstable project description draws a red herring across the path of public input." Id. at 198. "Only through an accurate view of the project may the public and interested parties and public agencies balance the proposed project's benefits against its environmental cost, consider appropriate mitigation measures, assess the advantages of terminating the proposal and properly weigh other alternatives." City of Santee v. County of San Diego (1989) 214 Cal.App.3d 1438, 1454; accord, Concerned Citizens of Costa Mesa, Inc. v. 32nd Dist. Agricultural Assn. (1986) 42 Cal.3d 929, 938 (citing County of Inyo).

Here, the applicant and City continue to repeatedly alter the Project parameters in expanding the development yet, refuse to significantly update the MND in violation of CEQA's requirement that there be an "accurate, stable and finite project description." The City has been "changing the rules of the game while it was being played." Gammoh v. City of Anaheim (1999) 73 Cal.App.4th 186, 191.

The Project's MND is based on an Initial Study released by the applicant in 2008 and prepared in 2005. The Initial Study avoids any cumulative analysis of significant related projects announced since 2005, and omits any reference to cumulative air quality impacts associated with the 101 Freeway, a major source of pollution and traffic congestion located one block west of the Project site (see photo at **Exhibit 1**). It is therefore an outdated and defective document, created for a different development, with no references to significant impacts that under CEQA must be properly addressed in an EIR.

The Project site formerly housed several auto repair and painting operations over a period of decades. The Initial Study performed a cursory sampling of soil on the site, and the MND acknowledges that an in-ground hydraulic hoist remains buried there. The MND also states that an underground storage tank may remain buried on the western portion of the site. Yet the MND proposes no remedial activity prior to approval of the Project, delaying further testing and containment excavation until after construction begins.

Former auto repair and paint shops at Project site, photo circa 2001

The applicant's representative, in his September 10, 2012 letter, dismisses environmental objections related to the proposed Project, stating that such objections "*provide no substance or analysis*," and that the appellant "*fails to present substantial evidence supporting a fair argument of significant environmental effect.*" Such comments apply an incorrect standard of review to determining whether or not the Lead Agency must prepare an EIR, and ignore a wealth of data showing a clear connection between the Project and significant impacts to both the health and welfare of the 536 children at Kingsley Elementary School (see **Exhibit 2**), and residents of the surrounding community.

Under CEQA, an EIR must be prepared where there is substantial evidence that significant effects "may" occur. League for Protection of Oakland's Architectural and Historic Resources v. City of Oakland (1997) 52 Cal.App.4th 896, 904-905. Substantial evidence is defined as "facts, reasonable assumptions predicated upon facts, and expert opinion supported by facts." Public Resources Code Section 21080(e)(1). The fair argument test is a "low threshold test." Stanislaus Audubon Society v. County of Stanislaus (1995) 33 Cal.App.4th 114, 151. Because of this "low threshold test," the City of Los Angeles recently issued a Notice of Preparation for an EIR to analyze the City Council's ordinance to ban the use of plastic carryout bags (see **Exhibit 3**). If banning a hazardous waste requires preparation of an EIR, then the low threshold test clearly applies to impacts related to the Project.

The appellant has presented expert testimony detailing the MND's inadequacy in relation to impacts from construction noise, air quality, and hazardous waste. Additional objections have been submitted related to impacts due to shade/shadow, light and glare, traffic, and other concerns.

The deleterious health effects to children and adults of diesel exhaust and road dust particulate exposure is clear and well established by the scientific community. As explained in a landmark study on the effect of air pollution on lung development published in The New England Journal of Medicine (see **Exhibit 4**): "*Lung development is not fully realized in children who grow up in communities with polluted air. The magnitude of this effect is clinically and physiologically significant.*" This study further pointed out that: "*Mortality studies suggest that the exposure-response relationships for particulate-matter pollution in the case of both short-term and long-term exposures are nearly linear,* ***with no discernible safe thresholds within relevant ranges of exposure.***"

Since release of this 2004 study, the scientific community has further analyzed the health impacts associated with fine particulate matter, identifying decreased lung capacity (see **Exhibit 5**), increased risk of autism (see **Exhibit 6**), higher death rates (see **Exhibit 7**), higher rates of asthma (see **Exhibit 8**), and increased risk of cardiovascular disease (see **Exhibit 9**). Many of these studies detail the relationship between proximity to diesel particulates and permanent physical and mental disabilities. Since the Project site is located one block east of the 101 Freeway, and is adjacent to the playfield of Kingsley Elementary School, cumulative and site specific air quality impacts associated with construction and operation of the Project within 1,000 feet of the Freeway are significant and without mitigation. The MND failed to properly identify the baseline or the existing conditions at the site against which the significance of the environmental impacts could be properly measured, and this issue must be addressed in an EIR.

Likewise, chronic noise exposure of both young children and adults has a particularly detrimental effect upon cognitive abilities (see **Exhibit 10**). Expert testimony submitted into the record clearly shows the inadequacy of the mitigation measures proposed by the City. In accordance with Section 112.05 of the Los Angeles Municipal Code ("LAMC"), construction related impacts would be significant if any powered equipment or powered hand tool produces a maximum noise level exceeding 75 dBA at a distance of 50 feet from the noise source when the construction and industrial machinery is located within 500 feet of a residential zone. Non-compliance with the provisions of LAMC Section 112.05 would constitute a significant impact requiring an EIR. Expert testimony has shown that Project construction impacts cannot be mitigated to adequately reduce impacts to sensitive receptors immediately adjacent to the site, including the playfield at Kingsley Elementary School and residential housing.

Roadway noise levels would also be dramatically increased by haul/delivery vehicles operating during the Project's construction. No haul route has been identified for the Project, and no analysis has been conducted in the MND to assess such vehicle noise and air quality impacts. Such questions need to be addressed in an EIR.

The applicant also dismisses objections related to shade/shadow, aesthetics, light and glare, and traffic. The Project would develop a building 60 feet in height, which would be the tallest structure on Santa Monica Blvd. for approximately two miles. In his September 10 letter, the applicant's representative misstates the height of Kingsley Elementary School, claiming that it is four stories when it is two, and claims that a four-story building sits across from the subject site but provides no documentation to identify its location.

Kingsley Elementary School -- which consists of one-level buildings on Virginia Ave. and two-level buildings on Santa Monica Blvd. -- at its highest is 28 feet in height, or 32 feet lower than the proposed project. Immediately west of the project site along Santa Monica Blvd. are single-level commercial buildings, including a 24-foot-tall Jon's Market on Hobart Blvd., which would be almost 36 feet shorter than the proposed development.

South of the project site at 5222 Santa Monica Blvd. is a two-story office building that is 28 feet in height, or approximately 32 feet shorter than the proposed development. Adjacent to this structure, and southwest of the project site at 5236 Santa Monica Blvd., is a 34-foot-tall office building that would be 26 feet shorter than the proposed development.

Building	**Proximity to Project**	**Height**	**Contrast w/ Project**
Approved Project		60 feet	
Kingsley Elementary School	Adjacent	12 – 28 feet	School is 32 – 48 feet shorter
5248 Virginia apartments	Adjacent	20 feet	Apt. bldg. is 40 feet shorter
Jon's Grocery Market	75' west	24 feet	Market is 36 feet shorter
Seta's home	Adjacent	22 feet	Home is 38 feet shorter
5222 Santa Monica Blvd. office	Across street	28 feet	Bldg. is 32 feet shorter
5236 Santa Monica Blvd. office	Across street	34 feet	Bldg. is 26 feet shorter

"Aesthetic issues, such as public and private views, are properly studied in an EIR to assess the impacts of a project. (§ 21100(d); Ocean View Homeowners Ass'n, Inc. v. Montecito Water Dist. (2004) 116 Cal.App.4th 396, 402-403. "As on other CEQA topics, the opinions of area residents, if based on direct observation, may be relevant as to aesthetic impact and may constitute substantial evidence in support of a fair argument; no special expertise is required on this topic." The Pocket Protectors v. City of Sacramento (2004),124 Cal.App.4th at 937; (emphasis added).

As noted previously, the Project's Initial Study is grossly outdated. Since its release in 2008, several significant Hollywood developments have been approved or proposed. Most relevant of these is the proposed Hollywood Central Park, which would be located one block west of the subject lot.

> **Project Description**: Hollywood's Central Park is proposed over the 101 Freeway from North Bronson Avenue and Hollywood Boulevard to Santa Monica Boulevard. A mile in length, it will provide 44 acres of park space.
>
> According to the Community Redevelopment Agency's ("CRA/LA") July 15, 2009 staff report, the "Cap Park" will include at the southeast corner of Fountain Avenue and St. Andrews Place a large plaza and baseball field, playgrounds, plaza spaces, viewing platforms, water features, picnic areas, open fields and community gardens. The CRA report also states that the project seeks to "transform a freeway corridor into a destination." The park is anticipated to generate 3,785 construction jobs. On Nov. 2, 2006, the CRA approved $100,000 for a feasibility study (later increased to $120,205), which was made public in November of 2008. On December 15, 2011, the CRA approved a Memorandum of Understanding with the Los Angeles Bureau of Engineering to transfer $2 million to fund the EIR. On July 3, 2012, the Los Angeles City Council approved $825,000 in funding for the Park. On August 22, 2012, the Aileen Getty Foundation donated an additional $1.2 million for the Park.

The failure of the Initial Study to accurately account for the cumulative impacts associated with the Hollywood Cap Park and other recent projects is particularly glaring in light of the significant environmental impacts stemming from the concurrent introduction of so many other massive developments in the Hollywood area. "Proper cumulative impacts analysis is absolutely critical to meaningful environmental review..." Bakersfield Citizens for Local Control v. City of Bakersfield. (2004) 124 Cal.App.4th 1184, 1203, 1217.

Cumulative impacts analysis is particularly important in the urban setting. King County Farm Bureau v. City of Hanford, supra, 221 Cal.App.3d at 720 ("absent meaningful cumulative analysis, there would never be any awareness or control over the speed and manner of downtown development. Without that control, 'piecemeal development would inevitably cause havoc in virtually every aspect of the urban environment'") citing San Franciscans for Reasonable Growth v. City and County of San Francisco (1984) 151 Cal.App3d 61. See also Los Angeles Unified School Dist. v. City of Los Angeles (1997) 58 Cal.App.4th 1019, 1025 (a project's impacts can assume "threatening dimensions...when considered in light of the other sources with which they interact").

"The requirement for a cumulative impact analysis must be interpreted so as to afford the fullest protection of the environment within the reasonable scope of the statutory and regulatory language." Citizens to Preserve the Ojai v. County of Ventura (1985) 176 Cal.App.3d 421, 431-432.

If it is "reasonable and practical" to include other projects in a project's cumulative impacts analysis, then the lead agency is required to do so." San Franciscans For Reasonable Growth v. City and County of San Francisco, supra, 151.App.3d at 77. "The Guidelines explain that a discussion of cumulative effects should encompass 'past, present, and *reasonably anticipated future projects.*'" Laurel Heights Improvement Assn. v. Regents of University of California (1988) 47 Cal.3d 376, 394; citing Guidelines § 15130 (b)(1)(A); italics in original.

For example, Citizens Assn., supra, 172 Cal.App.3d 151, explicitly states that while projects "currently under environmental review unequivocally qualify as probable future projects to be considered in a cumulative analysis...even projects anticipated beyond the near future should be analyzed for their cumulative effect." Id. at 168.

A project that is under environmental review is a "reasonably foreseeable probable future project" within the meaning of the Guidelines. (Guidelines, § 15355, subd. (b).). This is because once review is begun, a significant investment of time, money and planning has probably occurred. Thus, once environmental review commences, the project is probable rather than merely possible. Friends of the Eel River v. Sonoma County Water Agency, 108 Cal.App.4th at p. 870; San Franciscans for Reasonable Growth v. City and County of San Francisco, supra, 151 Cal.App3d at pp. 74-75

It is an abuse of discretion to fail to include projects under environmental review if the omission will cause the severity and significance of the impacts to be gravely understated. San Franciscans for Reasonable Growth v. City and County of San Francisco, supra, 151 Cal.App3d at pp. 77-78

"*Proper cumulative impacts analysis is absolutely critical to meaningful environmental review...*" Bakersfield Citizens for Local Control v. City of Bakersfield (2004) 124 Cal.App.4th 1217. "*[Q]uestions concerning...cumulative impacts constitute important issues of broad public interest that are likely to reoccur.*" (*Id.* at 1184, 1203).

Therefore, the Project must include proper analysis of all related projects.

In conclusion, the applicant's claims in his letter dated September 10 do not in any manner defeat the appellant's showing of a fair argument that the Project may cause significant impacts that cannot be mitigated. Under CEQA, the MND is inadequate and the Project must conduct an EIR.

Thank you for your consideration of this matter.

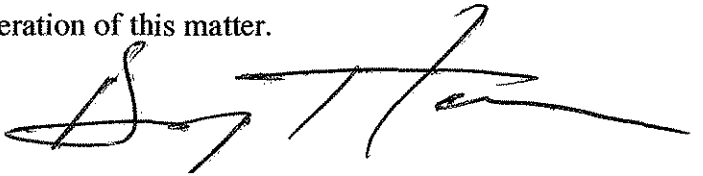
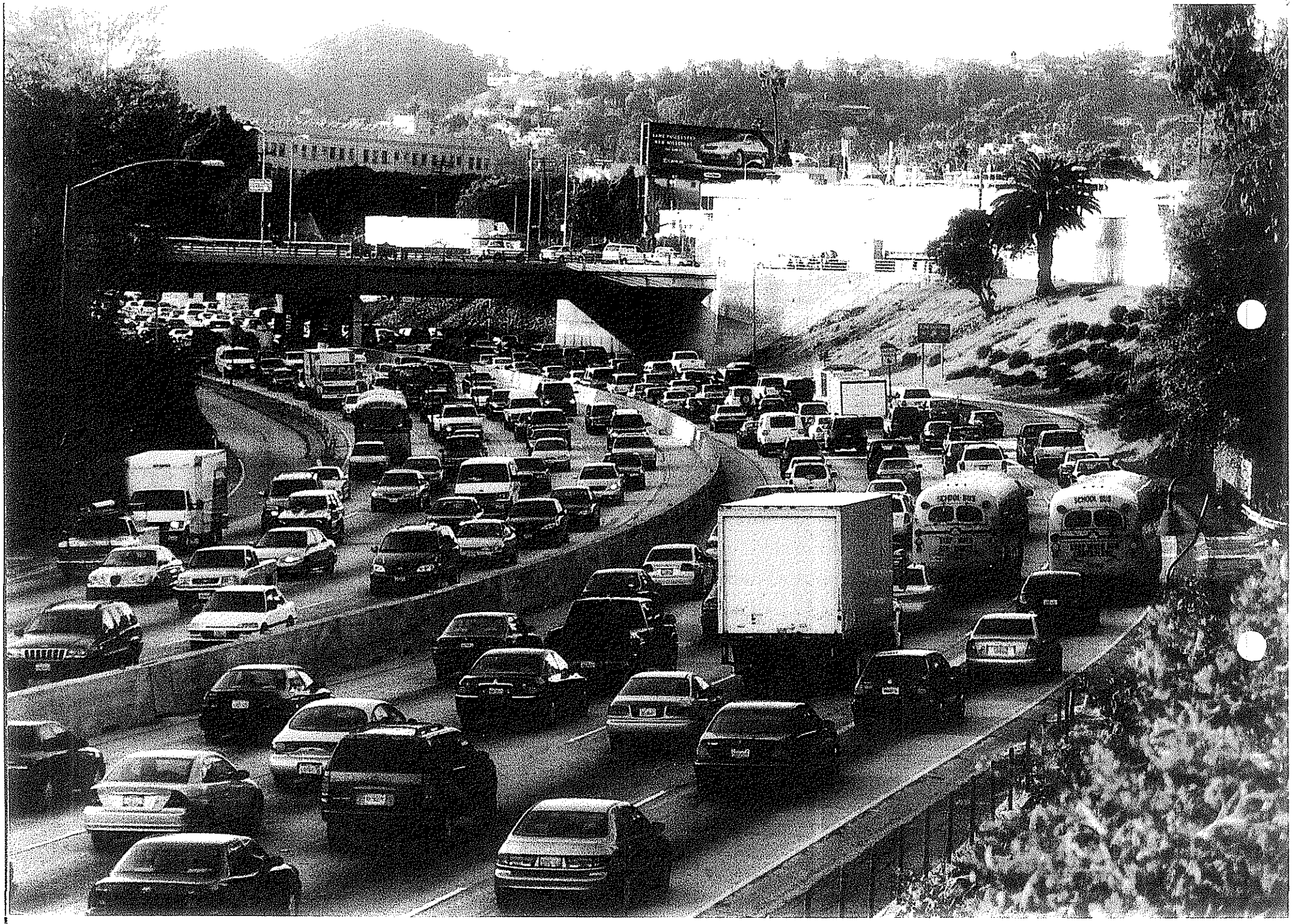


Exhibit 1



101 Freeway at Western Avenue overpass, Hollywood.

Exhibit 2

Kingsley Elementary School

School Overview

Address

5200 W Virginia Ave
Los Angeles, CA 90029
(323) 644-7700
School Website
View map

Profile

Grades: K - 5
School Type: Public
Student Enrollment: 550
Students Per Teacher: 20

Parent Reviews

3 Parent Reviews for Kingsley Elementary School

I like this school everyone here it's friendly. The principal it's wonderful, she knows each student by name. The special needs class it's one of the best in the area. I definetly would recommend it.

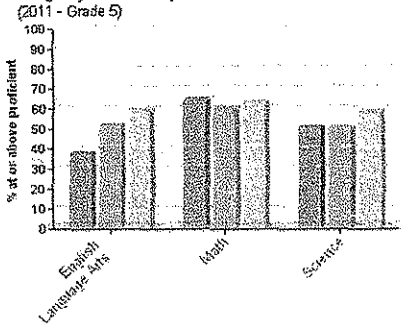
It is one of the best school I have found so far, the teachers and staff are great and really care about each student individually. The Special Ed classes are also the best I have seen in any district.

I love the school, we have a great principal, she communicate with everyone I can say that she knows each of her students, and the teachers work the best they can, we are happy with the school performance.

School Profile for Kingsley Elementary School

Test scores | Enrollment

Kingsley Elementary School Scores
(2011 - Grade 5)



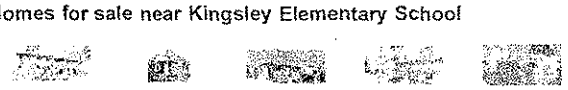
CST* Test Scores

Grade Level: 5

Test Year: 2011

Kingsley Elementary School
Los Angeles Unified School District
California

Homes for sale near Kingsley Elementary School



Related Info

Hollywood Real Estate Guide
Hollywood Stats and Trends
Hollywood Area Schools
Hollywood Community Info
Los Angeles Home Prices Map
Los Angeles Homes for Sale

Elementary	Middle	High

SCHOOL NAME	TYPE
Larchmont Charter School	Public
Van Ness Elementary School	Public
Harvard Elementary School	Public
Dayton Heights Elementary School	Public
Los Feliz Elementary School	Public

See all schools in Los Angeles Unified School District

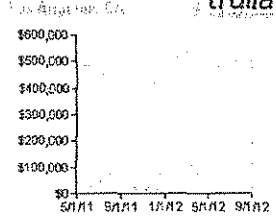
Discussions in Los Angeles, CA
1,504 followers
42 recent questions

Recent Activity

Where do you report unethical direct lender? 3 answers
Is this House for rent still available? 2 answers
What to do when a seller who decides they do not want to sell to you (once in a contract) but cannot cancel, tries to sabotage it other ways? 9 answers
Is it legal for a seller to force us to cancel the transaction by setting the deal up for failure? 9 answers
Im interested to look at it asap. When do I know if I can purchase it or not? thank you 5 answers
I am from Europe, planning to be in L.A. for 2 weeks in Dec 2012 or Jan 2013. Thinking of getting a condo as a holiday home or "buy-to-let" 5 answers
Is the price base on your credit ? 3 answers
View 42 recent questions

Charts and Data | More local advice

Average Sales Price in Los Angeles, CA



Los Angeles real estate prices

Average Listing Price:	$1,219,318
Median Sales Price:	$340,000
Average Price/Sqft.	$293

Exhibit 3

AME TIME TO
TEAM'S DEFEAT,
CH WAS THIS.

the circled letters
rprise answer, as
he above cartoon.

(Answers tomorrow)
ACTOR CLINIC
ver the railroad,
RIGHT" TRAINS

10, 2012

DRAFT EIRS

It has been determined that the following proposed projects have a significant effect on the environment and draft Environmental Impact Reports (EIRs) have been prepared.

City Clerk Case#: NOP-12-003-PW

NOTICE OF PREPARATION OF ENVIRONMENTAL IMPACT REPORT (EIR) FOR THE PROPOSED SINGLE-USE PLASTIC CARRYOUT BAG ORDINANCE

Proposed Project: The City of Los Angeles is proposing to adopt and implement an ordinance to ban the use of single-use plastic carryout bags, charge a fee on paper bags, and promote the use of reusable bags at specified retailers within the City. A six-month grace period would be provided for large retailers and a one-year grace period would be provided for small retailers, which would include a public education component.

The City of Los Angeles has completed an Initial Study which indicates that the proposed project may result in significant impacts and therefore an EIR will be prepared.

Public Review Period: The NOP and Initial Study are available for public review from September 20, 2012 to October 19, 2012. If you would like to comment, please send your written comments so that they are received no later than October 19, 2012 to Karen Coca, Division Manager, Solid Resources Citywide Recycling Division, City of Los Angeles Department of Public Works, Bureau of Sanitation, 1149 S. Broadway, 5th Floor, Los Angeles, CA 90015.

Public Meetings: The Bureau of Sanitation will hold meetings to receive public input on the proposed project and the Initial Study, as follows: October 2, 2012, 5:30 pm to 7:30 pm - Deaton Auditorium (in Police Administration Building), 100 W. 1st Street, Los Angeles, CA 90015

October 3, 2012, 5:30 pm to 7:30 pm - Willmington Recreation Center (Multi-Purpose Room), 325 Neptune Ave, Willmington, CA 90744

October 4, 2012, 5:30 pm to 7:30 pm - Cheviot Recreation Center Auditorium, 2551 Motor Ave, Los Angeles, CA 90064

October 10, 2012, 5:30 pm to 7:30 pm - Van Nuys City Hall, 14410 Sylvan Street, Van Nuys, CA 91401

Where to Find the NOP and Initial Study: The NOP and Initial Study are available for review at the City of Los Angeles Bureau of Sanitation at 1149 S. Broadway, 5th Floor, Los Angeles, CA 90015, www.lacitysan.org under What's new..., and at the following public libraries:

Central Library, 630 W. 5th Street, Los Angeles, CA 90071

Van Nuys Branch Library, 6250 Sylmar Ave., Van Nuys, CA 91401

West L. A. Regional Branch Library, 11360 Santa Monica Bl., Los Angeles, CA 90025

San Pedro Regional Branch Library, 931 S. Gaffey Street, San Pedro, CA 90731

San Pedro Street, Los Angeles, C
ANGELES COUNTY. **Registered O**
Rojo, 12618 South San Pedro Street, L
2. Vincent Valencia, 3910 West 1
Torrance, CA 90504; 3. Justin Garcia, 1
Los Angeles, CA 90037; 4. Ryan K
Avenue, Torrance, CA 90504. **Busine**
General Partnership. The registrant c
business under the fictitious business
above on **N/A.** I declare that all
statement is true and correct. (A reg
as true information which he or she
guilty of a crime) **REGISTRANT/**
Joseph Rojo. **Signature:** Joseph Rojo.
filed with the County Clerk of **LOS A**
July 30, 2012. **NOTICE-** in accorda
(a) of section 17920 A Fictitious Name
expires at the end of five years from
was filed in the office of the Cou
provided in subdivision (b) of sect
expires 40 days after any chan in
the statement pursuant to sectic 91
in the residence address of a regis
fictitious business name statement mu
expiration. The filing of this stateme
authorize the use in this state of fict
in violation of the rights of another u
common law (see section 14411 e
Professions code). Dean C. Logan,
Clerk. By: Josephina Jimenez, Deput
30, and September 6, 13, 20, 2012.

Exhibit 4

Next Week in the Journal

SEPTEMBER 16, 2004

Learner-Centered Medical Education

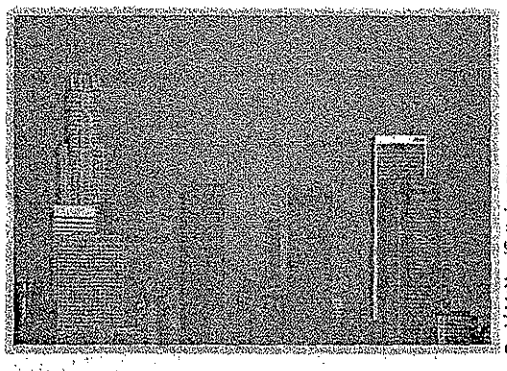
Kenneth Ludmerer

This Week in the Journal

SEPTEMBER 9, 2004

ORIGINAL ARTICLE

The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age



David McNew/Getty Images.

Between the ages of 10 and 18 years, the lung undergoes major growth. There has been reason to believe that exposure to air pollution during this period of lung growth leads to a restriction of lung growth, but strong supporting data have been lacking. In this study, conducted in southern California, children from communities with greater air pollution had significantly poorer lung function than children from communities with cleaner air.

Lung development is not fully realized in children who grow up in communities with polluted air. The magnitude of this effect is clinically and physiologically significant.

SEE P. 1057; EDITORIAL, P. 1132

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2004 VOL. 351 NO. 11

The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age

W. James Gauderman, Ph.D., Edward Avol, M.S., Frank Gilliland, M.D., Ph.D., Hita Vora, M.S., Duncan Thomas, Ph.D., Kiros Berhane, Ph.D., Rob McConnell, M.D., Nino Kuenzli, M.D., Fred Lurmann, M.S., Edward Rappaport, M.S., Helene Margolis, Ph.D., David Bates, M.D., and John Peters, M.D.

ABSTRACT

BACKGROUND

Whether exposure to air pollution adversely affects the growth of lung function during the period of rapid lung development that occurs between the ages of 10 and 18 years is unknown.

METHODS

In this prospective study, we recruited 1759 children (average age, 10 years) from schools in 12 southern California communities and measured lung function annually for eight years. The rate of attrition was approximately 10 percent per year. The communities represented a wide range of ambient exposures to ozone, acid vapor, nitrogen dioxide, and particulate matter. Linear regression was used to examine the relationship of air pollution to the forced expiratory volume in one second (FEV_1) and other spirometric measures.

RESULTS

Over the eight-year period, deficits in the growth of FEV_1 were associated with exposure to nitrogen dioxide (P=0.005), acid vapor (P=0.004), particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) (P=0.04), and elemental carbon (P=0.007), even after adjustment for several potential confounders and effect modifiers. Associations were also observed for other spirometric measures. Exposure to pollutants was associated with clinically and statistically significant deficits in the FEV_1 attained at the age of 18 years. For example, the estimated proportion of 18-year-old subjects with a low FEV_1 (defined as a ratio of observed to expected FEV_1 of less than 80 percent) was 4.9 times as great at the highest level of exposure to $PM_{2.5}$ as at the lowest level of exposure (7.9 percent vs. 1.6 percent, P=0.002).

CONCLUSIONS

The results of this study indicate that current levels of air pollution have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in attained FEV_1 as children reach adulthood.

From the Department of Preventive Medicine, University of Southern California, Los Angeles (W.J.G., E.A., F.G., H.V., D.T., K.B., R.M., N.K., E.R., J.P.); Sonoma Technology, Petaluma, Calif. (F.L.); Air Resources Board, State of California, Sacramento (H.M.); and the University of British Columbia, Vancouver, B.C., Canada (D.B.). Address reprint requests to Dr. Gauderman at the Department of Preventive Medicine, University of Southern California, 1540 Alcazar St., Suite 220, Los Angeles, CA 90089, or at jimg@usc.edu.

N Engl J Med 2004;351:1057-67.

THERE IS MOUNTING EVIDENCE THAT air pollution has chronic, adverse effects on pulmonary development in children. Longitudinal studies conducted in Europe[1-3] and the United States[4-6] have demonstrated that exposure to air pollution is associated with reductions in the growth of lung function, strengthening earlier evidence[7-12] based on cross-sectional data. However, previous longitudinal studies have followed young children for relatively short periods (two to four years), leaving unresolved the question of whether the effects of air pollution persist from adolescence into adulthood. The Children's Health Study[13] enrolled children from 12 southern California communities representing a wide range of exposures to ambient air pollution. We documented the children's respiratory growth from the ages of 10 to 18 years. Over this eight-year period, children have substantial increases in lung function. By the age of 18 years, girls' lungs have nearly matured, and the growth in lung function in boys has slowed considerably, as compared with the rate in earlier adolescence.[14] We analyzed the association between long-term exposure to ambient air pollution and the growth in lung function over the eight-year period from the ages of 10 to 18 years. We also examined whether any observed effect of air pollution on this eight-year growth period results in clinically significant deficits in attained lung function at the age of 18 years.

METHODS

STUDY SUBJECTS

In 1993, the Children's Health Study recruited 1759 fourth-grade children (average age, 10 years) from elementary schools in 12 southern California communities as part of an investigation of the long-term effects of air pollution on children's respiratory health.[6,12,13] Data on pulmonary function were obtained by trained field technicians, who traveled to study schools annually from the spring of 1993 through the spring of 2001 to perform maximal-effort spirometric testing of the children. Details of the testing protocol have been published previously.[12] We analyzed three measures of pulmonary function: forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and maximal midexpiratory flow rate (MMEF). Pulmonary-function tests were not performed on any child who was absent from school on the day of testing, but such a child was still eligible for testing in subsequent years. Children who moved away from their recruitment community were classified as lost to follow-up and were not tested further. From the initial sample of the 1759 children in 1993, the number of children available for follow-up was 1414 in 1995, 1252 in 1997, 1031 in 1999, and 747 in 2001, reflecting the attrition of approximately 10 percent of subjects per year.

A baseline questionnaire, completed at study entry by each child's parents or legal guardian, was used to obtain information on the children's characteristics, including race, presence or absence of Hispanic ethnic background, level of parental education, presence or absence of a history of asthma diagnosed by a doctor, exposure to maternal smoking in utero, and household exposure to gas stoves, pets, and environmental tobacco smoke. Questions administered at the time of annual pulmonary-function testing were used to update information on asthma status, personal smoking status, and exposure to environmental tobacco smoke. The distribution of baseline characteristics of all study subjects and of two subgroups defined according to the length of follow-up (all eight years or less than eight years) is shown in the Supplementary Appendix (available with the full text of this article at www.nejm.org). The length of follow-up was significantly associated with factors related to the mobility of the population, including race, presence or absence of Hispanic ethnic background, presence or absence of exposure to environmental tobacco smoke, and parents' level of education. However, the length of follow-up was not significantly associated with baseline lung function or the level of exposure to air pollution, suggesting that the loss to follow-up did not differ with respect to the primary variables of interest.

The study protocol was approved by the institutional review board for human studies at the University of Southern California, and written informed consent was provided by a parent or legal guardian for all study subjects. We did not obtain assent from minor children, since this was not standard practice when the study was initiated.

AIR-POLLUTION DATA

Air-pollution–monitoring stations were established in each of the 12 study communities and provided continuous data, beginning in 1994. Each station measured average hourly levels of ozone, nitrogen

dioxide, and particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}). Stations also collected two-week integrated-filter samples for measuring acid vapor and the mass and chemical makeup of particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$). Acid vapor included both inorganic acids (nitric and hydrochloric) and organic acids (formic and acetic). For statistical analysis, we used total acid, computed as the sum of nitric, formic, and acetic acid levels. Hydrochloric acid was excluded from this sum, since levels were very low and close to the limit of detection. In addition to measuring $PM_{2.5}$, we determined the levels of elemental carbon and organic carbon, using method 5040 of the National Institute for Occupational Safety and Health.[15] We computed annual averages on the basis of average levels in a 24-hour period in the case of PM_{10} and nitrogen dioxide, and a two-week period in the case of $PM_{2.5}$, elemental carbon, organic carbon, and acid vapor. For ozone, we computed the annual average of the levels obtained from 10 a.m. to 6 p.m. (the eight-hour daytime average) and of the one-hour maximal levels. We also calculated long-term mean pollutant levels (from 1994 through 2000) for use in the statistical analysis of the lung-function outcomes.

STATISTICAL ANALYSIS

The outcome data consisted of the results of 5454 pulmonary-function tests of 876 girls and 5300 tests of 883 boys over the eight-year period. We adopted a two-stage regression approach to relate the longitudinal pulmonary-function data for each child to the average air-pollution levels in each study community.

The first-stage model was a regression of each pulmonary-function measure (values were log-transformed) on age to obtain separate, community-specific average growth curves for girls and boys. To account for the growth pattern during this period, we used a linear spline model[14] that consisted of four straight lines over the age intervals of younger than 12 years, 12 to 14 years, 14 to 16 years, and older than 16 years, constrained to be connected at the three "knot" points. The model included adjustments for log values for height; body-mass index (the weight in kilograms divided by the square of the height in meters); the square of the body-mass index; race; the presence or absence of Hispanic ethnic background, doctor-diagnosed asthma, any tobacco smoking by the child in the preceding year, exposure to environmental tobacco smoke, and exercise or respiratory tract illness on the day of the test; and indicator variables for the field technician and the spirometer. In addition to these covariates, random effects were included to account for the multiple measurements contributed by each subject. An analysis of residual values confirmed that the assumptions of the model had been satisfied. The first-stage model was used to estimate the mean and variance of the growth in lung function over the eight-year period in each of the 12 communities, separately for girls and boys.

The second-stage model was a linear regression of the 24 sex- and community-specific estimates of the growth in lung function over the eight-year period on the corresponding average levels of each air pollutant in each community. Inverses of the first-stage variances were incorporated as weights, and a community-specific random effect was included to account for residual variation between communities. A sex-by-pollutant interaction was included in the model to evaluate whether there was a difference in the effect of a given pollutant between the sexes, and when this value was nonsignificant, the model was refitted to estimate the sex-averaged effect of the pollutant. Pollutant effects are reported as the difference in the growth in lung function over the eight-year period from the least to the most polluted community, with negative differences indicative of growth deficits with increasing exposure. We also considered two-pollutant models obtained by simultaneously regressing the growth in lung function over the eight-year period on pairs of pollutants.

In addition to examining the growth in lung function over the eight-year period, we analyzed the FEV_1 measurements obtained in 746 subjects during the last year of follow-up (average age, 17.9 years) to determine whether exposure to air pollution was associated with clinically significant deficits in attained FEV_1. We defined a low FEV_1 as an attained FEV_1 below 80 percent of the predicted value, a criterion commonly used in clinical settings to identify persons who are at increased risk for adverse respiratory conditions. To determine the predicted FEV_1, we first fitted a regression model for observed FEV_1 (using log-transformed values) with the following predictors: log-transformed height, body-mass index, the square of the body-mass index, sex, race or ethnic group, asthma status, field technician, and interactions between sex and log-transformed height, sex and asthma, and sex and

race or ethnic group. This model explained 71 percent of the variance in the attained FEV_1 level. For each subject, we then computed the predicted FEV_1 from the model and considered subjects to have a low FEV_1 if the ratio of observed to predicted FEV_1 was less than 80 percent. Linear regression was then used to examine the correlation between the community-specific proportion of subjects with a low FEV_1 and the average level of each pollutant from 1994 through 2000. This model included a community-specific random effect to account for residual variation. Regression procedures in SAS software[16] were used to fit all models. Associations denoted as statistically significant were those that yielded a P value of less than 0.05, assuming a two-sided alternative hypothesis.

RESULTS

From 1994 through 2000, there was substantial variation in the average levels of study pollutants across the 12 communities, with relatively little year-to-year variation in the annual levels within each community (Fig. 1). From 1994 through 2000, the

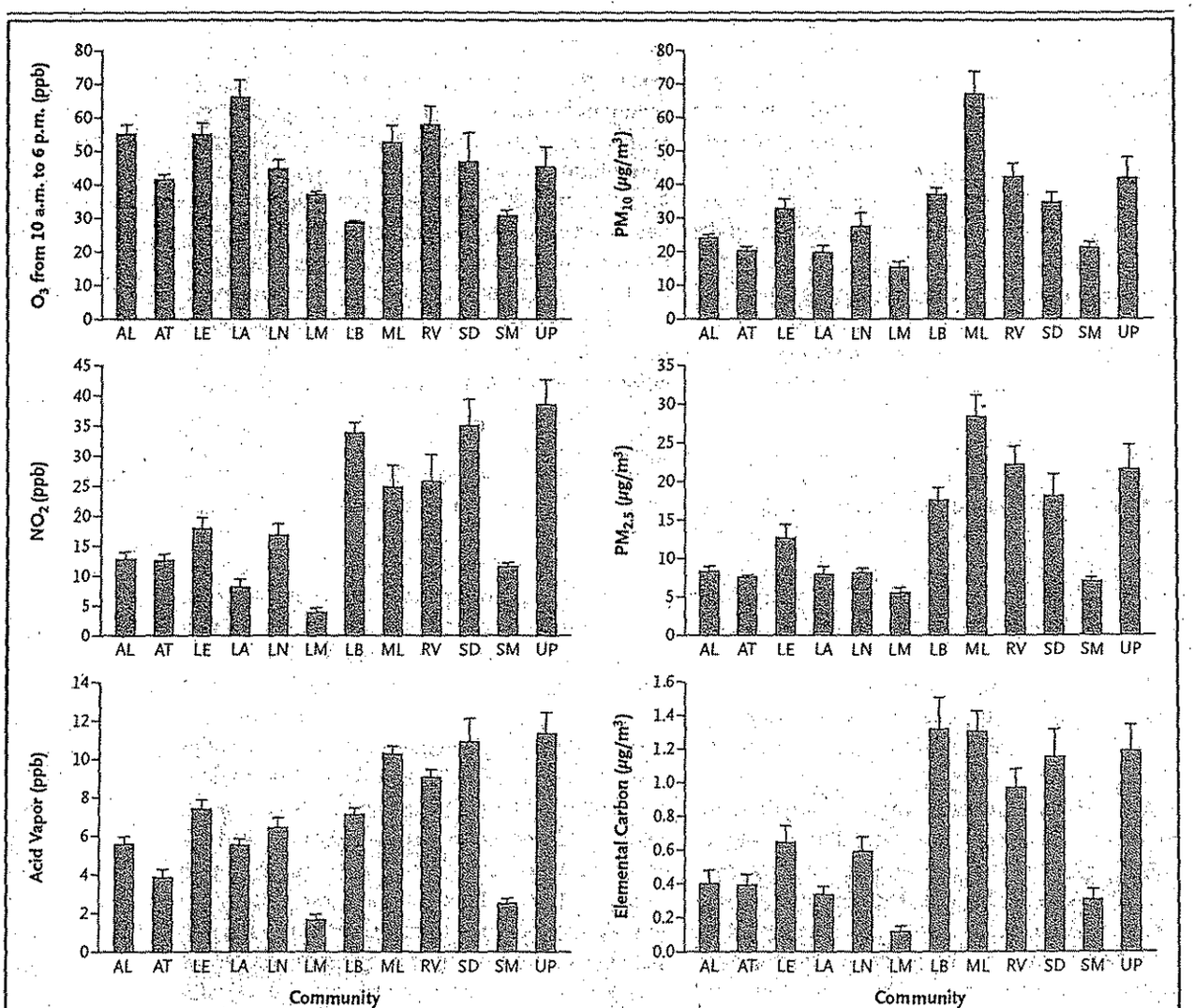


Figure 1. Mean (±SD) Annual Average Levels of Pollutants from 1994 through 2000 in the 12 Study Communities in Southern California.
AL denotes Alpine, AT Atascadero, LE Lake Elsinore, LA Lake Arrowhead, LN Lancaster, LM Lompoc, LB Long Beach, ML Mira Loma, RV Riverside, SD San Dimas, SM Santa Maria, and UP Upland. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.

average levels of ozone were not significantly correlated across communities with any other study pollutant (Table 1). However, correlations between other pairs of pollutants were all significant, ranging from an R of 0.64 ($P<0.05$) for nitrogen dioxide and organic carbon, to an R of 0.97 ($P<0.001$) for PM_{10} and organic carbon. Thus, nitrogen dioxide, acid vapor, and the particulate-matter pollutants can be regarded as a correlated "package" of pollutants with a similar pattern relative to each other across the 12 communities.

Among the girls, the average FEV_1 increased from 1988 ml at the age of 10 years to 3332 ml at the age of 18 years, yielding an average growth in FEV_1 of 1344 ml over the eight-year period (Table 2). The corresponding averages in boys were 2082 ml and 4464 ml, yielding an average growth in FEV_1 of 2382 ml over the eight-year period. Similar patterns of growth over the eight-year period were observed for FVC and MMEF (Table 2).

Although the average growth in FEV_1 was larger in boys than in girls, the correlations of growth with air pollution did not differ significantly between the sexes, as shown for nitrogen dioxide in Figure 2. The sex-averaged analysis, depicted by the regression line in Figure 2, demonstrated a significant negative correlation between the growth in FEV_1 over the eight-year period and the average nitrogen dioxide level ($P=0.005$). The estimated difference in the average growth in FEV_1 over the eight-year period from the community with the lowest nitrogen dioxide level to the community with the highest nitrogen dioxide level, represented by the slope of the plotted regression line in Figure 2, was −101.4 ml.

Estimated differences in the growth of FEV_1, FVC, and MMEF during the eight-year period with respect to all pollutants are summarized in Table 3. Deficits in the growth of FEV_1 and FVC were observed for all pollutants, and deficits in the growth of MMEF were observed for all but ozone, with several combinations of outcome variables and pollutants attaining statistical significance. Specifically, for FEV_1 we observed significant negative correlations between the growth in this variable over the eight-year period and exposure to acid vapor ($P=0.004$), $PM_{2.5}$ ($P=0.04$), and elemental carbon ($P=0.007$), in addition to the above-mentioned correlation with nitrogen dioxide. As with FEV_1, the effects of the various pollutants on FVC and MMEF did not differ significantly between boys and girls. Significant deficits in FVC were associated with exposure to nitrogen dioxide ($P=0.05$) and acid vapor ($P=0.03$), whereas deficits in MMEF were associated with exposure to nitrogen dioxide ($P=0.02$) and elemental carbon ($P=0.04$). There was no significant evidence that ozone, either the average value obtained from 10 a.m. to 6 p.m. or the one-hour maximal level, was associated with any measure of lung function. In two-pollutant models for any of the measures of pulmonary function, adjustment for ozone did not substantially alter the effect estimates or significance levels of any other pollutant (data not shown). In general, two-pollutant models for any pair of pollutants did not provide a significantly better fit to the data than the corre-

Table 1. Correlation of Mean Air-Pollution Levels from 1994 through 2000 across the 12 Study Communities.*

Pollutant	O_3 (10 a.m.–6 p.m.)	NO_2	Acid Vapor†	PM_{10}	$PM_{2.5}$	Elemental Carbon	Organic Carbon
			R value				
O_3							
1-Hour maximal level	0.98	0.10	0.53	0.31	0.33	0.17	0.25
10 a.m.–6 p.m.		−0.11	0.35	0.18	0.18	−0.03	0.13
NO_2			0.87	0.67	0.79	0.94	0.64
Acid vapor†				0.79	0.87	0.88	0.76
PM_{10}					0.95	0.85	0.97
$PM_{2.5}$						0.91	0.91
Elemental carbon							0.82

* Unless otherwise noted, values are the 24-hour average pollution levels. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.
† Acid vapor is the sum of nitric, formic, and acetic acid levels.

Table 2. Mean Levels of Growth in Pulmonary Function during the Eight-Year Study Period, from 1993 to 2001.*

Pulmonary-Function Measure	Girls			Boys		
	Age of 10 yr	Age of 18 yr	Average 8-yr growth	Age of 10 yr	Age of 18 yr	Average 8-yr growth
FVC (ml)	2262	3790	1528	2427	5202	2775
FEV_1 (ml)	1988	3332	1344	2082	4464	2382
MMEF (ml/sec)	2311	3739	1428	2287	4709	2422

* Levels at the ages of 10 and 18 years are derived from the growth model described in the Methods section. FVC denotes forced vital capacity, FEV_1 forced expiratory volume in one second, and MMEF maximal midexpiratory flow rate.

sponding single-pollutant models; this was not surprising, given the strong correlation between most pollutants.

The association between pollution and the growth in FEV_1 over the eight-year period remained significant in a variety of sensitivity analyses (Table 4). For example, estimates of the effect of acid vapor and elemental carbon (model 1 in Table 4) changed little with adjustment for in-utero exposure to maternal smoking (model 2), presence in the home of a gas stove (model 3) or pets (model 4), or parental level of education (model 5). To account for possible confounding by short-term effects of air pollution, we fitted a model that adjusted for the average ozone, nitrogen dioxide, and PM_{10} levels on the three days before each child's pulmonary-function test. This adjustment also had little effect on the estimates of the long-term effects of air pollution (model 6). Table 4 also shows that the effects of pollutants remained large and significant in the subgroups of children with no history of asthma (model 7) and those with no history of smoking (model 8). The effects of pollutants were not significant among the 457 children who had a history of asthma or among the 483 children who had ever smoked (data not shown), although the sample sizes in these subgroups were small. Model 9 demonstrates that the extremes in pollutant levels did not drive the observed associations; in other words, we found similar effect estimates after eliminating the two communities with the highest and lowest levels of each pollutant. Finally, model 10 shows the effects of pollutants in the subgroup of subjects who underwent pulmonary-function testing in both 1993 and 2001 (i.e., subjects who participated in both the first and last year of the study). The magnitudes of effects in this subgroup were similar to those in the entire sample (model 1), suggesting that observed effects of pollutants in the entire sample cannot be attributed to biased losses to follow-up across communities. These sensitivity analyses were also applied to the other pollutants and to FVC and MMEF, with similar results.

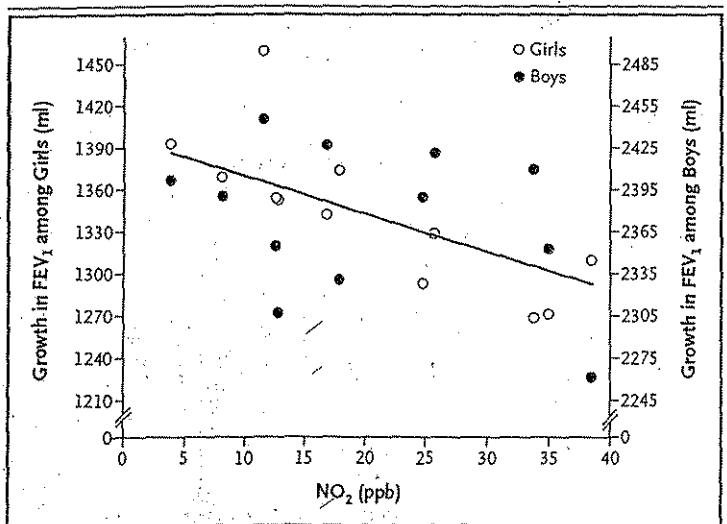


Figure 2. Community-Specific Average Growth in FEV_1 among Girls and Boys During the Eight-Year Period from 1993 to 2001, Plotted against Average Nitrogen Dioxide (NO_2) Levels from 1994 through 2000.

Pollution-related deficits in the average growth in lung function over the eight-year period resulted in clinically important deficits in attained lung function at the age of 18 years (Fig. 3). Across the 12 communities, a clinically low FEV_1 was positively correlated with the level of exposure to nitrogen dioxide (P=0.005), acid vapor (P=0.01), PM_{10} (P=0.02), $PM_{2.5}$ (P=0.002), and elemental carbon (P=0.006). For example, the estimated proportion of children with a low FEV_1 (represented by the regression line in Fig. 3) was 1.6 percent at the lowest level of exposure to $PM_{2.5}$ and was 4.9 times as great (7.9 percent) at the highest level of exposure to $PM_{2.5}$

Table 3. Difference in Average Growth in Lung Function over the Eight-Year Study Period from the Least to the Most Polluted Community.*

Pollutant	FVC		FEV_1		MMEF	
	Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
	ml		*ml*		*ml/sec*	
O_3						
10 a.m.–6 p.m.	−50.6 (−171.0 to 69.7)	0.37	−22.8 (−122.3 to 76.6)	0.62	85.6 (−130.0 to 301.1)	0.40
1-Hour maximal level	−70.3 (−183.3 to 42.6)	0.20	−44.5 (−138.9 to 50.0)	0.32	45.7 (−172.3 to 263.6)	0.65
NO_2	−95.0 (−189.4 to −0.6)	0.05	−101.4 (−164.5 to −38.4)	0.005	−211.0 (−377.6 to −44.4)	0.02
Acid vapor	−105.2 (−194.5 to −15.9)	0.03	−105.8 (−168.8 to −42.7)	0.004	−165.0 (−344.8 to 14.7)	0.07
PM_{10}	−60.2 (−190.6 to 70.3)	0.33	−82.1 (−176.9 to 12.8)	0.08	−154.2 (−378.3 to 69.8)	0.16
$PM_{2.5}$	−60.1 (−166.1 to 45.9)	0.24	−79.7 (−153.0 to −6.4)	0.04	−168.9 (−345.5 to 7.8)	0.06
Elemental carbon	−77.7 (−166.7 to 11.3)	0.08	−87.9 (−146.4 to −29.4)	0.007	−165.5 (−323.4 to −7.6)	0.04
Organic carbon	−58.6 (−196.1 to 78.8)	0.37	−86.2 (−185.6 to 13.3)	0.08	−151.2 (−389.4 to 87.1)	0.19

* Values are the differences in the estimated rate of eight-year growth at the lowest and highest observed levels of the indicated pollutant. Differences are scaled to the range across the 12 study communities in the average level of each pollutant from 1994 through 2000 as follows: 37.5 ppb of O_3 (measured from 10 a.m. to 6 p.m.), 46.0 ppb of O_3 (the one-hour maximal level), 34.6 ppb of NO_2, 9.6 ppb of acid vapor, 51.4 μg of PM_{10} per cubic meter, 22.8 μg of $PM_{2.5}$ per cubic meter, 1.2 μg of elemental carbon per cubic meter, and 10.5 μg of organic carbon per cubic meter. CI denotes confidence interval.

(P=0.002). Similar associations between these pollutants and a low FEV_1 were observed in the subgroup of children with no history of asthma and the subgroup with no history of smoking (data not shown). A low FEV_1 was not significantly correlated with exposure to ozone in any group.

DISCUSSION

The results of this study provide robust evidence that lung development, as measured by the growth in FVC, FEV_1, and MMEF from the ages of 10 to 18 years, is reduced in children exposed to higher levels of ambient air pollution. The strongest associations were observed between FEV_1 and a correlated set of pollutants, specifically nitrogen dioxide, acid vapor, and elemental carbon. The effects of these pollutants on FEV_1 were similar in boys and girls and remained significant among children with no history of asthma and among those with no history of smoking, suggesting that most children are susceptible to the chronic respiratory effects of breathing polluted air. The magnitude of the observed effects of air pollution on the growth in lung function during this age interval was similar to those that have been reported for exposure to maternal smoking[17,18] and smaller than those reported for the effects of personal smoking.[17,19]

Cumulative deficits in the growth in lung function during the eight-year study period resulted in a strong association between exposure to air pollution and a clinically low FEV_1 at the age of 18 years. In general, lung development is essentially complete in girls by the age of 18 years, whereas in boys it continues into their early 20s, but at a much reduced rate. It is therefore unlikely that clinically significant deficits in lung function at the age of 18 years will be reversed in either girls or boys as they complete the transition into adulthood. Deficits in lung function during young adulthood may increase the risk of respiratory conditions — for example, episodic wheezing that occurs during a viral infection.[20] However, the greatest effect of pollution-related deficits may occur later in life, since reduced lung function is a strong risk factor for complications and death during adulthood.[21-27]

Deficits in lung function were associated with a correlated set of pollutants that included nitrogen dioxide, acid vapor, fine-particulate matter ($PM_{2.5}$), and elemental carbon. In southern California, the primary source of these pollutants is motor vehicles, either through direct tailpipe emissions or downwind physical and photochemical reactions of vehicular emissions. Both gasoline- and diesel-powered engines contribute to the tons of pollutants exhausted into southern California's air every day, with diesel vehicles responsible for disproportionate amounts of nitrogen dioxide, $PM_{2.5}$, and ele-

Table 4. Sensitivity Analysis of the Effects of Acid Vapor and Elemental Carbon on Growth in FEV_1 over the Eight-Year Study Period.*

Model	Acid Vapor	Elemental Carbon
	Difference (95% Confidence Interval)	
Main model (model 1)†	−105.8 (−168.8 to −42.7)	−87.9 (−146.4 to −29.4)
Additional covariates‡		
Main model + in-utero exposure to maternal smoking (model 2)	−108.8 (−173.3 to −44.2)	−85.8 (−147.4 to −24.1)
Main model + exposure to gas stove (model 3)	−106.0 (−181.5 to −30.6)	−84.8 (−154.7 to −14.9)
Main model + pets in home (model 4)	−108.4 (−171.6 to −45.2)	−89.8 (−149.1 to −30.6)
Main model + parental level of education (model 5)	−100.7 (−167.2 to −34.2)	−80.9 (−142.7 to −19.0)
Main model + short-term effects of pollution (model 6)§	−112.4 (−201.4 to −23.3)	−103.2 (−181.8 to −24.5)
Subgroup effects		
No history of asthma (model 7)¶	−98.1 (−166.4 to −29.8)	−88.9 (−149.2 to −28.6)
No history of smoking (model 8)‖	−115.6 (−233.7 to 2.5)	−113.3 (−214.9 to −11.6)
After exclusion of communities with lowest and highest levels of pollution (model 9)**	−106.7 (−192.3 to −21.2)	−94.7 (−173.7 to −15.7)
Complete follow-up (model 10)††	−132.4 (−226.2 to −38.7)	−97.4 (−195.6 to 0.9)

* Values are the differences in the estimated rate of eight-year growth at the lowest and highest observed levels of the indicated pollutant. Differences are scaled to the range across the 12 study communities in the average level of each pollutant from 1994 through 2000 as follows: 9.6 ppb of acid vapor and 1.2 μg of elemental carbon per cubic meter.
† Model 1 is equivalent to effect estimates for FEV_1 in Table 3 and is based on data on 1759 children.
‡ The main model was adjusted for each of the covariates listed.
§ Values were adjusted for the average levels of O_3, NO_2, and PM_{10} on the three days before each child's pulmonary-function test.
¶ The analysis includes data on 1302 children with no history of doctor-diagnosed asthma.
‖ The analysis includes data on 1276 children with no history of active tobacco smoking at any time during follow-up.
** The analysis excludes children from the two communities with the lowest and highest levels of each pollutant. This leaves 1507 children (excluding those from Lompoc and Upland) in the analysis of acid vapor and 1484 children (excluding those from Lompoc and Long Beach) in the analysis of elemental carbon.
†† The analysis includes 713 children who underwent pulmonary-function testing in both 1993 and 2001 (i.e., those observed throughout the study).

mental carbon. In the current study, however, we could not discern the independent effects of pollutants because they came from common sources and there was a high degree of intercorrelation among them; similar difficulties have also been encountered in other studies of lung function and air-pollutant mixtures.[1,2,9,28-30] Since ozone is also formed during photochemical reactions involving fuel-combustion products, one might expect ozone to be correlated with the other study pollutants and therefore to show similar associations with lung function. However, the Children's Health Study was specifically designed to minimize the correlation of ozone with other pollutants across the 12 study communities. Thus, although ozone has been convincingly linked to acute health effects in many other studies,[11] our results provide little evidence that ambient ozone at current levels is associated with chronic deficits in the growth of lung function in children. Only a few other studies have addressed the long-term effects of ozone on lung development in children, and results have been inconsistent.[31] Although we found little evidence of an effect of ozone, this result needs to be interpreted with caution given the potential for substantial misclassification of exposure to ozone.[32,33]

The mechanism whereby exposure to pollutants could lead to reduced lung development is unknown, but there are many possibilities. Our observation of associations between air pollution and all three measures of lung function — FVC, FEV_1, and MMEF — suggests that more than one process is involved. FVC is largely a function of the number and size of alveoli, with differences in volume pri-

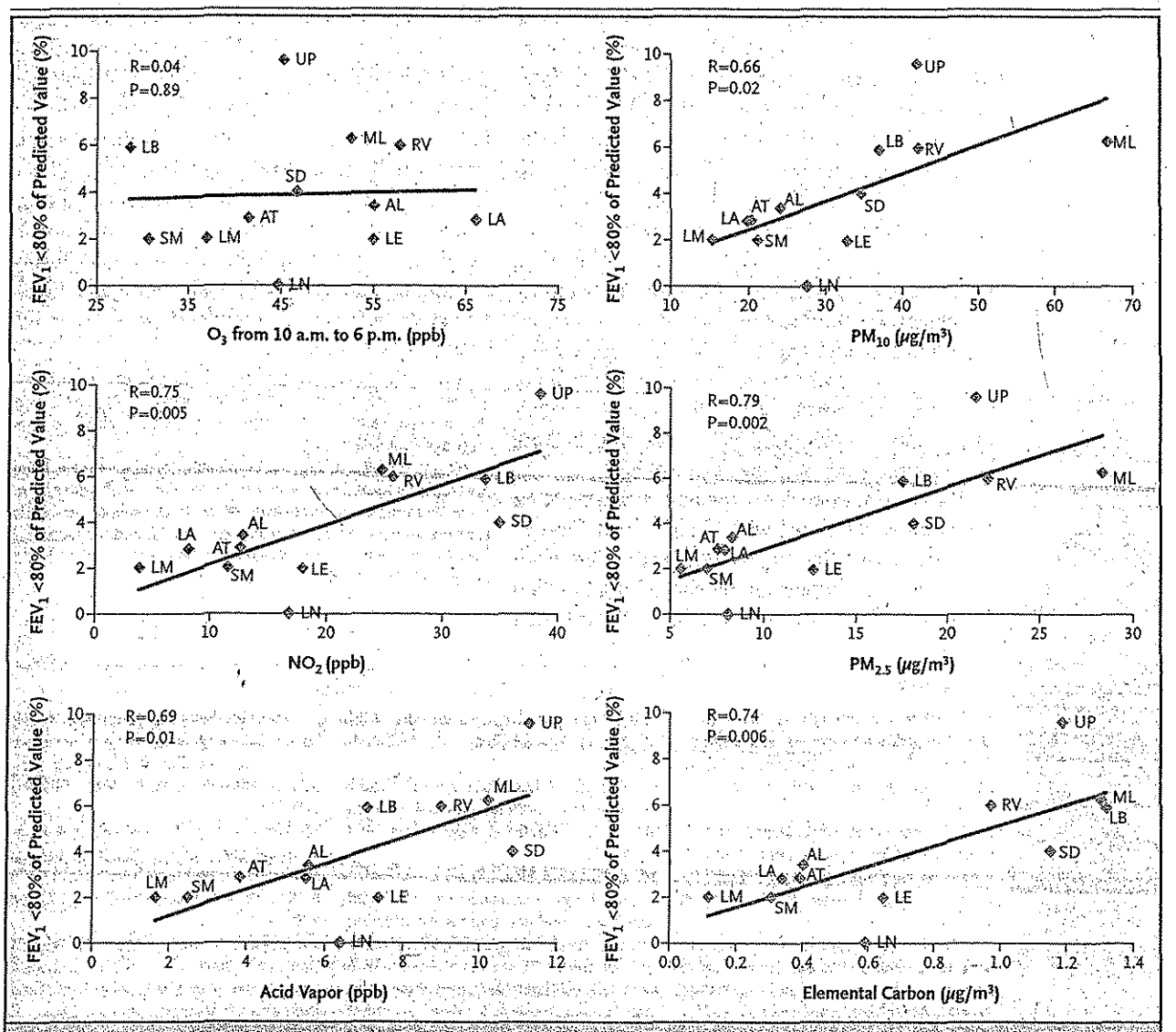


Figure 3. Community-Specific Proportion of 18-Year-Olds with a FEV_1 below 80 Percent of the Predicted Value Plotted against the Average Levels of Pollutants from 1994 through 2000.

The correlation coefficient (R) and P value are shown for each comparison. AL denotes Alpine, AT Atascadero, LE Lake Elsinore, LA Lake Arrowhead, LN Lancaster, LM Lompoc, LB Long Beach, ML Mira Loma, RV Riverside, SD San Dimas, SM Santa Maria, and UP Upland. O_3 denotes ozone, NO_2 nitrogen dioxide, and PM_{10} and $PM_{2.5}$ particulate matter with an aerodynamic diameter of less than 10 μm and less than 2.5 μm, respectively.

marily attributable to differences in the number of alveoli, since their size is relatively constant.[34] However, since the postnatal increase in the number of alveoli is complete by the age of 10 years, pollution-related deficits in the growth of FVC and FEV_1 during adolescence may, in part, reflect a reduction in the growth of alveoli. Another plausible mechanism of the effect of air pollution on lung development is airway inflammation, such as occurs in bronchiolitis; such changes have been observed in the airways of smokers and of subjects who lived in polluted environments.[35,36]

A strength of our study was the long-term, prospective follow-up of a large cohort, with exposure and outcome data collected in a consistent manner throughout the study period. As in any epidemiologic study, however, the observed effects could be biased by underlying associations of the exposure and outcome to some confounding variables. We adjusted for known potential confounders, includ-

ing personal characteristics and other sources of exposure to pollutants, but the possibility of confounding by other factors still exists. Over the eight-year follow-up period, approximately 10 percent of study subjects were lost to follow-up each year. Attrition is a potential source of bias in a cohort study if loss to follow-up is related to both exposure and outcome. However, we did not see evidence that the loss of subjects was related to either baseline lung function or exposure to air pollution. In addition, we observed significant associations between air pollution and lung growth in the subgroup of children who were followed for the full eight years of the study, with effects that were similar in magnitude to those in the group as a whole, thus making loss of subjects an unlikely source of bias.

We have shown that exposure to ambient air pollution is correlated with significant deficits in respiratory growth over an eight-year period, leading to clinically important deficits in lung function at the age of 18 years. The specific pollutants that were associated with these deficits included nitrogen dioxide, acid vapor, $PM_{2.5}$, and elemental carbon. These pollutants are products of primary fuel combustion, and since they are present at similar levels in many other areas,[37,38] we believe that our results can be generalized to children living outside southern California. Given the magnitude of the observed effects and the importance of lung function as a determinant of morbidity and mortality during adulthood, continued emphasis on the identification of strategies for reducing levels of urban air pollutants is warranted.

Supported in part by a contract (A033-186) with the California Air Resources Board, grants (5P30ES07048 and 1P01ES11627) from the National Institute of Environmental Health Sciences, and the Hastings Foundation.

We are indebted to Morton Lippmann, Jonathan Samet, Frank Speizer, John Spengler, Scott Zeger, Paul Enright, William Linn, and Dane Westerdahl for important advice; to the school principals, teachers, students, and parents in each of the 12 study communities for their cooperation; and especially to the members of the health testing field team for their efforts.

REFERENCES

1. Frischer T, Studnicka M, Gartner C, et al. Lung function growth and ambient ozone: a three-year population study in school children. Am J Respir Crit Care Med 1999;160:390-6.
2. Jedrychowski W, Flak E, Mroz E. The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ Health Perspect 1999;107:669-74.
3. Horak F Jr, Studnicka M, Gartner C, et al. Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. Eur Respir J 2002; 19:838-45.
4. Gauderman WJ, McConnell R, Gilliland F, et al. Association between air pollution and lung function growth in southern California children. Am J Respir Crit Care Med 2000;162:1383-90.
5. Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. Am J Respir Crit Care Med 2001; 164:2067-72.
6. Gauderman WJ, Gilliland GF, Vora H, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. Am J Respir Crit Care Med 2002;166:76-84.
7. Ware JH, Ferris BG Jr, Dockery DW, Spengler JD, Stram DO, Speizer FE. Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am Rev Respir Dis 1986;133: 834-42.
8. Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG Jr. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 1989;139: 587-94.
9. Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ Res 1989; 50:309-21.
10. Raizenne M, Neas LM, Damokosh AI, et al. Health effects of acid aerosols on North American children: pulmonary function. Environ Health Perspect 1996;104:506-14.
11. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. Am J Respir Crit Care Med 1996;153:3-50, 477-98.
12. Peters JM, Avol E, Gauderman WJ, et al. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am J Respir Crit Care Med 1999;159:768-75.
13. Peters JM, Avol E, Navidi W, et al. A study of twelve Southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am J Respir Crit Care Med 1999; 159:760-7.
14. Wang X, Dockery DW, Wypij D, et al. Pulmonary function growth velocity in children 6 to 18 years of age. Am Rev Respir Dis 1993;148:1502-8.
15. Elemental carbon (diesel exhaust). In: NIOSH manual of analytical methods. No. 5040. Issue 3 (interim report). Cincinnati: National Institute for Occupational Safety and Health, 1999.
16. SAS/STAT user's guide, version 9. Cary, N.C.: SAS Institute, 2002.
17. Tager IB, Weiss ST, Munoz A, Rosner B, Speizer FE. Longitudinal study of the effects of maternal smoking on pulmonary function in children. N Engl J Med 1983;309: 699-703.
18. Wang X, Wypij D, Gold DR, et al. A longitudinal study of the effects of parental smoking on pulmonary function in children 6-18 years. Am J Respir Crit Care Med 1994; 149:1420-5.
19. Tager I, Munoz A, Rosner B, Weiss ST, Carey V, Speizer FE. Effect of cigarette smoking on the pulmonary function of children and adolescents. Am Rev Respir Dis 1985;131:752-9.
20. Mckean M, Leech M, Lambert PC, Hewitt C, Myint S, Silverman M. A model of viral wheeze in nonasthmatic adults: symptoms and physiology. Eur Respir J 2001;18: 23-32.
21. Schroeder EB, Welch VL, Couper D, et al. Lung function and incident coronary heart disease: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2003; 158:1171-81.
22. Schunemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 2000; 118:656-64.
23. Knuiman MW, James AL, Davitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. Ann Epidemiol 1999;9:297-306.
24. Hole DJ, Watt GC, Davey Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired

EDITORIALS

Air Pollution and Health — Good News and Bad

C. Arden Pope III, Ph.D.

Early concerns regarding the health-related effects of air pollution originated from severe episodes in Meuse Valley, Belgium, in 1930; Donora, Pennsylvania, in 1948; and London, in 1952. Although the overall effects of these episodes continue to be debated, well-documented, episode-related increases in morbidity and mortality from cardiopulmonary causes provided dramatic evidence that extremely high concentrations of air pollution can have serious adverse effects on health. Early public-policy efforts to improve air quality in the United States, Britain, and elsewhere were largely attempts to avert such "killer" episodes of air pollution. In the United States, a series of national legislative and regulatory efforts to control air pollution were initiated (Fig. 1); National Ambient Air Quality Standards were mandated and established; and dramatic, extremely severe episodes of air pollution were essentially eliminated.

From the 1960s through the 1980s, a few scattered studies continued to suggest that air pollution had adverse effects on health.[1,2] Then, during the relatively short period of 1989 through 1995, several loosely connected epidemiologic studies reported adverse effects of unexpectedly low levels of particulate-matter air pollution.[3-6] Although highly controversial,[7] these results prompted serious reconsideration of the particulate-matter standards and health guidelines (Fig. 1). They also prompted extensive efforts to reanalyze key studies[8] (which were largely confirmatory) and motivated rapid growth in epidemiologic, toxicologic, and other studies of fine particulate matter and other combustion-related air pollutants.

Research has continued to suggest that a level of air pollution that is common in many urban and industrial environments is an important risk factor for various adverse health effects in humans. Although many such studies have focused on respiratory disease, substantial and growing evidence indicates that fine particulate air pollution is also a risk factor for cardiovascular disease.[9,10] Short-term exposure exacerbates existing pulmonary and cardiovascular disease and increases the risk of symptoms, the need for medical attention, and death.[1] Long-term, repeated exposure increases the cumulative risk of chronic pulmonary and cardiovascular disease and death.[9-13]

One notable research effort that began in the early 1990s in the midst of the controversies about air quality was the Children's Health Study. This study prospectively monitored the lung function of schoolchildren from the ages of 10 to 18 years in 12 southern California communities with a relatively wide range of air pollutants. As reported by Gauderman et al. in this issue of the *Journal*,[14] air pollution was significantly associated with deficits in lung development. Within the context of the overall literature on air pollution and human health, this article makes several important and confirmatory contributions.

The Children's Health Study evaluated the cumulative exposure to various pollutants over an eight-year period. Deficits in the growth of lung function over the eight-year period were associated with a correlated set of pollutants that included fine particulate matter with an aerodynamic diameter of less than 2.5 μm, nitrogen dioxide, acid vapor, and elemental carbon. These results are consistent with those of previous epidemiologic studies that have implicated fine particulate matter and associated combustion-related air pollutants as being largely responsible for the observed health effects of air pollution.[1,2,5,11-13] Various physiological and toxicologic findings suggest that exposure to fine particulate matter may be an important pub-

lic health concern. Such matter, which can be breathed deeply into the lungs, includes sulfates, nitrates, acids, metals, and carbon particles with various chemicals adsorbed onto their surfaces. Furthermore, fine particulate matter is ubiquitous because it is largely derived from common combustion processes (such as engines in motor vehicles, manufacturing, power generation, and burning of biomass) and because it is transported over long distances and readily penetrates indoors.

Understanding the shape of the exposure–response relationship and determining whether there are safe thresholds are important for the formulation of public health policies for pollution control. Mortality studies suggest that the exposure–response relationships for particulate-matter pollution in the case of both short-term[15] and long-term[11] exposures are nearly linear, with no discernible safe thresholds within relevant ranges of exposure. Likewise, in the Children's Health Study, the exposure–response relationships appear to be nearly linear, without discernible safe thresholds.

An issue with clinical implications concerns the identification of groups that are most at risk or that are most susceptible to the effects of pollution. One evaluation of the literature[1] suggests that the proportion of a given population that is at risk for death, hospitalization, or life-threatening conditions owing to short-term exposure to air pollution is very small and limited to the elderly, infants, and persons with chronic cardiopulmonary disease, influenza, or asthma. There appears to be a much broader susceptibility to small, transient changes in lung function, low-grade pulmonary inflammation, or other subclinical physiological changes in response to short-term exposure.

With regard to the cumulative effects of long-term, repeated exposure, there is little evidence of a unique, well-defined, susceptible subgroup. The Children's Health Study reports pollution-related deficits in the development of lung function in boys and girls, children with asthma and those without asthma, and smokers and nonsmokers — results "suggesting that most children are susceptible to the chronic respiratory effects of breathing polluted air." The authors of the current study also note that reduced lung function is a risk factor for complications and death during adulthood and suggest that the effect of these pollution-related deficits in lung function may occur later in life. In fact, studies have shown that long-term, repeated exposure to air pollution is associated with an increased risk of death from cardiopulmonary causes in broad-based cohorts or samples of adults.[5,6,9,11,13]

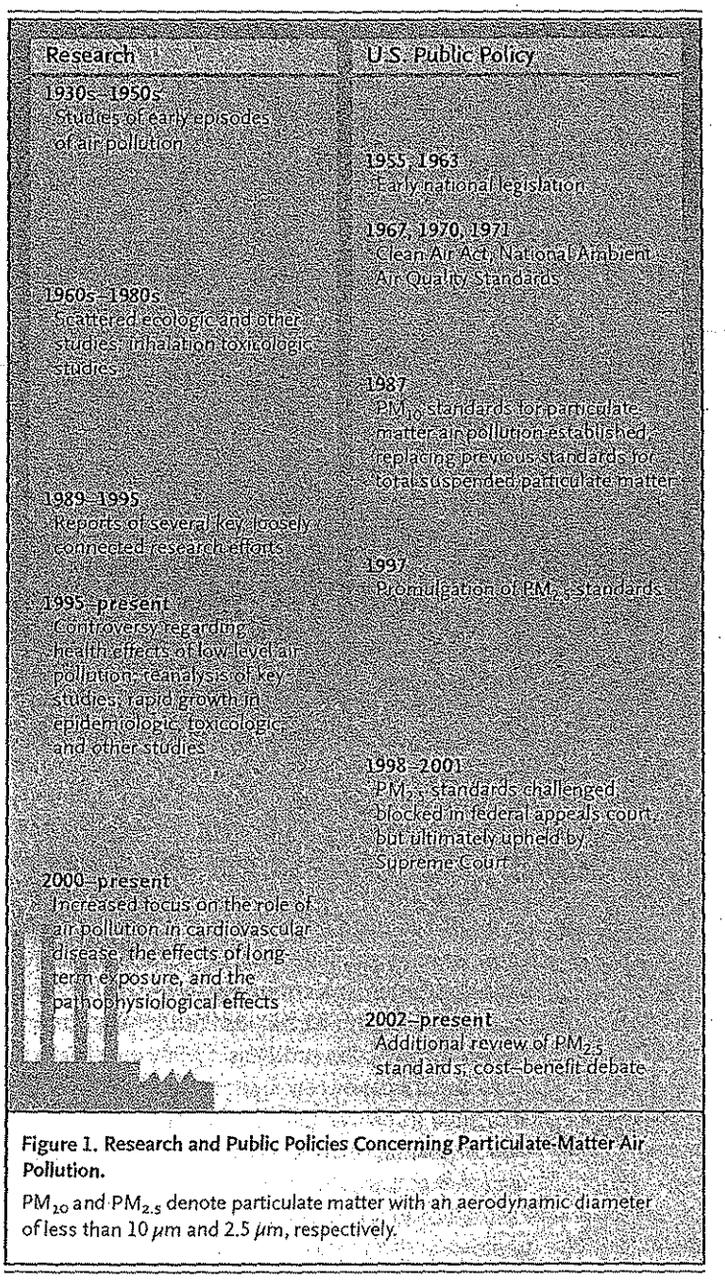


Figure 1. Research and Public Policies Concerning Particulate-Matter Air Pollution.

PM_{10} and $PM_{2.5}$ denote particulate matter with an aerodynamic diameter of less than 10 μm and 2.5 μm, respectively.

Much additional research is required to understand the biologic mechanisms that link exposure to fine particulate matter with increases in morbidity and mortality from cardiopulmonary causes. However, several recent studies suggest that general mechanistic pathways probably include pulmonary and systemic oxidative stress and inflammation, enhanced initiation and progression of atherosclerosis, and altered cardiac autonomic function.[9,10]

Secondhand cigarette smoke has also been shown to promote inflammation and atherosclerosis and to be a risk factor for illness and death from cardiopulmonary causes — suggesting that exposure to fine particles from common outdoor sources of combustion and from tobacco smoke may invoke similar pathophysiological processes.[9,10] The Children's Health Study does not provide direct evidence regarding the mechanisms of air-pollution effects, but the authors suggest a role of airway inflammation, such as that observed in smokers and persons who have lived in polluted environments. Although there has been much interest recently in the importance of pulmonary inflammation, atherosclerosis, and cardiovascular disease, the Children's Health Study reminds us not to forget or ignore potentially important effects of pollution on pulmonary function.

From at least one perspective, the overall results of research involving air pollution are good news — the control of air pollution represents an important opportunity to prevent disease. Air pollution is just one of many risk factors for pulmonary and cardiovascular disease, but it is one that can be modified. In the United States and elsewhere, commendable progress has been made on improving air quality and, with regard to fine particulate pollution, new standards have been implemented (Fig. 1). Extremely high concentrations of air pollution remain in many areas of the world, and decreasing these concentrations offers substantial opportunities for disease prevention. As efforts to reduce air pollution progress, debates over the relative benefits and costs associated with additional marginal improvements are inevitable. Nevertheless, continued efforts to improve our air quality are likely to provide additional health benefits.

From Brigham Young University, Provo, Utah.

1. Pope CA III. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? Environ Health Perspect 2000;108:Suppl 4:713-23.
2. Lave LB, Seskin EP. Air pollution and human health. Science 1970;169:723-33.
3. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 1989;79:623-8.
4. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. Am Rev Respir Dis 1992;145:600-4.
5. Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.
6. Pope CA III, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med 1995;151:669-74.
7. Kaiser J. Showdown over clean air science. Science 1997;277:466-9.
8. Krewski D, Burnett RT, Goldberg MS, et al. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and mortality: special report. Cambridge, Mass: Health Effects Institute, 2000.
9. Pope CA III, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 2004;109:71-7.
10. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004;109:2655-71.
11. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132-41.
12. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. Lancet 2002;360:1210-4.
13. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002;360:1203-9.
14. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004;351:1057-67.
15. Daniels MJ, Dominici F, Samet JM, Zeger SL. Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am J Epidemiol 2000;152:397-406.

Allergen Avoidance to Reduce Asthma-Related Morbidity

Albert L. Sheffer, M.D.

Central to the reduction of the severity of allergic disease is a decrease in — and preferably the removal of — the offending environmental allergen. Such allergen avoidance is particularly relevant to the successful treatment of allergic asthma. However, statistically significant reductions in such asthma-inducing allergen concentrations have been difficult to accomplish. Until recently, strategies to reduce exposure to environmental allergens have not decreased asthma-related morbidity. In fact, a meta-analysis failed to demonstrate the efficacy of any environmental-control measures in reducing the severity of asthma.[1] Such interventions, however, have usually focused on a single maneuver[2] — for example, the use of semipermeable bedcovers to exclude dust mites, floor polishing, or the use of high-efficiency particulate air filters — but have not been accompanied by detailed educational pro-

Exhibit 5

Los Angeles Times

, January 26, 2007

COPYRIGHT 2007 112 PAGES DESIGNATED AREAS HIGHER 50¢

LUIS SINCO Los Angeles Times

BEACH AFFRONT

: finds that many sewage spills in Los Angeles County are neither reported nor cleaned
)lames myriad regulations for the communication breakdown. CALIFORNIA, B1

Cooperative tone of Sadr surprises U.S.

The cleric's movement, long a foe of America, says it backs the new Iraq security plan.

SOME DOUBT MOTIVES

By BORZOU DARAGAHI
Times Staff Writer

BAGHDAD — Muqtada Sadr, the radical anti-American cleric, has backed away from confrontation with U.S. and Iraqi forces in recent weeks, a move that has surprised U.S. officials who long have characterized his followers as among the greatest threats to Iraq's security.

Thursday, a leader of the Sadr movement in one of its Baghdad strongholds publicly endorsed President Bush's new Iraq security plan, which at least some U.S. officials have touted as a way to combat Sadr's group.

"We will fully cooperate with the government to make the plan successful," said Abdul-Hussein Kaabai, head of the local council in the Shiite Muslim-dominated Sadr City neighborhood. "If it is an Iraqi plan done by the government, we will cooperate."

Over the last several weeks, the Shiite cleric and his followers have dropped their threats to quit Iraq's U.S.-backed government, and after years of shunning the "occupier," they have allowed their emissaries to meet with U.S. officials.

Many U.S. officials are skeptical of Sadr's moves, citing his history as leader of a violent group and wondering whether he and his movement have really changed or are merely lying low at a time of particular scrutiny and potential peril.

"There's a change of behavior that we can see," U.S. Ambassador Zalmay Khalilzad told reporters this week. "If it's a change of heart, that's a good thing. If it's a change of tactic, we need to be cautious."

Allies of Sadr suggest he has begun heeding the appeals of other Shiite leaders, including Prime Minister Nouri Maliki, to temper his actions in order to preserve unity in the Shiite-dominated government.

"We were not going to be dragged into a trap to clash with the government or any other of our people," said Nassar Rubaie, a member of parliament who is close to Sadr. "We are aware such a thing could happen."

Others suggest the cleric has been mellowed by the realities of exercising power. The Sadr movement controls several government ministries, including Health and Transportation.

Control of those bureaucra-

QUAQUEAU ZIANI AFP/Getty Images

MUQTADA SADR
Allies suggest he has begun heeding the appeals of other Shiite leaders.

IN ONE

vice
t's
base

lumn 'Dear Ms.
Army wife
l worker at Ft.
l offers candid
o soldiers and
She can relate.

D FAUSSET
iter

Ft. Campbell, Ky. STER unveiling his plan for a troop increase in Iraq this month, President Bush spoke of the ne by America's mili- s — of "the quiet sac- iely holidays and s at the dinner ta-

e, elegant phrase ole longing worthy of Hopper painting. tends to be messier fe.

here, on the sprawl- ian home of the t Airborne Division, ore intimate catalog dens — a running he cheating hearts, rmas, exasperated l emotionally wound- that has flourished deployments to Iraq

Prison pay hikes drain staff at state hospitals

Lack of health workers forces Atascadero to turn away new patients.

By LEE ROMNEY
Times Staff Writer

ATASCADERO — Court orders mandating drastic pay increases for health personnel in California prisons have led to an exodus of workers from state mental hospitals and left the facilities struggling to provide adequate patient care.

Staff shortages at Atascadero State Hospital, where psychiatrist vacancies stand at 70%, have caused the facility to all but freeze new admissions.

All the state's mental hospitals, which like the prisons are also under federal scrutiny, report staff departures for prison jobs that now pay about 40% more. And they fear that many more staffers will leave.

At Patton State Hospital in San Bernardino, the medical staff chief pleaded with the federal court-appointed monitor in a December letter, saying a mass exodus of Department of Mental Health "psychiatrists and physicians is expected, and we are already seeing the start of it affecting our institution. Recruiting new people has become increasingly difficult."

In order to keep Napa State Hospital licensed, the state had to hire contract pharmacists after many fled for higher-paying prison jobs. Workers at Metropolitan State Hospital in Norwalk now refer to the facility as "the Titanic" as psychologists apply in droves for prison system jobs. Recruiting e-mails featuring a photo of happy correctional staff members were sent directly to hospital psychologists this month, noting that 1,000 posi-

[See Atascadero, Page A14]

FREEWAY AIR DAMAGES YOUNG LUNGS

Children living nearby show signs of lifelong harm, USC study finds.

By THOMAS H. MAUGH II
Times Staff Writer

In the largest and longest study of its kind, USC researchers have found that children living near busy highways have significant impairments in the development of their lungs that can lead to respiratory problems for the rest of their lives.

The 13-year study of more than 3,600 children in 12 Central and Southern California communities found that the damage from living within 500 yards of a freeway is about the same as that from living in communities with the highest pollution levels, the team reported Thursday in the online version of the medical journal Lancet.

"If you live in a high-pollution area and live near a busy road, you get a doubling" of the damage, said lead author W. James Gauderman, an epidemiologist at the Keck School of Medicine of USC.

"Someone suffering a pollution-related deficit in lung function as a child will probably have less than healthy lungs all of his or her life," he said.

Inside Today's Times

CHENEY'S KEY ROLE IN LEAK CASE DETAILED

A former aide testifies in Libby's trial that the vice president directed the effort to discredit a CIA agent's husband

stigma of the contamination is hurting the economy of the upper Hudson," said David King, the EPA's Hudson River project manager.

Twenty-six years after Congress passed the Superfund law to clean up the nation's most dangerous dumping grounds, the list of mega sites keeps growing as more mines, landfills, military bases and factories qualify.

Superfund's national priority list includes more than 1,200 chemical sites, but only one of every eight rises to "mega" status. New Jersey leads with 18, but California's 16 megas will soon more than double, with 18 others expected to meet the $50-million mark.

"State programs can deal with garden-variety sites, but mega sites are ones that nobody but the federal government can deal with," said Katherine Probst, a senior fellow at Resources for the Future, an environmental think tank in Washington, who has researched Superfund for 15 years.

Mega cleanups averaged $140 million each in 2000, 10 times the standard Superfund project, according to Resources for the Future. California's 16 mega sites' cost estimates range from $100 million to $450 million, said Elizabeth Adams, the EPA's regional Superfund cleanup chief in San Francisco.

"Today, a real mega site is well over the $100-million mark. Sadly, $50 million may not be what it once was," Probst said.

Funding lags behind

Yet federal funding for Superfund oversight has not kept up with the surge in mega sites, and many cleanups remain in the early stages. At 22% of all sites, human exposure to chemicals is not under control, the EPA says.

Polluters pay for most cleanups, but Superfund's annual budget, which supports EPA analyses, has remained at about $1.2 billion since 1987. With inflation, that is a 40% decline.

Excluding the Hudson River — are underwater. Dredging them risks uncovering more polluted layers or leaving toxic residue.

"It's not like vacuuming your carpet," said Richard Luthy, Stanford University's chairman of civil and environmental engineering and a member of a National Research Council committee on mega sites. "You are, in every case, left with some material on the bottom that you haven't completely picked up. Just because you can dredge doesn't mean you can get everything."

At a small cleanup in San Francisco Bay's Richmond Harbor, DDT-laden sludge was dredged in 1997. But high concentrations of the PCBs, which are likely human carcinogens and can disrupt immune systems and brain development, rendered the river's fish inedible.

GE maintained that removing PCBs from the Hudson was too risky, and in 1984, the EPA agreed. The agency reversed course in 2001, concluding that dredging could be done safely and setting performance standards. Finally, in a November court settlement, GE agreed to dredge 10%. If an independent panel approves the results, GE can voluntarily dredge the rest or face a likely EPA order.

The main risk, King said, is unleashing buried PCBs. To reduce that danger, the dredging is expected to last six to eight years, but after decades of delay in the start-up, Hudson River Valley residents are skeptical about when the toxic mud will be gone.

In Fort Edward's museum, a sign reads: "The roots of the present lie deep in the past." For residents of mega-site communities, the past, present and future are defined by a toxic legacy.

"We could come back two decades from now, and it will still be going on," said Peter Berle, New York's former environmental commissioner. "Hopefully, someday, we'll be free of PCBs."

marla.cone@latimes.com

Tainted freeway air harms children's lungs, study says

[Pollution, *from Page A1*]
to be in the small airways of the lung and is normally associated with the fine particulate matter emitted by automobiles.

"This tells me that I wouldn't want to be raising my children near a significant source of fine-particle air pollution," said economist C. Arden Pope III of Brigham Young University, an expert on air pollution and health who was not involved in the study. "I, myself, would want to be living in areas where the exposure is lower."

The research is part of an ongoing study of the effects of air pollution on children's respiratory health. Previous findings have detailed how smog can stunt lung growth and how living close to freeways can increase the risk of children being diagnosed with asthma.

This latest study of freeway proximity and lung capacity was funded by the California Air Resources Board; the National Institute of Environmental Health Sciences; the Environmental Protection Agency; the National Heart, Lung and Blood Institute; and the Hastings Foundation.

Gauderman and his colleagues recruited groups of fourth-grade students, average age 10, in 1993 and 1996. Their schools were scattered from Atascadero in San Luis Obispo County to Alpine in San Diego County.

The team collected extensive information about each child's home, socioeconomic status and other facts that might impinge on health.

Once each year, the team visited the schools and measured the children's lungs, assessing how much air could be expelled in one breath and how quickly it could be expelled.

These cohorts of children "are truly an important resource because the study has been going on so long," said epidemiologist Jonathan Samet of Johns Hopkins University's Bloomberg School of Public Health, who also did not take part in the study. The size and scope of the study make it very difficult to replicate, he said.

Results from the study reported in 2004 indicated that children in the communities with the highest average levels of pollution suffered the greatest long-term impairment of lung function.

In the new study, Gauderman and his colleagues found that by their 18th birthday, children who lived within 500 yards of a freeway had a 3% deficit in the amount of air they could exhale and a 7% deficit in the rate at which it could be exhaled compared with children who lived at least 1,500 yards, or nearly a mile, from a freeway. The effect was independent of the overall pollution in their community.

Gauderman had no estimate for the percentage of people in Southern California living within 500 yards of a freeway, but he noted that in a typical city such as Long Beach, it is about 17%.

The most severe impairment was observed in children living near freeways in the communities with the highest average pollution — Upland, Mira Loma, Riverside and Long Beach. Those children had an average 9% deficit in the amount of air they could expel from the lungs.

"Even if you are in a relatively low regional pollution area, living near a road produces [lung problems]," Gauderman said.

About one-third of the children moved during the course of the study but stayed in the same community. Lung impairment was smaller among those who moved farther from the freeways.

The finding is important "because it shows that within communities, some children are at higher risk than others," Dr. Thomas Sandstrom and Dr. Bert Brunekreef wrote in an editorial accompanying the paper. "Thus, environmental equity is an issue of local rather than regional dimensions."

The results were also independent of the children's initial health and whether they were smokers. "This suggests that all children, not just susceptible subgroups, are potentially affected by traffic exposure," Gauderman said.

Although the deficit in lung growth seems small, it could have long-term effects, Samet said.

"The concern is that the exposure leaves young adults with smaller lungs than they might have had otherwise," he said. That could leave them more vulnerable to lung diseases and more susceptible to the effects of pneumonia and other infections.

All the researchers conceded that there is little that can be done to mitigate the effects of the traffic pollution now.

But when local governments are planning new schools and new housing developments, Gauderman said, "this should be taken into account."

thomas.maugh@latimes.com

Los Angeles Times
LENDAR
Arts
Entertainment
Style
Culture
Tuesday, January 30, 2007
calendarlive.com

CRITIC'S NOTEBOOK

It may be time to hit the brakes

Putting homes, schools and parks by freeways was seen as a final frontier in L.A., but a USC study on pollution could force a rethinking.

By Christopher Hawthorne
Times Staff Writer

A new study from researchers at USC about the effects of local highway pollution on children's health would be alarming under any circumstances, especially for parents. But it happens to arrive just as Los Angeles is building or planning scores of projects — including housing, parks and schools — right on the edge of major freeways.

Seen in that light, the study carries significant implications not just for antipollution efforts but also for the future shape of the city. It should make us think not just about cleaning the air but about how and where we build.

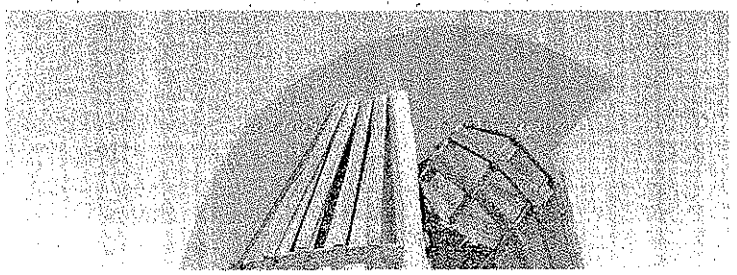
In the last few years, we've come to view land near freeways as a last frontier in a Los Angeles that grows more crowded by the year. When developers and public agencies such as the Los Angeles Unified School District are searching for large, empty parcels of land, they often find that the only ones that they can afford are freeway-adjacent, in the unlovely jargon of the real estate business.

And when planners, architects or academics get together to talk about and sketch designs for the Los Angeles of the future, their proposals inevitably call for new buildings swarming like kudzu along and across freeways.

In the same way that the futuristic city plans of the last century looked to the air, calling for buildings on stilts or stacked like pancakes or connected by floating zeppelins, architects these days tend to see L.A.'s ribbon of highways as the unlikely foundation for a new kind of post-sprawl urbanism.

Last month, Eric Owen Moss won a competition sponsored by the History Channel that asked architects to imagine and help design the Los Angeles of 2106.

[*See Notebook, Page E8*]



Building near freeways is an issue of public health

[*Notebook, from Page E1*]

"We intend to build over, under, around and through the freeways" of the city, he declared in his winning entry.

Of course, it's hardly surprising to learn that pollution levels are higher near freeways than in other parts of the city. But the data from USC are compelling enough to suggest that when it comes to zoning, we should give up the idea of that land as a means for reshaping L.A. and increasing density and see it instead as territory to be avoided — at least when it comes to placing facilities where kids spend a good portion of the day.

Proposals such as Moss' may anticipate the day when we'll no longer use cars, at least in their current form, and the freeways that once carried them will be empty and ready for reinvention. But even in the most optimistic scenarios, we still face several decades of highway pollution.

The USC study, which tracked 3,600 children for 13 years, found that those living within 500 yards of a highway faced risk of permanent health damage, including stunted lung growth and respiratory problems.

"Someone suffering a pollution-related deficit in lung function as a child will probably have less than healthy lungs all of his or her life," the study's lead author, USC epidemiologist W. James Gauderman, told The Times last week.

Even within that fairly tight 500-yard radius, we are building a number of high-profile projects, quite a few of which are designed for children or would be used heavily by them.

Housing continues to sprout along the edges of the region's highways — including stucco boxes and high-end, themed apartment complexes such as the Medici, which practically leans out over the 110 as it cuts through downtown.

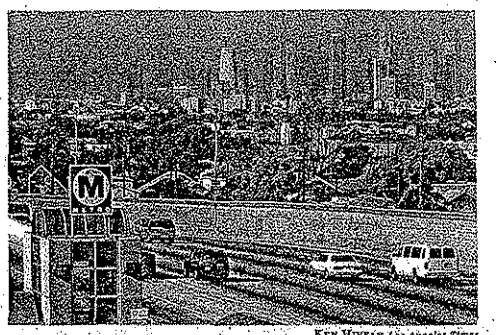
And the LAUSD's massive construction campaign includes a number of new schools next to some of our busiest roadways. Nearing completion is a new high school designed by Perkins + Will at the so-called Metromedia site. Commuters on the 101 have watched the school rise on North Wilton Place, no more than 100 feet from the freeway. The architectural flagship of the construction effort is a new high school for the arts, designed by the Austrian firm Coop Himmelblau. It will be built facing another stretch of the 101, across the freeway from the Cathedral of Our Lady of the Angels downtown.

As architectural solutions to tricky, overlooked sites, the schools are impressive. But through the lens of public health, they look altogether different.

In Hollywood, meanwhile, planners are working to gain approval for a new park that would be built directly atop a curving portion of the 101, between Bronson Avenue and Wilton Place. Preliminary designs for the park have been greeted as an ingenious solution to the open-space crunch in Los Angeles — and, in many ways, a sign of things to come. Councilman Eric Garcetti, who represents the neighborhood, said as much three weeks ago, after the City Council voted to spend $100,000 studying the feasibility of a park in that site.

"We've come to a place in Los Angeles [where], for better or for worse, it's actually cheaper to look at putting a cap over the Hollywood Freeway to build a park than buying land in the middle of Hollywood," he told a broadcast reporter.

It's a good thing the park is still being studied. Maybe the act of capping the freeway will reduce pollution levels inside the park enough to reduce the risk to the children who play there to an acceptable level. But if it won't, "buying land in the middle of Hollywood," no matter how expensive, will be a more responsible option, environmentally, morally and probably legally.



KEN HIVELY Los Angeles Times

POLLUTION: *The Harbor Freeway at Slauson Avenue. A new study shows the ill effects of freeway air on young lungs.*

At the very least, local governments will have to dig deep into the results of the USC study and similar reports as they begin to decide how big a health risk is presented by putting kids in schools, apartments or parks adjacent to freeways. They will have to look not just at proximity to freeways but also at wind patterns and other factors that affect the quality of neighborhood air. And as they do that they will have to be ready to reassess their planning strategies, perhaps in dramatic ways.

But the mechanism for doing so is not as powerful or as centralized as it needs to be, according to Roger Sherman, an architect in Santa Monica and co-director, with Dana Cuff, of City Lab, a new urban planning think tank at UCLA. Cuff and Sherman teamed up in the History Channel competition.

"Caltrans has one approach to thinking about these pieces of land, LAUSD has another and various cities have still others," Sherman said. "There's really a need for a regional coordinating authority. Without one, I think we're going to see neighborhood councils take more active measures to deal with these issues."

The councils, whose clout has been growing in recent years, could push for exclusionary zoning, for example, to make development near freeways impossible or more difficult. But that approach raises its own risks.

"You may see a kind of Balkanization," Sherman said. "Some communities along the freeway will decide to deal with the problem by putting up barriers along the freeway or planting to affect their microclimates, and others won't."

Most controversial of all, the USC study may open a discussion on the possibility of local governments using eminent domain to carve out new space for housing or parks a safe distance from local freeways. To a limited degree, the LAUSD has already relied on eminent domain simply to find school parcels it considers appropriate to its needs.

Determining the fate of buildings already planned or under construction near freeways will be no less tricky. Given the statistics gathered in the USC study, it's hard to imagine the LAUSD cutting the ribbon on the Perkins + Will high school overlooking the 101 with much enthusiasm about its location. Still, it's equally hard to imagine the district shutting down the school altogether over traffic pollution fears.

Perhaps the district will be able to plausibly argue that it didn't understand the full range of risks that come with building so close to freeways. But it's getting more and more difficult for any of us in this city to make that claim.

christopher.hawthorne@latimes.com

Smithsonian to open its 'Vault' on TV series

From the Associated Press

WASHINGTON — Actor Tom Cavanagh's newest gig is taking him behind the scenes at ries and documentaries focusing on the Smithsonian's treasured artifacts.

David Royle, executive vice research complex, which houses millions of items from art, history, technology and science.

Smithsonian Networks,

It's worse than dirty

L.A.'s notorious air pollution is hardest on kids. The closer to a freeway they live, play or attend school, the more likely it is that their developing lungs' capacity will be reduced.

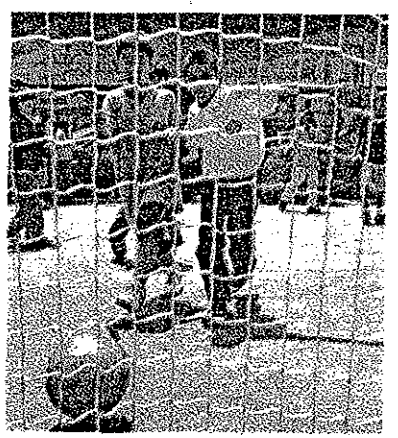
By Erin Cline Davis
Special to The Times

EVERYONE is familiar with the gray-brown haze that often blankets Los Angeles, and the fact that the city consistently ranks as one of the most polluted in America.

But what many may forget is that the dismal reports of L.A.'s air pollution only capture the *average* amounts of toxins in the air, and that some places within the urban sprawl are far dirtier than others. Official numbers do not take into account the fact that pollutants are at much higher levels within a few hundred feet of the freeways that crisscross the city — and for the adults and kids who live, work or go to school there, the effects add up.

For kids, whose lungs are still growing, these effects can be especially damaging.

Mounting scientific evidence reveals that exposure to air pollution interferes with the development of children's lungs, reducing their capacity to breathe the air they need. Although the long-term consequences aren't known, it is known that growth in lung function is nearly complete by the end of adolescence.



Ricardo DeAratanha *Los Angeles Times*

RISKY: *The nose's natural filter is bypassed when kids play hard and breathe through the mouth.*

Because lung capacity diminishes as people grow older, children exposed to air pollution may enter adulthood with the deck stacked against them.

Proximity to freeways appears to matter. Recently, studies have shown that the lung capacity of children who live within 500 meters (1,650 feet) of a freeway is significantly reduced compared with those who live more than 1,500 meters (4,950 feet) away.

For kids who already live in an area with high levels of pollution, living near a freeway is "adding insult to injury," says Dr. John Balmes, professor of medicine at UC San Francisco and professor of public health at UC Berkeley.

To help protect children from the heightened effects of this extra dose of air pollution, California passed a law in 2003 prohibiting schools from being built within 500 feet of major roadways. Districts are allowed to build within this buffer zone only if space limitations leave no option or the district can find ways to mitigate the increased air pollution. Yet a September article in The Times reported that the L.A. Unified School District was building five schools within 500 feet of a freeway and had plans for two more.

The district is now reconsidering its plans and working on new policies aimed at limiting students' exposure to pollution at schools built near freeways, but such laws can do only so much. Even if they aren't going to school near a freeway, children may still be walking down the street or playing in their backyard near one. Thousands will still be exposed to dangerous levels of air pollution.

Stunted lung development

In 2004, USC researchers reported that children living in areas with higher pollution, such as San Dimas and Riverside, had stunted lung development compared with children living in areas with lower pollution, such as Atascadero and Alpine.

The findings came from the Children's Health Study, which in 1993 recruited about 1,700 fourth-graders from 12 California communities and studied their lung function over

[See Smog, Page F6]

a bett

By Jan Greene
Special to The Times

Cathy Barnes
eling on busines
years ago when
pain in her abdo
medical center t
and carried out
heart. The tests c

When she got
her regular doc
exam found a m
scan showed a ki
immediately sch
move it be
the

Barnes
liev
time in her treat
enough to ask for
cords from the P
show them to her
nating the need
"Having copies o
all that time," she

WEIGHING IN

Protein h
the bottl

We taste new
protein-packed
waters.

IN THE LAB

Errant
stem cell

They emerge a
a possible canc
culprit.

A clear pattern of risk emerges from haze

[*Smog, from Page F1*]
eight years.

The effects on children's lungs were both statistically and clinically significant: The proportion of children with low lung function was 4.9 times greater in the community with the highest level of fine-particle pollution (Mira Loma) compared with the community (Lompoc) with the lowest levels (7.9% versus 1.6%). Results were similar when the researchers looked at other categories of pollution, such as nitrogen dioxide and elemental carbon.

In February, the USC group published another report, in the journal the Lancet, showing that living near a freeway could further affect a child's lung development.

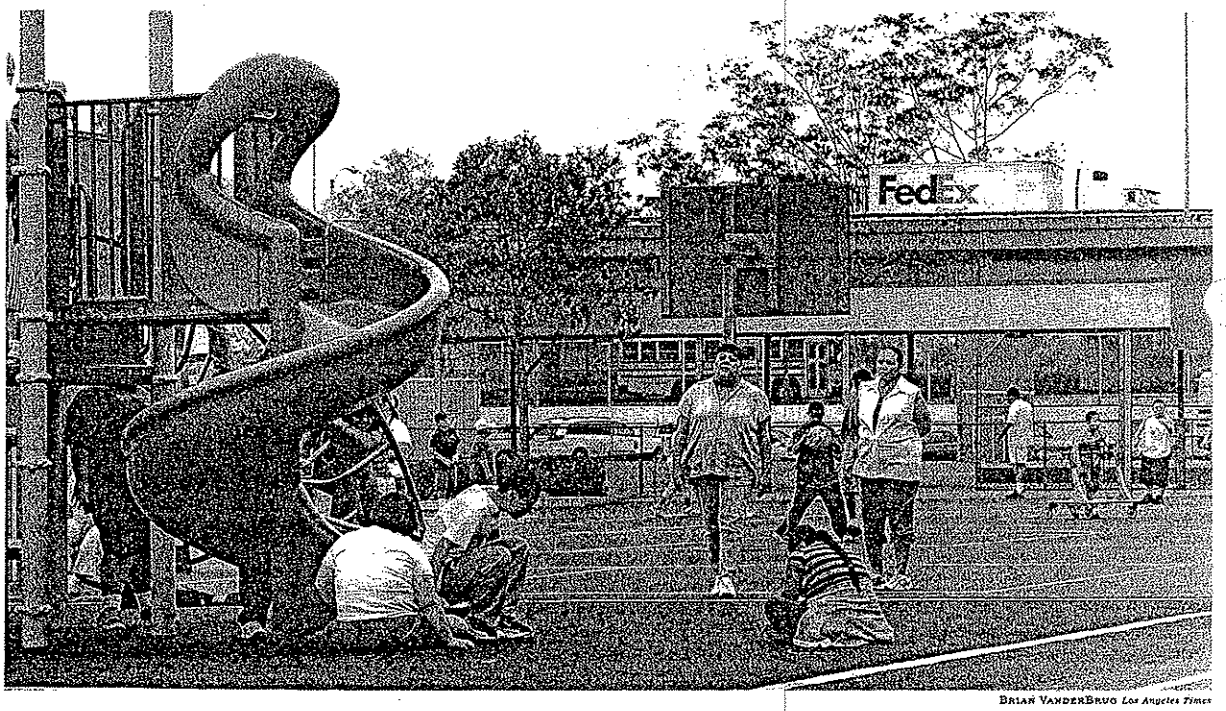
As in the 2004 study, researchers followed the group of fourth-graders recruited in 1993, as well as a later group recruited in 1996. In this study, however, the children in each city were further subdivided into those who lived close to (within 500 meters) or far (more than 1,500 meters) from a freeway or other major road.

As in the other study, researchers would visit the children every year at their schools and measure with a device called a spirometer how much and how fast each child could exhale.

They found that children who lived close to a freeway in a low-pollution community had about a 4% decrease in their lung function compared with children living in the same community but far from a freeway. This decrease was similar to that seen in children who lived in highly polluted communities but far from a major road.

The results were worst for the children who lived near a freeway within a polluted city. They had the greatest reduction in lung function over the course of the eight years each child was tracked — about 9%, compared with the kids in clean cities who lived at least 1,500 meters from a major road.

Lung development is nearly complete by age 18 — meaning that someone with a deficit in lung function at the end of adolescence will probably continue to have less than healthy lung function for the rest of his or her life. And that could lay the adult



BRIAN VANDERBRUG *Los Angeles Times*

LOCATION, LOCATION: *The Perez Alfonso Special Education Center is by a freeway ramp. A 2003 California law limits schools' proximity to major roadways.*

adult life is known to be a major risk factor for respiratory and cardiovascular diseases, as well as for mortality," said W. James Gauderman, an epidemiologist at the USC Keck School of Medicine and leader of both studies.

The results of the USC study make sense, given what scientists know about the concentrations of tailpipe pollutants near major roads.

Jean Opital, an officer for the South Coast Air Quality Management District who evaluates studies on the health effects of air pollution, says that pollution concentrations are highest in the first 150 meters of a large road but then start to drop off. But calculations predict that to get down to the levels seen upwind of a freeway, you have to get about the best air quality, proximity to sources does matter," he says.

Taking in more pollutants

Children are especially vulnerable to air pollution because they breathe more rapidly than adults relative to their body weight and lung size. This results in exposure to a relatively larger dose of any air pollutants. Kids also spend a lot of time engaged in vigorous physical activity, leading to even heavier breathing.

When they play hard, they tend to breathe more through their mouths, bypassing the natural filtering effects of the nose, allowing more pollutants into their lungs. And unlike adults, who are likely to stop their activities when effects of pollution — continuing to expose themselves to pollution.

The heady brew they are exposed to has various toxic components — carbon monoxide, sulfur dioxide, nitrogen dioxide — and the two that pose the greatest threat to human health: ground-level ozone and particulate matter.

Ground-level ozone is formed by a chemical reaction between volatile organic compounds and oxides of nitrogen emitted by cars and other sources such as power plants that takes place in the presence of sunlight. In L.A., the onshore breeze usually pushes the ingredients of ozone farther inland. But calm days provide the perfect conditions for a blanket of ozone to cover the city.

ing, throat irritation and difficulty breathing.

It can also worsen asthma attacks and increase the susceptibility of the lungs to infections, allergens and other air pollutants — making exposure especially risky for those with asthma and other lung conditions such as chronic obstructive pulmonary disease.

Particulate matter in the air is a mixture of solids and liquid droplets that vary in size. Particles larger than 10 microns (about one-tenth the diameter of a human hair) do not usually reach a person's lungs, but they can irritate the eyes, nose and throat.

Exposure to "coarse" particles (in the range of 2.5 to 10 microns in diameter) and "fine" and lung diseases.

A study of more than 4,000 Swiss adults ages 18 to 60 during the course of 11 years, which appeared last week in the online edition of the New England Journal of Medicine, has shown that the inevitable decline in lung function seen in adults is lessened in those who are exposed to reduced levels of particle pollution.

The smallest particles of all — so-called "ultra-fine" particles — are of increasing concern to air pollution experts. Air levels of these tiny bits of air pollution, which measure less than 0.1 micron or one-thousandth the diameter of a human hair, are not regulated by state or federal agencies, and their health effects are only now beginning to be

Dirty air has toxic components

[*Smog, from Page F6*]

What researchers do know is that ultra-fine particles travel far deeper into the lungs than other types of particle pollution. They can even pass through the lining of the lungs, gaining access to the bloodstream. This allows them to travel to other organs and possibly interfere with their function.

Ultra-fine particles might also make their way into the brain, USC's Gauderman says. He says there is some suspicion in the research community that they can actually travel straight to the brain through the olfactory nerve at the top of the nasal passage.

They are so small that standard air filters cannot remove them. "They act like a gas, getting in around doors and windows," Gauderman says.

When pollutants are inhaled, gases such as ozone and the chemicals stuck to the surfaces of various sizes of particulate matter react with molecules in the lungs, injuring cells. The body's response to this injury is inflammation, which causes the airways in the lungs to constrict.

Children have narrower airways than adults, so pollution that might cause only a mild inflammatory response in an adult can significantly constrict the airways in a young child. This can be especially dangerous for children with asthma.

Long-term exposure to air pollution can cause chronic inflammation. In response, the body will attempt to wall off the damaged parts of the lungs, creating tissue that's less pliable than healthy tissue. That, Balmes says, explains why decreased lung function like that seen in the Children's Health Study comes about.

"It's basically a scarring process," he says.

Reducing risks at schools

Angelo Bellomo, head of the Office of Environmental Health and Safety for the Los Angeles Unified School District, says his office is taking the dangers posed by freeway pollution seriously.

"We've got to do everything we can do that is within our power to reduce that risk," he says.

As a start, his office has begun taking ultra-fine particles, which were not previously considered, into account when analyzing new locations for schools.

There are more than 70 district campuses within 500 feet of freeways, housing more than 60,000 students. Bellomo's office is compiling a list that ranks the schools by level of risk based on the number of students, the number of years students spend at the school, distance to freeways and the volume of diesel trucks that travel the nearby freeways.

The office will be developing a range of options and associated costs for upgrades to existing schools that would reduce school occupants' exposure to nearby sources of air pollution. Its report is due at the beginning of March.

Bellomo says his office will be looking at all options, including some promising new filtration technologies.

He admits that the school district can't do much to reduce the risks of air pollution when children are outside, but he aims to reduce the risks indoors enough so as to offset the outdoor exposure.

The district will do what it can, Bellomo says, but the most effective way to reduce the risk from freeway pollution for children would be for state and federal regulators to enact rules that reduce pollution at the source.

Angela Beach, 41, of Sherman Oaks, will be following the district's progress.

Her 6-year-old son, who suffers from chronic asthma, attends Hesby Oaks School, a recently reopened campus in Encino that is within 500 feet of the 101 Freeway. Firmament Avenue, a bit of greenbelt and a sound wall are all that stand between the athletic fields and the constant rush of cars on the 101 and 405 interchange.

Beach says her son's asthma was well controlled when he was in preschool. He didn't have trouble playing outside like all the other children.

But now, she says, "he just can't do it."

The effects of the pollution near the freeway aren't just physical for her son, Beach says. He doesn't understand why he can't play at school. He gets frustrated and angry when he has to abandon basketball practice because he can't get the air he needs. Beach has had to explain to his coach that it isn't that he doesn't want to play, it's that he's isn't able to.

Beach says her daughter, who is 8 and does not have asthma, has also commented on the changes on her body since she started at her new school, even though the issue of air quality is never discussed with her. She comes home from school, Beach says, and tells her mother how she struggles on the playground, complaining, "It's harder here," comparing Hesby to her previous school, Sherman Oaks Elementary, which is just shy of a mile from the 101 and 405 freeways.

Beach wants the district to do all it can with filtration systems at Hesby and other schools. She is also lobbying the city and school district to plant trees behind Hesby because some research has shown that they could absorb some of the pollution that is flowing into the outdoor hallways and lunchroom of the campus.

"These," Beach says, "are problems that affect the lives of every child, forever."

REED SAXON *Associated Press*

INHALING EXHAUST: *Pollution concentrations are higher in neighbohoods close to large thoroughfares.*

Trees may help fight pollution

Can trees help fight smog? Thomas Cahill, a professor of physics and atmospheric sciences at UC Davis, has results suggesting they can reduce levels of ultra-fine particle pollution near freeways.

He has found that in windy conditions, trees along the side of a freeway can help mix the air and dilute the concentration of ultra-fine particles. In calm conditions, trees seem able to capture the particles, preventing them from traveling to nearby homes or schools.

Cahill says that once ultra-fine particles stick to the leaves of trees, they will not blow off. Instead, they will remain on the tree until the leaves drop or they are washed away in the rain.

He says that other researchers have not been interested in looking at trees as mitigation for ultra-fine particles because older research had shown that trees could not block *fine* particles (which are about 25 times larger than ultra-fine particles) from blowing off roadways.

Cahill says it's important to use the right trees to block ultra-fine particles. Some trees may not absorb enough particles. Others emit chemicals that can contribute to ozone formation. Trees with lots of needles, such as redwoods and deodar cedars, he says, are best.

— ERIN CLINE DAVIS

Highway Exhaust Stunts Lung Growth, Study Finds

More Articles in Health »

A new study suggests that children who grow up within a third of a mile of a freeway may be sustaining permanent respiratory problems.

Researchers studied developing lung function in 1,445 children living in 12 Southern California communities for eight years, from age 10 to 18. They found that the closer the children lived to a freeway, the more likely they were to experience reduced growth in lung function as measured by the standard tests.

"That living near freeways is a health issue is something we've known about for a long time," said Gennet Paauwe, a spokeswoman for the California Air Resources Board, which financed part of the research. "All of this points to the fact that California's air pollution control program needs to continue with its aggressive reduction in air pollutants. But I think this would translate to any other part of the U.S. where people are living near heavily trafficked roadways."

The findings were published online Friday by the British journal Lancet.

"Our finding of a larger impact on small lung airways is consistent with what is known about the types of pollutants that are emitted from the tailpipe," said W. James Gauderman, the lead author and an associate professor of preventive medicine at the University of Southern California. These pollutants, he continued, "can be inhaled deeply into the lung and may have the largest impact on the smallest lung airways."

The study was not restricted to the notoriously smoggy Los Angeles basin. "Our findings were observed in all of these children, including those living in areas of lower pollution," Dr. Gauderman said, "so it suggests that in any urban area where children are living near busy roads, they are likely to have adverse respiratory effects. It's not just L. A."

The development of lung function was also lower in nonasthmatic and nonsmoking teenagers living near freeways, suggesting that the highways had an adverse effect on otherwise healthy children. Growth of lung strength and capacity, the researchers write, is largely complete by age 18, and this means that a child with a deficit at that age will probably suffer lifelong diminished lung function.

"The study is significant in the finding that it isn't just regional air pollution, which policy makers have focused on," said Frederica Perera, director of the Columbia Center for Children's Environmental Health at the Mailman School of Public Health in New York. "These results indicate that it's also important to consider local variations in air pollution."

The researchers started with a group of 3,600 children, using questionnaires to gather information on parental income, history of asthma, prenatal exposure to maternal smoking and household exposure to smoking and pets. Then, using yearly questionnaires, they tracked asthma status, personal smoking and exposure to secondhand smoke. They also recorded the distance of each child's home from the nearest limited-access highway and from other major nonfreeway roads.

To determine lung function, the scientists used standard tests that measure how much air a child can exhale during a forced expiration and how forcefully he can do so. Normally, these numbers gradually increase as children grow. The children were tested an average of six times over the eight years of the study.

About 11 percent of subjects per year dropped out of the study for various reasons.

Although the authors controlled the study for socioeconomic status, an editorial with the

paper points out that social factors are difficult to define and may affect lung capacity no matter where a child lives. Other studies, for example, have shown that poor children in the Los Angeles area are more likely to attend schools near freeways than those who are more affluent. Also, the study did not examine exposures at ages younger than 10.

Tips

To find reference information about the words used in this article, hold down the ALT key and click on any word, phrase or name. A new window will open with a dictionary definition or encyclopedia entry.

Related Articles

- A Study Links Trucks' Exhaust to Bronx Schoolchildren's Asthma (October 29, 2006)
- [illegible] (September 27, 2006)
- [illegible] (May 16, 2006)
- [illegible] (September 9, 2004)

Related Searches

- Lungs
- Air Pollution
- Children and Youth

INSIDE NYTIMES.COM

BOOKS »

"This Is How You Lose Her," by Junot Díaz

SUNDAY REVIEW »

Borderlines: The New World

N.Y. / REGION »

New York's 50 Objects: Wait! There's More

TRAVEL »

Pleased by Fees When You Travel?

SUNDAY REVIEW »

Diane Ackerman: A Little Night Music

As summer wanes, the evening air is alive with the symphonies of a cornucopia of insects.

MOVIES »

Tim Burton, at Home in His Own Head

MANY CHILDREN BEING RAISED IN L.A.'S HIP, NEW FREEWAY-ADJACENT HOUSING ARE DAMAGED FOR LIFE

BY PATRICK RANGE McDONALD

PHOTOS BY TED SOQUI

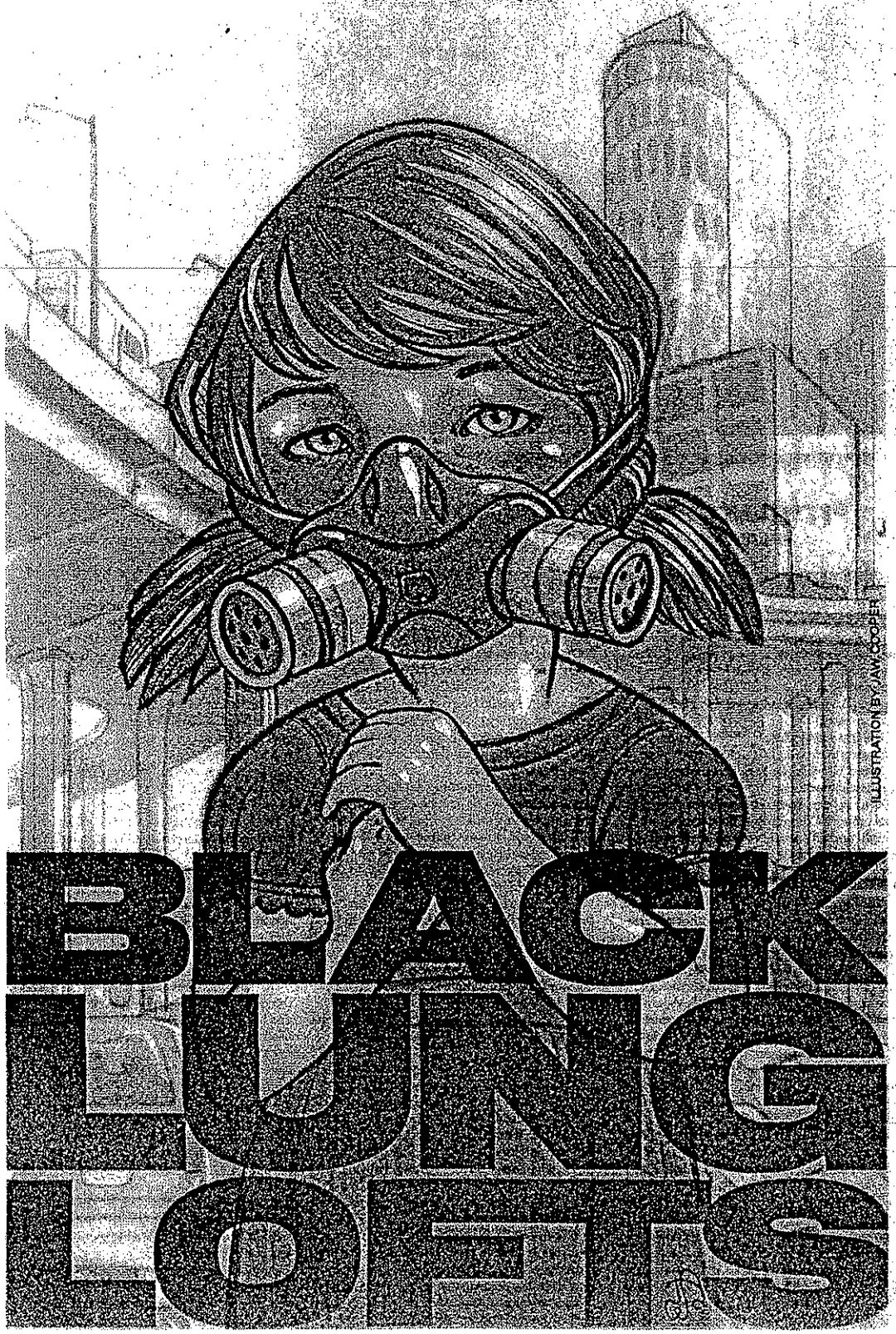


ILLUSTRATION BY JAW COOPER

BLACK LUNGS

On a recent afternoon in the Eastside neighborhood of Lincoln Heights, Fay Green stands in the hallway of her apartment complex, which sits just feet above the bumper-to-bumper traffic of the I-5 freeway. A soft-spoken black woman, she lives with her five kids and one grandson in an urban planner's idea of perfection: the dense, "Avenue 26" master-planned community, touted by Mayor Antonio Villaraigosa and the city's Department of Housing as an environmentally smart "transit-oriented development" in the city's core, efficiently served by light rail.

From the outside, the stylish-looking village of 156 condos, called Puerta del Sol, and 378 other apartments squeezed between Avenue 26 and the thundering I-5 gives off a Crate & Barrel vibe. But Green's four-bedroom unit, in the building dubbed Tesoro del Valle Family Apartments, is regularly dirtied by a heavy film of what she calls "dust." She explains, "I clean the place up, and in two or three days, I have to wipe again."

The bedroom of her young son, who has a sinus problem, requires extra attention so he can breathe; Green herself suffers from asthma. She says these sicknesses started before she moved to Avenue 26, erected less than 100 feet from one of the world's busiest, and filthiest, freeways, used by 285,000 vehicles per day. But when the weather is hot, or other conditions create smog, Green notices that many of her kids start to cough. She won't feel well, either.

Green moved into the new apartment in 2006. She vaguely remembers a TV news report about the health risks of living near a freeway, but had never really thought about whether she or her young family could become sick from the clouds of vehicle exhaust and tire-brake dust that hover above, and directly next to, the I-5.

Her neighbors tell a similar story. Jesse A. Flores, in his 60s, says he never thought about the problems of living adjacent to a major freeway. "So far, I'm okay," he says. "Nothing wrong with me."

Aura Sanabria, a 20-something mother of three young kids, has the same concerns Green has. She too complains about the heavy "dust" that builds up in her apartment. "I'm always cleaning and dusting," she says.

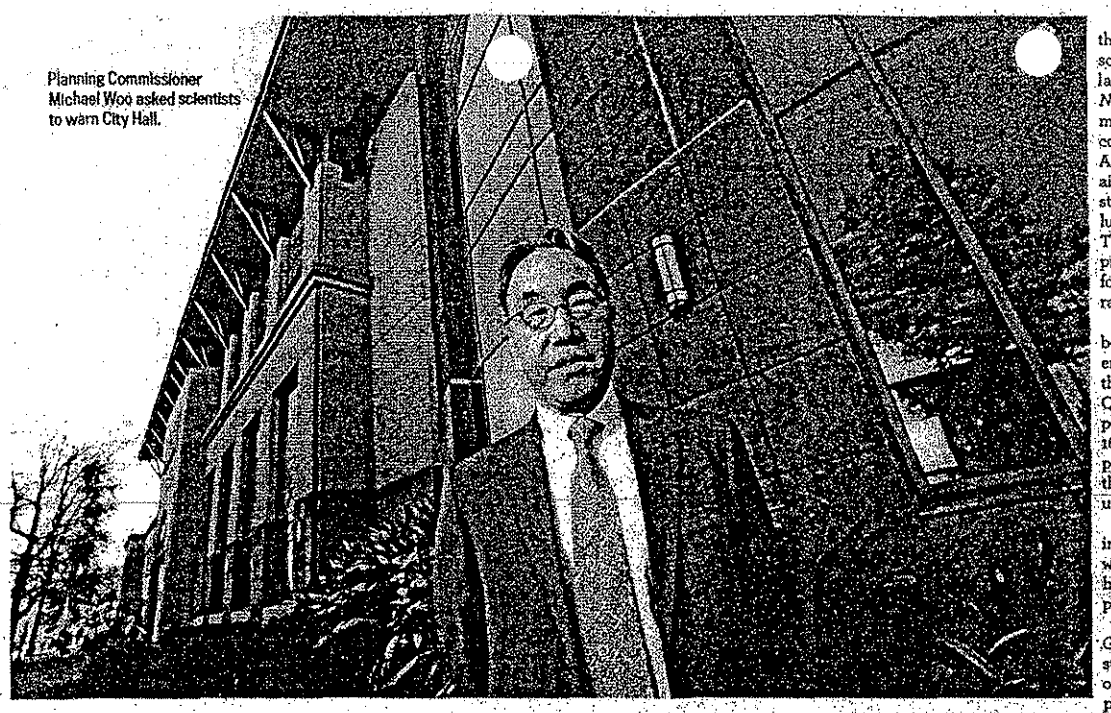
Teenager Andrew Garcia says he and his parents never think about the invisible particles that work their way into the family home. "All we think about is that it's easier to get on the freeway or to the Metro," says Garcia, who takes the Gold Line to high school.

These residents don't know what the science shows, but L.A.'s elected leaders do.

In 2004, USC's landmark Children's Health Study made waves nationally, confirming that thousands of Southern California children living in near high-traffic roadways were contracting higher levels of crippling asthma and children living in smoggy areas were suffering impaired lung development.

The study proved long-held beliefs that fine particles such as those caused by tire rubber and brake metal — so tiny that scientists say the dust seeps through the smallest cracks and holes and thus is not blocked by air filtration systems or triple-paned windows — were burrowing into people's lungs.

When the revelations broke in *The New England Journal of Medicine*, L.A. was in the grips of a badly overheated housing bubble. City Hall politicians and planning officials were embracing trendy housing projects alongside freeways, especially downtown, where urbanists touting a "sustainable" lifestyle, (16 >>)



Planning Commissioner Michael Woo asked scientists to warn City Hall.

>> 15) free of suburban commuting, were moving into places like the Medici and Orsini luxury complexes — a stone's throw from the Harbor and Hollywood freeways, respectively.

L.A. officials were so thrilled with the new apartments rising next to freeways that they got into an ugly tussle with Orsini developer Geoff Palmer when he rebuffed City Hall's pressure to make room in his freeway-adjacent Medici building — for low-income families including children.

Meanwhile, on the other side of downtown, the Los Angeles Housing Department provided down payments to buyers to move into Puerta del Sol, a stylish condo complex in the Avenue 26 community where teenager Andrew Garcia breathes in the factorylike emissions and particulates created daily by 285,000 vehicles.

Since then, with the city's enthusiastic backing, including that of Councilman Ed Reyes, who represents Lincoln Heights, the village's politically well-connected developer, Percy Vaz, has marketed the project to families tired of commuting — in effect, targeting parents to live in an area scientists now know is unusually hazardous to their children's health.

"We've known for eight or 10 years there have been these impacts," says Dr. Joe Lyou, executive director of California Environmental Rights Alliance, an environmental justice group. He sees the politicians at City Hall as knowingly endangering children.

In January 2007, USC scientists followed up their widely hailed Children's Health Study with an even more detailed and damning longitudinal study of 3,600 Southern California children — and this time the scientists went down to L.A. City Hall to get the attention of the politicians.

"I woke up one morning and read about [the study] in the newspaper," says Michael Woo, who sits on the Los Angeles planning commission and is dean of Cal Poly's College of Environmental Design. "That's when I started to put two and two together" — to realize that the city's residential zoning policies were making kids sick.

The new study showed that alarming numbers of children ages 10 to 18 who live within about a block — 528 feet — of a Southern California freeway suffer reduced lung development, a deficit likely to persist through adulthood, and which may increase the risk of respiratory disease and premature death. (Three weeks ago, a group of USC and European scientists delivered more bad news: Hardening of the arteries is twice as common among Angelenos living within a block of an L.A. freeway.)

"IT'S WORSE THAN I THOUGHT."
–PLANNING COMMISSIONER MICHAEL WOO

But instead of playing a key role in the city's planning decisions, USC's 2007 study was ignored. City Hall leaders, dominated by the desires of developer-contributors and a strong chorus of "density hawks," were rewriting hard-fought Community Plans, tossing out height and size restrictions on apartment complexes citywide, and permitting the destruction of thousands of units of historic and affordable housing.

Through city zoning laws, subsidies, city pension-fund investments and other policies, city leaders have peddled freeway-abutting housing as "smart" land use that satisfies developers' push for "in-fill" projects on "underutilized" land. At one point during the frenetic housing boom in 2006, Villaraigosa and city pension trustees held a press conference at the Puerta del Sol condos in the Avenue 26 development perched above the I-5 freeway. The mayor touted the development as a model example of middle-class housing in which to "raise a family" — a view that remains unshaken inside City Hall today.

Today, in fact, the Department of City Planning chief Gail Goldberg and the Office of Mayor Antonio Villaraigosa concede to *L.A. Weekly* that nobody in City Hall is tracking, or can even estimate, the number of children who have moved into housing erected within 500 feet of freeways since scientists documented the chilling health effects. Los Angeles lawmakers are making no effort to measure the human health costs of such housing. And with the shattered L.A. housing market now showing the first few signs of recovery, City Hall is set, once again, to embrace freeway-adjacent housing that's marketed to families.

One of the few elected leaders willing to be open about the unfolding situation is Hollywood-area City Councilman Tom LaBonge, who says, "It would be great if we could call a time-out and try to plan better, but it's not practical." He's given his blessing to freeway-adjacent housing in his district, and he insists, "We need to save jobs."

Nor do the city's planning department, Villaraigosa and the Los Angeles City Council warn buyers and tenants about the hazards of moving kids right next to freeways — the relatively modest disclosure rule sought two years ago by USC's scientists that some developers say they could live with.

"Regulation is years behind the science," says Bahram Fazeli, a researcher and policy analyst for Communities for a Better Environment, a grassroots environmental-justice organization that focuses on issues like addressing the "cumulative impacts" of smog. Of the Southern California freeway studies, Fazeli stresses, "The evidence that children are harmed is overwhelming."

L.A.'s major freeways were mostly built in the 1950s and 1960s, slashing through cohesive residential neighborhoods and creating strange dead-end streets in places like Hollywood, Westwood, Toluca Lake, Boyle Heights and Lincoln Heights. In the 1980s and 1990s, when new housing sprouted up beside freeways in West L.A., Reseda, Studio City, Hollywood and many other areas, environmentalists warned that purposely placing housing next to the world's busiest and most polluted freeways was a bad idea. They argued that any public good — providing affordable housing or addressing pent-up ownership demand for condos — was outweighed by extensive health costs to people and society.

But the science wasn't there to back up the activists — until a team of mostly USC scientists published the 2004 multimillion-dollar Children's Health Study in the prestigious *New England Journal of Medicine*. Studying more than 1,700 children, scientists compared communities that enjoy clean air, such as Lake Arrowhead and Alpine, to those with dirty air, such as Riverside and Long Beach. The study showed high rates of underdeveloped lungs among children in the polluted areas. The implications were clear: long-term health problems ranging from asthma to early death for significant numbers of children being raised in Southern California.

"That study had a tremendous impact because of the quality of the research," says environmentalist Lyou, who also sits on the governing board of the South Coast Air Quality Management District, which sets air pollution–control policies affecting more than 16 million people. "It really shocked a lot of people. It not only confirmed what people in the field already knew, but it also created an undebatable view on the issue."

Around the same time, UCLA also published important findings showing that pregnant women who lived within 750 feet of a freeway had a greater-than-normal risk of delivering premature babies.

When USC scientists Rob McConnell, Jim Gauderman and others followed up the 2004 study by researching a much larger group of children — specifically to look into health problems caused by living within 528 feet of Southern California's crammed freeways — the findings worried epidemiologist Gauderman enough to testify before the City Council.

In Council chambers on April 25, 2007, he warned: "It's not just watery eyes or coughing after a particularly polluted day. ... We're talking about long-term risks of asthma, long-term risks of reduced lung development in children."

Scientists are especially concerned about nitrogen oxide and "particulate matter," essentially a dust that sometimes can't be seen. Particulates can be metals, gas emissions from cars and trucks, tire rubber and tire-brake dust. When mothers like Fay Green and Aura Sanabria complain about never-ending "dust" that settles inside their apartments in the Puerta del Sol development next to the I-5, they are actually talking about particulate matter.

When kids breathe in this highly toxic particulate, it goes deep into their lungs and can cause long-term health problems.

After listening to researcher Gauderman, several City Council members sounded ready to act.

Council District 12 representative Greig Smith, from the San Fernando Valley, announced that he and Council District 1 representative Ed Reyes, from the city's Eastside, had put forth a motion to study the idea of changing zoning laws to discourage or stop new housing within 500 feet of freeways.

"Maybe we should change the way of doing things around here," Smith told Gauderman and his council colleagues. And City Council District 6 representative Tony Cardenas, also from the San Fernando Valley, declared, "We have a lot of issues in my district we'd like to address, but with science, in my opinion, it's the best way for us to create the best defense in order to defend the community."

Janice Hahn, who represents Council District 15 in San Pedro and is running this year for California's lieutenant governor as an environmental candidate, was even more forceful, announcing, "I think the time for studies is over. I think the time for action is now."

L.A.'s lawmakers talked a big game. But it was nothing more.

Councilman LaBonge, who set up Gauderman's visit to the City Council, concedes today that, after that downtown hearing nearly three years ago, the City Council did nothing. Smith

nd Reyes' motion to "look into" a 500-foot arrier zone between new homes and freeways ever turned into anything substantive; Smith nd Reyes recently declined to comment to the *Weekly* about their long-abandoned motion.

Within months of USC's appeal to the City Council, in fact, one of L.A.'s most brash examples of freeway-abutting housing, the Universal Lofts, rose in Cahuenga Pass at 3450 Cahuenga Blvd., with a banner exhorting Angelenos to both "live" and "work" in the pricey, corrugated metal–and–cinder block buildings.

City zoning approvals allowed the developer to cram his $4,000-per-month, three-bedroom apartments and $1 million condos into a strip of land no more than 20 feet from the 234,000 vehicles that rumble by daily on the Hollywood Freeway.

LaBonge says such housing will continue to rise because "environmental issues need to compete with all other issues," and averting a city fiscal disaster is the only thing on the City Council members' minds.

But critics say that hardly explains the City Council's failure to warn residents or to pursue better planning when the city was flush with funds. Bill Gallegos, executive director of Communities for a Better Environment, says, "They can't ignore the science. It just can't be shunted off to the side because of the economic crisis."

LaBonge's logic probably wouldn't go over well with an activist parent like Elaine Lyles, whose daughter Itanza developed asthma when she was 10 years old — she's now a sophomore in college. Lyles, a commercial real estate broker, volunteers at a healthy-lungs advocacy organization, and she doesn't want any parent or child to go through the ordeals her family suffered.

For years, Lyles has lived near the 10 freeway in the South Robertson neighborhood; Itanza attended a nearby school. Years ago, upon receiving harrowing calls from school that her young daughter couldn't breathe, Lyles was told by her doctor that the girl had contracted asthma due to "pollutants in the atmosphere." The diagnosis changed Itanza Lyles' life.

"She would have difficulty breathing and I would tell her to calm down and be patient," Elaine Lyles recalls. She sometimes clashed with doctors, who pushed her daughter to scale back her athletic activities in order to improve her health. "But she's full of life and active, and she would get angry because she couldn't live life to the fullest."

Lyles witnessed Itanza suffer horrific asthma attacks, which can kill victims via suffocation, and she remains haunted by the fear that her daughter could die at anytime. A friend at church tragically lost a child during a severe asthma attack, devastating her and shocking the Lyles family. "Your kid can't get air," Lyles says. "You have as many inhalers as possible around, but you never know. As a parent, you're never free of the idea that your child could succumb."

Lyles' oldest daughter doesn't have asthma. The first five years of her life, when her tiny lungs were undergoing a critical stage of development, the Lyles family lived far from a major Los Angeles freeway, in the Hollywood Hills near Griffith Park. "It's probably why she has better lung health," Lyles says. Many scientists today would probably agree.

Percy Vaz, developer of the Lincoln Heights master-planned community where Fay Green and Aura Sanabria clean up thick "dust" in the Tesoro del Valle apartments, opposes a buffer zone between housing and freeway lanes. "I think there are apartment buildings just as susceptible on a major thoroughfare," says Vaz, a prominent local developer and founder of AMCAL Housing, which specializes in for-sale and rental affordable housing. "Would we have a buffer zone on Wilshire Boulevard? On a gut level, 500 feet is far overreaching."

But even crowded Wilshire Boulevard doesn't carry anything approaching 285,000 cars per day, nor does any L.A. surface street. The sheer volume on the city's freeways is a key reason why people are getting sick.

Yet Vaz doesn't think a health-hazard warning for renters or buyers is necessary. In fact, his tenant Sanabria, the mother of three young children, is more concerned about homeless people sleeping nearby, and neighbor Jesse Flores worries about gang activity in the area. "They're killing each other like fools," Flores says.

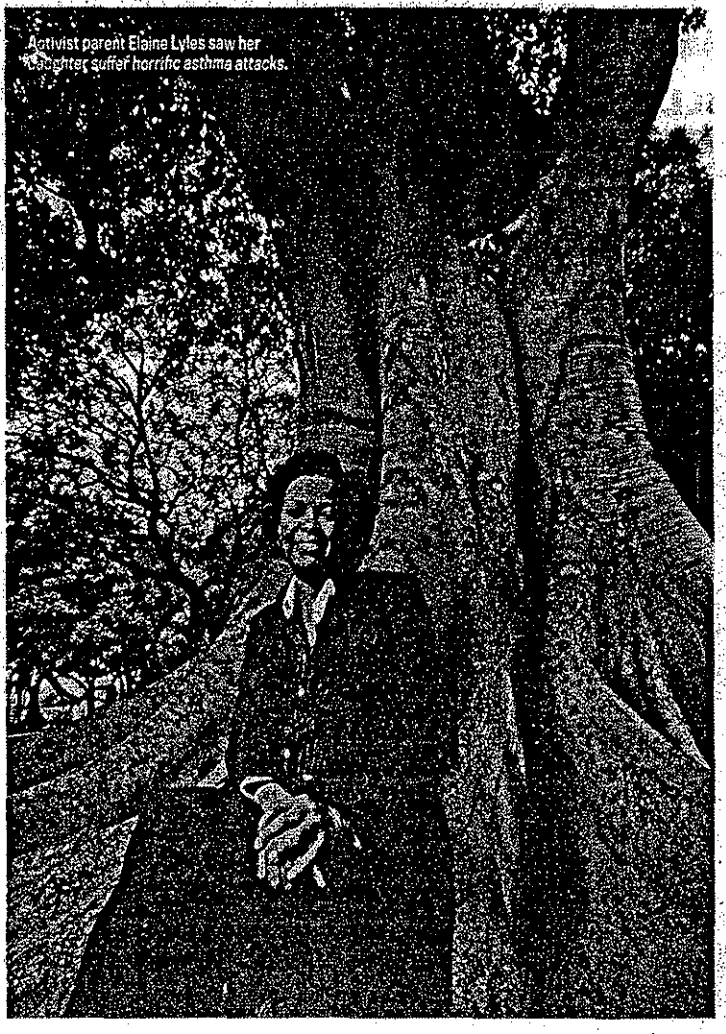
Vaz reports that no one — not the city Planning Department nor Ed Reyes, chairman of the City Council's Planning and Land Use Management Committee, who represents Lincoln Heights — has spoken to him about enacting buffer zones or requiring a disclosure statement for housing placed within 500 feet of freeways. (Through a spokeswoman, Reyes tells the *Weekly* he's "unavailable" to talk about the health impacts caused when City Hall approves housing that abuts freeways.)

"If you're buying a home near a freeway, you know it's there," Vaz says. "The freeway is hitting you in the face. Most people are buying and renting because there is a freeway." Moreover, he is seeing more and more units erected near the freeways, in part, because "there's a shortage of land and people will build where they can," even on often-expensive freeway-adjacent land.

With city officials now focused on preventing the city government of Los Angeles from sliding into a deeper fiscal crisis, a debate over the health of tens of thousands of local children is unlikely to be welcomed by the City Council or Villaraigosa.

According to Woo, neither the City Council, led by electric car–driving Council President Eric Garcetti, nor Villaraigosa, who wants Los Angeles to be "the cleanest and greenest city" in America, has shown an interest in the 500-foot buffers or hazard-disclosure regulations suggested by the scientists. Inside City Hall, where real estate developers have enjoyed outsized influence for the past 100 years or so, such restrictions, Woo says, would "probably be very controversial."

"THE VERY SMALLEST PARTICLES PASS RIGHT INTO THE BRAIN."
–USC ENVIRONMENTAL-HEALTH RESEARCHER ROB MCCONNELL



Activist parent Elaine Lyles saw her daughter suffer horrific asthma attacks.

But neither is the issue being pushed by the environmental community in Southern California, which has been much more focused on lobbying the California Legislature on state environmental laws and global warming.

"I can't think of an [environmental] group that's fighting development near freeways," says Martha Arguello, executive director of the Los Angeles chapter of Physicians for Social Responsibility, a nonprofit, public-health advocacy group. "I'm hard-pressed."

The nonprofit organization Breathe L.A. — which promotes itself as a 107-year-old public-benefit group dedicated to "clean air and healthy lungs in Los Angeles County" — is giving its 2010 Breath of Life Award to District 9 City Councilwoman Jan Perry. The strongly pro-development Perry has pushed for lofts, condos and apartments next to and near downtown's jammed freeways. She has not pushed any plan to warn Angelenos about the serious health effects on children who move into that housing.

According to Breathe L.A.'s announcement, sent to the media a few days ago, Jan Perry promotes "clean air and healthy lungs ... each and every day."

Environmentalists, says Bahram Fazeli of Communities for a Better Environment, have perhaps missed an opportunity by focusing on other issues, such as cleaning up the ports and working with the Mayor's Office to sign off on a "cumulative-impacts" directive.

Although the directive has been slow in coming, it would ideally force city departments to look into how specific, major projects, such as a new oil refinery or airport expansion, add overall pollution to neighborhoods — and then plan accordingly. But the cumulative-impacts rule probably would be silent on the more direct threat to human health — housing being built right next to L.A. freeways.

"Maybe we made a mistake, maybe we should have gone with (freeway-adjacent housing)," Fazeli offers. "But we always think about these things, and think about strategy, and we only have limited resources."

Some environmentalists also act as cheerleaders for dense urban housing, including that along freeways, arguing that it helps to combat global warming by discouraging suburban living. Their focus is not on the health of individuals but the planet.

For all of these reasons, the people who move their children into unusually unhealthy, freeway-frontage projects fall into the cracks.

Romel Pascual, Los Angeles acting deputy mayor for energy and environment, says Villaraigosa "is someone who looks at public health and thinks it's very important."

But the mayor has yet to look seriously at the danger of living next to the freeway. Says Pascual: "It's worth exploring."

On August 14, 2008, USC preventive medicine professor Rob McConnell and the university's community outreach expert Andrea Hricko sat before Villaraigosa's political appointees on the city Planning Commission to share USC's 2007 freeway-housing findings. The meeting had been arranged by planning commissioner Mike Woo, who was worried about freeway-adjacent housing.

Jim Gauderman's USC colleague, environmental-health researcher McConnell, told the Los Angeles Planning Commission, "The very smallest particles pass right through the respiratory system and into the body, including the brain." McConnell and Hricko urged city planners to push for a 500-foot buffer zone between new housing and freeways or, at least, pursue an ordinance requiring developers to disclose to prospective renters or buyers the risks of living within one block of freeways.

Hricko cited Puerta del Sol, the city-backed condos near the I-5 freeway in Lincoln Heights, and the massive, 1,000-unit, walled-in, University Village directly abutting (18 »

>> 17) the 405 freeway in West L.A., as two troubling, real-life examples of housing developments that could make residents sick. "There are a lot of small kids in that housing," Hricko said of University Village.

It's ironic that UCLA, with great ballyhoo, touted the new University Village as affordable college housing in the 1990s and filled it with university students and employees. University Village immediately flanks both sides of the 405 freeway along Sawtelle and Sepulveda boulevards, where 281,000 passing cars and trucks create one of the world's most congested freeways. The roar of traffic necessitated towering sound walls, yet the University Village Web site boasts a playground and "state-of-the-art" child-care center — for 200 children.

The pale-stucco apartment buildings have a hipster feel that has attracted many young medical-school students and other student residents, as well as UCLA employees. They probably think it's a great deal because the rents are set below market rates for the pricey Westside.

According to a UCLA scientist who works with the EPA Southern California Particle Center, no studies of health effects were conducted at University Village. But in 2004 scientists measured the shape and size of the indoor and outdoor ultrafine "nano" particles in the village — which are of concern to scientists because nano particles can act as miniature transporters of toxins into the human respiratory tract.

Just like developer Geoff Palmer's upscale Orsini and Medici residences in L.A.'s "new downtown," and the Avenue 26 project, University Village sits well inside the 500-foot zone scientists [illegible] hazardous to kids — and, they fear, almo[illegible]mount of mitigation can change that. Some scientists say that air-filtration systems designed into buildings — and even double-paned and triple-paned windows that are common in the luxury downtown condos next to the Harbor and Hollywood freeways — cannot stop the finest pollutants from finding their way in.

As McConnell told the city's planning commission in 2008, when pollution is tested next to Southern California freeways "you see a huge increase in a number of traffic-related pollutants, and it diminishes quite rapidly when you go back to 300 meters" or 984 feet, about two city blocks. The number of asthma cases among children, McConnell explained, tracks the same way — more sick kids near the freeway, more healthy kids farther away.

That day, the USC professor gave the planning commissioners an unusually firm recommendation: "I think there's strong health-science justification for regulating exposures within 500 feet of roadways with heavy traffic," he said. "I'm not sure that will guarantee the health of our children, but I think that there's very good evidence that within that margin, what might be thought of as a margin of safety, that there are health effects that children are going to be suffering."

Hricko concurred, saying a 500-foot buffer zone was merely a "start" and strongly suggested that real estate developers be required to disclose to prospective buyers and tenants the facts about possible health risks of living right next to a freeway.

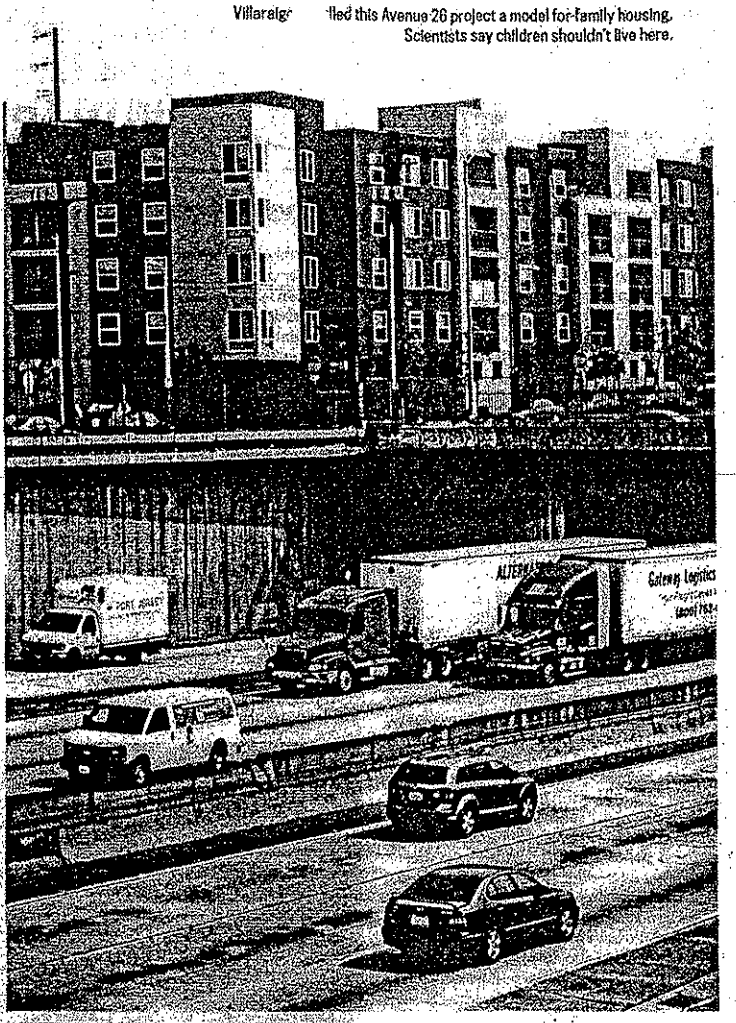
By the end of the two-hour City Hall meeting in the late summer of 2008, Michael Woo, the planning commissioner, was shaken to the bone. "My reaction was, 'This is a very serious problem,' that it's worse than I thought," Woo tells *L.A. Weekly*.

Then-planning commission President Jane Usher ordered Los Angeles City Planning Department staffer Charlie Rausch to return in three months with "next-steps" suggestions from the planning department for the planning commission to consider, and potentially enact.

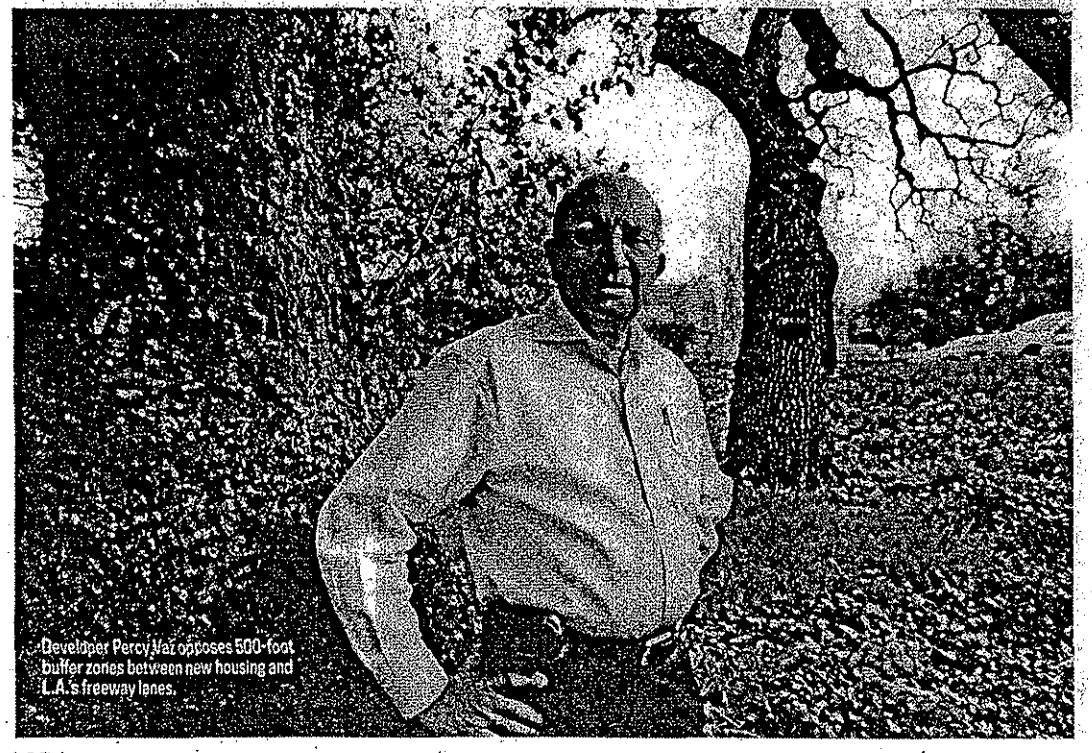
But by the deadline in November 2008, Rausch's boss, planning chief Gail Goldberg, had failed to produce any "next steps" for the planning commission. Goldberg and Usher, in fact, were busy sparring over City Hall's controversial push to increase housing density in neighborhoods citywide. Goldberg led City Hall's so-called density hawks, and Usher was on the other side, upset that carefully designed Community Plans were too often ignored by Goldberg's planning department — for example, that developers seeking height and size "variances" to override local zoning were regularly given the green light. Usher resigned as planning commission president that December, in a very public parting.

The next month, in January 2009, with the outspoken Usher gone, Goldberg finally delivered her list of freeway-adjacent housing recommendations, which Woo describes as "weak." Goldberg suggested several mitigation ideas she said had been "proven very effective." Among other things, Goldberg said vegetation could be planted between housing and freeways — but some scien- (20 >>

Villaraigo[illegible]lled this Avenue 26 project a model for family housing. Scientists say children shouldn't live here.



"PEOPLE WILL BUILD WHERE THEY CAN."
–PERCY VAZ, DEVELOPER OF FREEWAY-ADJACENT HOUSING FOR FAMILIES



Developer Percy Vaz opposes 500-foot buffer zones between new housing and L.A.'s freeway lanes.

>> 18) tists say a thick and deep stand of mature trees would be required.

She suggested the installation of home air-filtration systems and proposed that developers install windows that don't open — both measures that scientists say do not keep fine-particulate matter out of the lungs of children and others because the dust is so pervasive and works its way through a building's tiniest cracks and holes.

The planning department and Goldberg "never really accommodated anything from that [August] meeting" with the scientists, says Angelo Logan, executive director of East Yard Communities for Environmental Justice, who was present and also testified.

Goldberg's halfhearted recommendations have now become a forgotten, and possibly lost, public document.

City Planning Department Deputy Director Vincent Bertoni could not find the year-old "first steps" report for the *Weekly* after repeated requests in January, according to Bertoni's aide. And although that list of recommendations is clearly a public document, another staffer said it's something that the Los Angeles City planning department would not keep for future reference — a claim that drew an incredulous response from former commissioner Usher.

The *Weekly* finally obtained a copy of the forgotten Gail Goldberg plan from an environmental activist. It contains no suggestions that families or others be warned before renting or buying housing within a block of an L.A. freeway.

Today, years after scientists warned City Hall leaders, Woo says the planning commission has "no legal tools to prevent a developer from building" family housing right next to a freeway. And environmentalist Logan backs this up, saying that the problems of "planning near freeways has been ignored."

Developers of the "vast majority" of housing in L.A. don't need permission from Villaraigosa's planning commissioners because the developers are not seeking special variances to get around height or density rules, Woo says. As a result, the planning commission has limited chances to challenge freeway-adjacent housing. "We don't have a very good process for at least questioning housing projects near freeways," he says.

One developer who would oppose a freeway buffer zone is Jeremy Byk, vice president of real estate development at Sherman Oaks–based IMT Residential. IMT builds apartments near the 101 and 405 freeways in the San Fernando Valley, with literature promoting "easy freeway access." One luxury project in Encino, with a towering lobby and grape-arbor façade still under construction, will soon offer two- and three-bedroom, mostly market-rate apartments 70 feet from the humming roadbed of the Ventura Freeway.

For IMT, if it can place an apartment building on land directly adjacent to a busy freeway, it can advertise, without paying a penny, to thousands of motorists every day. The complex in Encino, at 5501 Newcastle Ave., had for months a banner festooned across the front reading "Multi-Family Housing," which could be seen by the roughly 291,000 cars and trucks that pass that stretch daily.

"We like to be near as highly trafficked and high-visibility roadways as possible," says Byk. "It drives our sales that way."

He says he hasn't read the USC studies and didn't know about the push by scientists for the 500-foot buffers or a disclosure statement warning parents. He says he's fine with the idea of a health-hazard disclosure statement, but not a buffer zone. "It's ridiculous."

The developer says he is "always concerned" about the health of his tenants. But he is apparently unaware that some scientists don't believe current mitigation measures sufficiently keep out the pervasive toxic particles. He explains, "We're building modern buildings with air filters and dual-paned windows. We mitigate as much as possible."

Byk argues that in the future, vehicles will be far cleaner, and that current levels of lung damage will be reduced. "Emissions from cars and diesel trucks are ever diminishing ... I don't see it as a long-term, significant issue."

But, as Lyou of AQMD points out, California is many years from attaining lower, federally mandated emissions standards — and the volume of traffic is not decreasing but increasing. Even if radically lower tailpipe emissions were achieved in the next decade, Lyou says, cars and trucks will continue to produce vast amonts of hazardous freeway particulate matter from tire rubber and brake dust.

If leading scientists are shocked that their years of effort researching the health of thousands of children in Southern California produced zero action from L.A.'s mayor and 15 council members, many are unwilling to say so — or even to discuss their disappointment — publicly.

Andrea Hricko, director of community outreach at USC's Keck School of Medicine, though not a scientist, is charged with educating elected officials about important studies conducted by scientists like Rob McConnell and Jim Gauderman. But she doesn't play the kind of political hardball needed to get City Council members and the Mayor's Office involved in a controversial issue that would almost certainly infuriate developers — who are big campaign contributors to many City Hall politicians.

"This particular issue about buffer zones and freeways is a difficult one for city policy," Hricko says politely.

Although researcher McConnell strongly and very publicly supported 500-foot buffer zones in 2008, and Hricko backed him up and firmly put forth the idea of a health-hazard disclosure statement, she backtracked recently, telling the *Weekly* that she and McConnell "haven't advocated for a particular thing." The city of Los Angeles, she now says, has "plans to develop" regulations to address the problem of new housing next to freeways.

In fact, city leaders have no such plan. Officials in the Planning Department can't even find the old ideas from Gail Goldberg's January 2009 "first-steps" list. Comments from Councilman LaBonge, commissioner Woo, and acting deputy mayor Pascual make clear that no elected City Hall politician is taking up the cause.

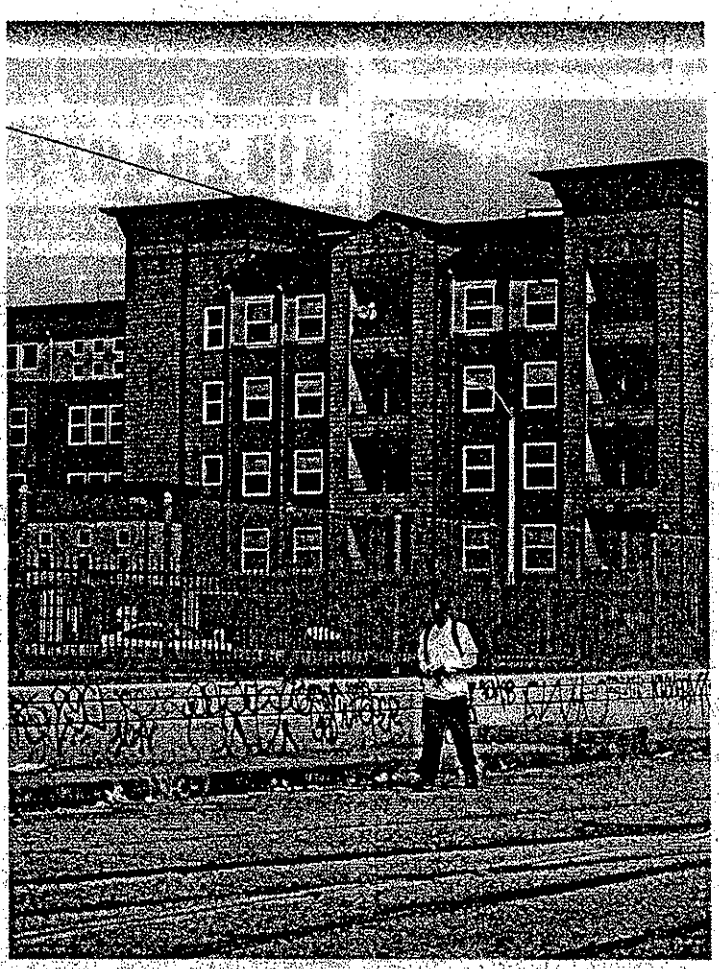
Yet Los Angeles City Council members do approve headline-grabbing environmental policies that tend to portray them as benevolent guardians of human health.

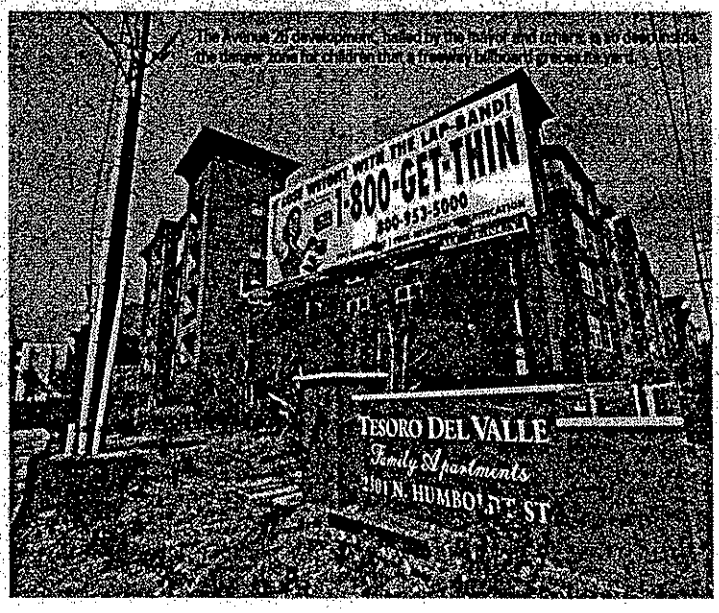
The council has banned smoking outdoors in or near restaurant patios, and in 2008, the council placed a controversial temporary ban on new fast-food outlets in a 32-square-mile area of South Los Angeles after Jan Perry said her constituents were eating too much fat. She and other council members used the scientifically dubious argument that fast-food chains were to blame, only to be embarrassed by a Rand Corp. study some months later clearly showing that South Los Angeles actually has fewer fast-food chains than several areas of L.A.

The council is not considering a disclosure ordinance, however, to warn people about the well-researched and proven risks, especially for children, of living right next to a freeway. Joe Lyou finds the situation "outrageous," saying, "To create housing near areas that are dangerous for your health just seems so fundamentally wrong."

Contact Patrick Range McDonald at pmcdonald@laweekly.com.

"IT CAN'T BE SHUNTED OFF JUST BECAUSE OF THE ECONOMIC CRISIS."
–ENVIRONMENTALIST BILL GALLEGOS





The Avenue 26 development, backed by the factory and others, is so close to the danger zone for children that a freeway billboard greets you.

Exhibit 6

Study Links Close Proximity to Freeways With Autism

Report Finds Heightened Risks for Families Within 1,000 Feet of Highways

BY ELLIN KAVANAGH

Living near a freeway may be associated with increased risk of autism, according to a study published by a team of researchers from the USC Keck School of Medicine, Childrens Hospital Los Angeles and the UC Davis MIND Institute.

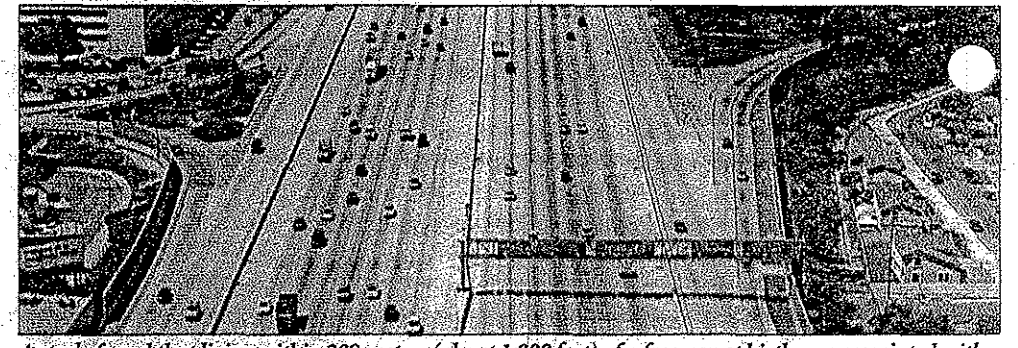
The paper appears online in the journal *Environmental Health Perspectives.*

Children born to mothers living within 309 meters of a freeway (or just over 1,000 feet) appeared to be twice as likely to have autism, said Heather Volk, first author on the study. Volk holds joint appointments at the Community, Health Outcomes & Intervention Research Program at The Saban Research Institute of Childrens Hospital Los Angeles, the Zilkha Neurogenetic Institute and the Department of Preventive Medicine at the Keck School.

Autism is a developmental disorder that has long been ascribed to genetic factors. While changes in diagnostic criteria and increased awareness have been thought to contribute to the rising incidence of the disorder, these factors alone cannot explain the dramatic increase in the number of children affected. The Centers for Disease Control and Prevention reported a 57% increase between 2002 and 2006. The new study supports the theory that environmental factors, in conjunction with a strong genetic risk, may be one possible explanation for the increase.

Data from children with autism and typically developing children, who served as controls, were drawn from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, a population-based case-control study of preschool children. Children were between the ages of 24 and 60 months at the start of the study and lived in communities around Los Angeles, San Francisco and Sacramento.

Population-based controls were recruited from state of California birth files and were frequency matched to the autism cases by age, gender and broad geographic area. Each participating family was evaluated in person. All children were assessed for autism using well-validated instruments.



A study found that living within 309 meters (about 1,000 feet) of a freeway at birth was associated with a two-fold increase in autism risk.

The study examined the locations where the children's families lived during the first, second and third trimesters of the mother's pregnancies, and at the time of the baby's birth, and looked at the proximity of these homes to a major road or freeway. The participants' gestational ages were determined using ultrasound measurements and prenatal records.

Volk and her colleagues found that living within 309 meters of a freeway at birth was associated with a two-fold increase in autism risk. This association was not altered by adjustment for child gender or ethnicity, maximum education in the home, maternal age or prenatal smoking. The researchers found no consistent pattern of association of autism with proximity to major roads, as opposed to freeways, however.

Traffic-related air pollutants have been observed to induce inflammation and oxidative stress in toxicological and human studies e emerging evidence that oxidative stress and inflammation are involved in the pathogenesis of autism supports the findings of this study.

"We expect to find many, perhaps dozens, of environmental factors over the next few years, with each of them probably contributing to a fraction of autism cases. It is highly likely that most of them operate in conjunction with other exposures and/or with genes," said Irva Hertz-Picciotto, chief of the division of environmental and occupational health in the Department of Public Health Sciences at UC Davis, and principal investigator on the CHARGE study.

Article courtesy USC HSC Weekly.

Proximity to freeways may raise autism risk

SHARI ROAN

Children born to mothers who live close to freeways have twice the risk of autism, researchers reported Thursday. The study, its authors say, adds to evidence suggesting that certain environmental exposures could play a role in causing the disorder in some children.

"This study isn't saying exposure to air pollution or exposure to traffic causes autism," said Heather Volk, lead author of the paper and a researcher at the Saban Research Institute of Children's Hospital Los Angeles. "But it could be one of the factors that are contributing to its increase."

Reported cases of autism cases increased by 57% between 2002 and 2006, according to the Centers for Disease Control and Prevention, although professionals still debate whether rates have actually risen or a greater proportion of autistic children is being diagnosed.

An estimated 1 in 110 children is diagnosed with autism today. There is no cure, although research has shown that various therapies can mitigate some symptoms, especially if begun early in life.

In the current study, published online in the journal Environmental Health Perspectives, researchers looked at 304 children with autism and, for comparison, 259 children who were developing normally. The children, between the ages of 24 months and 60 months at the start of the study, lived in communities around Los Angeles, San Francisco and Sacramento.

Each family was evaluated in person, and all of the children received developmental assessments. Researchers collected data on where each child's mother lived during pregnancy and at the time of birth, and the proximity of the homes to a major road or freeway.

Children living about 1,000 feet from a freeway at birth — about 10% of the sample — had a two-fold increase in autism risk. The link held up even after researchers controlled for other factors that may influence development, such as ethnicity, parental education, maternal age and exposure to tobacco smoke.

The study did not find a link between autism development and proximity to a major road, as opposed to a freeway. That may be due to the type and quantity of chemicals dispersed on freeways compared with major roads, Volk said.

Gayle Windham, chief of the epidemiology surveillance unit with the California Department of Health Services Environmental Investigations Branch, said the study did not directly implicate air pollution as a risk factor for autism because it did not have a way of measuring how much pollution the mothers were exposed to during pregnancy.

"They are using a proxy measure for air pollution, which is distance to a freeway," she said. "But you still don't know how much time the women spent at home or working or commuting." Windham was not involved in the study.

Families residing close to freeways may have to wait for more research before scientists can issue advice or recommendations on what to do about this potential risk, Volk said.

shari.roan@latimes.com

Exhibit 7

More deaths in state are linked to air pollution

By JANET WILSON
Times Staff Writer

As many as 24,000 deaths annually in California are linked to chronic exposure to fine particulate pollution, triple the previous official estimate of 8,200, according to state researchers.

The revised figures are based on a review of new research across the nation about the hazards posed by microscopic particles, which sink deep into the lungs.

"Our report concludes these particles are 70% more dangerous than previously thought, based on several major studies that have occurred in the last five years," said Bart Croes, chief researcher for the California Air Resources Board. Croes will present his findings at a board meeting in Fresno this morning.

The studies, including one by USC tracking 23,000 people in greater Los Angeles, and another by the American Cancer Society monitoring 300,000 people across the United States, have found rates of heart attacks, strokes and other serious disease increase exponentially after exposure to even slightly higher amounts of metal, dust or other fragments from tailpipes and smokestacks.

It is difficult to attribute individual deaths to particulate pollution, Croes conceded, but he said long-term studies that account for smoking, obesity and other risks have increasingly zeroed in on fine particulate pollution as a killer.

"There's no death certificate that says specifically someone died of air pollution, but cities with higher rates of air pollution have much greater rates of death from cardiovascular diseases," he said.

Californians exposed to high levels of fine particulates had their lives cut short on average by 10 years, the board staff found.

Researchers also found that when particulates are cut even temporarily, death rates fall.

"When Dublin imposed a coal ban, when Hong Kong imposed reductions in sulfur dioxide, when there was a steel mill strike in Utah . . . they saw immediate reductions in deaths," Croes said.

More measures will be needed, air board officials said, including eventually lowering the maximum permissible levels of soot statewide. California already has the lowest thresholds in the world, at 12 micrograms per cubic meter, but researchers say no safe level of exposure has been found. More regulations are being drafted, including one requiring cleaner heavy-duty trucks.

"We must work even harder to cut short these life-shortening emissions," Air Resources Board Chairwoman Mary Nichols said in a statement.

Clean air advocates said they would be watching closely.

"These numbers are shocking; they're incredible," said Tim Carmichael, senior policy director for the Coalition for Clean Air, a statewide group. He and others said the board must strengthen a soot cleanup plan submitted to them by the San Joaquin Valley Air Pollution Control District. A hearing and vote on the plan is scheduled for today.

Numerous Central Valley public health groups wrote Nichols this week, urging bans on the use of industrial equipment on bad air days, tougher controls on boilers and crop drying equipment, and other action. The economic cost attributed to premature deaths and illnesses linked to particulate exposure in the Central Valley has been estimated at $3 billion a year, and $70 billion statewide, according to separate studies. Those figure are expected to be revised upward based on the new report.

"We must clean up the air. We cannot afford further delay," the group wrote.

Agricultural and construction industry groups have fought such provisions, saying that they could cripple the region's economy, but have not publicly complained about the plan as proposed. Board spokesman Leo Kay said that given the new mortality findings, "I certainly don't expect a rubber-stamp approval."

janet.wilson@latimes.com

MARCIO JOSÉ SANCHEZ *Associated Press*

NO MANSON VICTIMS FOUND

Jeff Hollowell, left, a detective with the Inyo County Sheriff's Department, and Sheriff Bill Lutze wrap up the search for human remains at a ranch west of Death Valley where Charles Manson and his followers hid in 1969

LA Times 5/22/08 P. B-3

Exhibit 8

Science News

... from universities, journals, and other research organizations

Traffic-Related Pollution Near Schools Linked to Development of Asthma in Pupils, Study Suggests

ScienceDaily (Apr. 3, 2008) — Living near major highways has been linked to childhood asthma, but a new study led by researchers at the Keck School of Medicine of the University of Southern California (USC) suggests that traffic-related pollution near schools is also contributing to the development of asthma in kids

Share This:

See Also:

Health & Medicine
- Asthma
- Children's Health
- Workplace Health

Earth & Climate
- Air Quality
- Air Pollution
- Pollution

Reference
- Indoor air quality
- House dust mite
- Wheeze
- Hypoallergenic

The researchers found that the risk of developing asthma due to exposure at school was comparable to that of children whose exposure occurred primarily at home, even though time spent at school only accounted for about one third of waking hours. Children in schools located in high-traffic environments had a 45 percent increased risk of developing asthma. The study appears in the journal *Environmental Health Perspectives* and is now available online.

Asthma is the most common chronic childhood illness in developed countries and has been linked to environmental factors such as traffic-related air pollution.

"While residential traffic-related pollution has been associated with asthma, there has been little study of the effects of traffic exposure at school on new onset asthma," said lead author Rob McConnell, M.D., professor of preventive medicine at the Keck School of Medicine of USC. "Exposure to pollution at locations other than home, especially where children spend a large portion of their day and may engage in physical activity, appears to influence asthma risk as well."

The study drew upon data from the Children's Health Study (CHS), a longitudinal study of children in Southern California communities that was designed to investigate the chronic effects of air pollution on respiratory health. Using a cohort of 2,497 kindergarten and first grade children who were asthma-free when they entered the CHS, researchers examined the relationship of local traffic around schools and homes to diagnosis of new onset asthma that occurred during three years of follow-up.

Traffic-related pollution exposure was assessed based on a model that took into account traffic volume, distance to major roadways from home and school and local weather conditions. Regional ambient ozone, nitrogen dioxide and particulate matter were measured continuously at one central site in each of the 13 study communities. The design allowed investigators to examine the joint effects of local traffic-related pollution exposure at school and at home and of regional pollution exposure affecting the entire community.

Researchers found 120 cases of new asthma. The risk associated with traffic-related pollution exposure at schools was almost as high as for residential exposure, and combined exposure accounting for time spent at home and at school had a slightly larger effect.

Although children spend less time at school than at home, physical education and other activities that take place at school may increase ventilation rates and the dose of pollutants getting into the lungs, McConnell noted. Traffic-related pollutant levels may also be higher during the morning hours when children are arriving at school.

Despite a state law that prohibits school districts from building campuses within 500 feet of a freeway, many Southern California schools are located near high-traffic areas, including busy surface streets.

"It's important to understand how these micro-environments where children spent a lot of their time outside of the home are impacting their health," McConnell said. "Policies that reduce exposure to high-traffic environments may help to prevent this disease."

The study was funded by grants from the National Institute of Environmental Health Sciences, the U.S. Environmental Protection Agency, the South Coast Air Quality Management District and the Hastings Foundation.

Story Source:

The above story is reprinted from [illegible] provided by University of Southern California. Note: Content may be edited for style and length.

A new study suggests that traffic-related pollution near schools contributes to the development of asthma in kids. (Credit: iStockphoto/Robert Hadfield)

Related Stories

Asthma Rate and Costs from Traffic Pollution Higher Much Higher Than Past Traditional Risk Assessments Have Indicated [illegible] — A team of resource economist researchers has revised the cost burden sharply upward for childhood asthma and for the first time include the number of cases attributable to air pollution, in a new ... > read more

Big Air Pollution Impacts On Local Communities; Traffic Corridors Major Contributors To Illness From Childhood Asthma [illegible] — Heavy traffic corridors in the cities of Long Beach and Riverside are responsible for a significant proportion of preventable childhood asthma, and the true impact of air pollution and ship emissions ... > read more

Parental Stress And Air Pollution Linked To Children's Risk For Developing Asthma [illegible] — Children with stressed out parents may be more susceptible to developing asthma associated with environmental triggers such as high levels of traffic-related pollution and tobacco smoke, according to ... > read more

Traffic Exhaust Can Cause Asthma, Allergies And Impaired Respiratory Function In Children [illegible] — Children exposed to high levels of air pollution during their first year of life run a greater risk of developing asthma, pollen allergies, and impaired respiratory function. However, genetic factors ... > read more

Heavy Traffic Makes Breathing A Burden In Children [illegible] — Exposure to traffic pollution may increase respiratory problems and reduce lung volumes in children with asthma, according to researchers who studied the effects of road and traffic density on ... > read more

Just In:
Horticultural Hijacking: Bacteria's 'Dark ...
more breaking science news

Social Networks

*Recommend ScienceDaily on **Facebook**, **Twitter**, and **Google +1**:*

Tweet Follow

Other bookmarking and sharing tools:

Breaking News ... from NewsDaily.com

- GE pairs medical technology acquisitions in Germany
- Honeywell homicide case against Syngenta pesticide unproven
- Author defends Monsanto GM study as EU orders review
- Study on Monsanto GM corn concerns draws skepticism
- NASA rover snaps pictures of an eclipse from Mars
- Quantum teleportation hoped for Nobel Prize: Thomson Reuters
- Trees must fall to make way for space shuttle's L.A. road trip
- Arctic sea ice thaw may be accelerated by ... shipping
- more news ...

In Other News ...

- Daughter of former Iranian president Rafsanjani taken to prison
- Top China official visits Afghanistan, signs security deal
- Romney pulls in big bucks in southern California
- Strauss-Kahn group says inquiry to be shelved: report
- Crews extinguish fire at Venezuela's El Palito refinery
- U.S. stops 20 Iran officials entering U.N. assembly
- Afghanistan bars Pakistani pastors over proselytizing
- Analysis: iPhone 5 defines Apple success. Turn ... risky s...
- more top news

Free Subscriptions ... from ScienceDaily

Get the latest science news with our free email

Exhibit 9

Hindawi Publishing Corporation
Journal of Toxicology
Volume 2012, Article ID 782462, 23 pages
doi:10.1155/2012/782462

Review Article

The Adverse Effects of Air Pollution on the Nervous System

Sermin Genc,[1] Zeynep Zadeoglulari,[1] Stefan H. Fuss,[2] and Kursad Genc[1]

[1] *Department of Neuroscience, Health Science Institute, Dokuz Eylul University, Inciralti, 35340 Izmir, Turkey*
[2] *Department of Molecular Biology and Genetics, Bogazici University, 34342 Istanbul, Turkey*

Correspondence should be addressed to Kursad Genc, kkursadgenc@hotmail.com

Received 30 May 2011; Accepted 15 November 2011

Academic Editor: Cinta Porte

Exposure to ambient air pollution is a serious and common public health concern associated with growing morbidity and mortality worldwide. In the last decades, the adverse effects of air pollution on the pulmonary and cardiovascular systems have been well established in a series of major epidemiological and observational studies. In the recent past, air pollution has also been associated with diseases of the central nervous system (CNS), including stroke, Alzheimer's disease, Parkinson's disease, and neurodevelopmental disorders. It has been demonstrated that various components of air pollution, such as nanosized particles, can easily translocate to the CNS where they can activate innate immune responses. Furthermore, systemic inflammation arising from the pulmonary or cardiovascular system can affect CNS health. Despite intense studies on the health effects of ambient air pollution, the underlying molecular mechanisms of susceptibility and disease remain largely elusive. However, emerging evidence suggests that air pollution-induced neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction, and alterations in the blood-brain barrier contribute to CNS pathology. A better understanding of the mediators and mechanisms will enable the development of new strategies to protect individuals at risk and to reduce detrimental effects of air pollution on the nervous system and mental health.

1. Introduction

Air pollution collectively describes the presence of a diverse and complex mixture of chemicals, particulate matter (PM), or of biological material in the ambient air which can cause harm or discomfort to humans or other living organisms. The sources of air pollution can either be natural (e.g., volcanic eruptions) or manmade (e.g., industrial activities), and air pollution emerges as a serious health problem especially in rapidly growing countries. Millions of people worldwide are chronically exposed to airborne pollutants in concentrations that are well above legal safety standards [1]. Therefore, morbidity and mortality attributable to air pollution continue to be a growing public health concern worldwide. Air pollution ranks eighth among the leading risk factors for mortality and accounts for 2.5% of all deaths in developed countries [2]. The World Health Organization (WHO) estimates that air pollution is responsible for over 3 million premature deaths each year [3]. Epidemiological and observational studies identified a strong link between the exposure to contaminants in the ambient air and adverse health outcomes, such as hospitalization and mortality [4]. Exposure to air pollutants has been associated with marked increases in cardiovascular disease morbidity and deaths resulting from myocardial ischemia, arrhythmia, heart failure, and respiratory diseases such as lung cancer and asthma [3, 4].

About a decade ago, the central nervous system (CNS) has also been proposed to be a target organ for the detrimental effects of airborne pollutants [5]. Indeed, emerging evidence from recent epidemiological, observational, clinical, and experimental studies suggest that certain neurological diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, may be strongly associated with ambient air pollution.

Mechanistically, air pollution may affect the nervous system through a variety of cellular, molecular, and inflammatory pathways that either directly damage brain structures or lead to a predisposition to neurological diseases. Although ischemic stroke (chronic exposure to ambient air pollution), multiple sclerosis (MS, exposure to second-hand smoking), and PD (manganese content in the ambient air) are currently the only neurological disorders for which a strong link to ambient air pollution has been established, it is not unlikely

that other CNS disorders are also attributable to air pollution [6–8].

It has been suggested from epidemiological and observational studies that exposure to airborne pollutants can contribute to neurodegenerative disease processes already from early childhood on, especially if the individuals are chronically exposed to the contaminants [1, 9–11]. Air pollutants affect the CNS either directly by transport of nano-sized particles into the CNS or secondarily through systemic inflammations. Either of the effects can be caused by the physical characteristics of the particle itself or by toxic compounds that adsorb on the particles [12, 13]. Although the exact mechanisms underlying brain pathology induced by air pollution are not fully understood, several lines of current evidence point out that neuroinflammation, oxidative stress, glial activation, and cerebrovascular damage might be the primary pathways [1, 14].

In this paper, we provide an overview of the different classes of air pollutants and their potential ways to entry by which they could get into contact with the CNS. We summarize findings of epidemiological, observational, clinical, and experimental studies which describe a link between air pollution and neurological diseases or neurodevelopmental disturbances. Finally, we summarize the current understanding of the adverse effects of air pollutants on the nervous system and mental health on a cellular and molecular level.

2. Components of Air Pollution

Air pollution represents a diverse mixture of substances including PM, gases (e.g., ground-level ozone, carbon monoxide, sulfur oxides, and nitrogen oxides), organic compounds (e.g., polycyclic aromatic hydrocarbons and bacterial endotoxins), and toxic metals (e.g., vanadium, lead, nickel, copper, and manganese) that can be found in outdoor and indoor air [1, 15]. Among these, PM and ground-level ozone, which are formed primarily from nitrogen oxides and volatile organic compounds, appear to be the most widespread and harmful components. Of those, PM is especially relevant for nervous system damage and can be found as a mixture of solid particles and liquid droplets, that are suspended in the air [1]. Most individual components of atmospheric PM are not especially dangerous and some major constituents, such as sodium chloride, are harmless [16].

PM is characterized by its size and aerodynamic property which is directly related to its biological effects. For instance, only particles less than 10 μm in diameter can be inhaled deep into the lungs, whereas larger particles usually get trapped in the upper airways. Generally, coarse particles with an aerodynamic diameter of 2.5 to 10 μm (PM_{10}), fine particles of less than 2.5 μm ($PM_{2.5}$), and ultrafine (UFPs), or nano-sized (NP) particles of less than 0.1 μm can be classified [15, 17].

Road and agricultural dust, tire wear emissions, products of wood combustion, construction and demolition works, and mining operations are the primary sources of PM_{10}. $PM_{2.5}$ particles commonly originate from oil refineries, metal processing facilities, tailpipe and brake emissions, residential fuel combustion, power plants, and wild fires [15]. They are formed from gas and condensation of high-temperature vapors that are formed during combustion and industrial activities. $PM_{2.5}$ can be composed of both organic and inorganic compounds, including sulfates, nitrates, carbon, ammonium, hydrogen ions, lipopolysaccharide (LPS), metals, and water [1]. Diesel exhaust particles (DEPs), however, are the major components found among ambient fine particles.

UFPs are mostly combustion-derived NPs, which can be produced by internal combustion engines, power plants, incinerators, and other sources of thermodegradation. They can carry soluble organic compounds, polycyclic aromatic hydrocarbons, and oxidized transition metals on their surface [18]. UFPs have distinct features that render them more dangerous than other PMs. For instance, they have been shown to inhibit phagocytosis and to stimulate inflammatory responses [16]. Although the effects of UFPs have been studied less extensively than those of $PM_{2.5}$ and PM_{10}, there is evidence that the size of the particles is negatively correlated with their adverse health effects [19].

Indeed, ambient UFP concentrations are found to be directly correlated with mortality [20]. Current national air quality standards are based on the mass concentration of PM. However, when compared to fine particles at similar mass concentrations in the air, UFPs are much more numerous and have a larger combined surface area, enhanced oxidant capacity, greater inflammatory potential, and higher pulmonary deposition efficiency [16, 17, 21, 22]. A major risk of UFPs arises from the fact that they are not filtered out during their passage through the nose and bronchioles but are able to penetrate deep into the lung where they eventually enter the blood circulation and can get distributed throughout the body.

3. Entry of Air Pollutants into the Central Nervous System

Sustained exposure to significant levels of airborne UFPs, PM, and LPS may result in the direct translocation of these pollutants to the CNS where they can result in neuropathology through a variety of pathways and mechanisms (Figure 1). Alternatively, air pollutants might not enter the CNS directly, but could exert adverse effect on the CNS by triggering the release of soluble inflammatory mediators from primary entry organs or secondary deposition sites. The release of inflammatory agents could then lead to or alter the susceptibility for neuroinflammation and neurodegeneration in the CNS.

Once taken up by the body, fine PM or NPs could rapidly enter the circulatory system with the potential to directly affect the vascular system. For instance, NPs could be inhaled and cross the alveolar-capillary barrier in the lungs. The ability of NPs to cross this barrier is influenced by a number of factors that include the size of the particles, their charge, their chemical composition as well as their propensity to form aggregates. Even though the translocation of inhaled or instilled NPs across the alveolar-capillary barrier has been clearly demonstrated in animal studies for a range of NPs [23, 24], it has been more difficult to directly demonstrate this mechanism in humans [3].

activated endothelial cells and UFP-loaded erythrocytes [1, 33, 34].

Another important and more direct route for UFPs to enter the nervous system is through the olfactory mucosa, which is a neuronal epithelium that is in direct contact with the environmental air [35–37]. Thus, fine and UFPs may reach the brain through olfactory receptor neurons or the trigeminal nerve. Olfactory receptor neurons are bipolar sensory neurons that mediate the sense of smell by conveying sensory information from the nose to the CNS. The olfactory epithelium is covered by a layer of sustentacular cells, but olfactory sensory neurons extend their dendrites into the mucous layer covering the olfactory epithelium where they directly interact with odorants inhaled with the air. Nasally inhaled pollutants that reach the olfactory mucosa could enter the cilia of olfactory receptor neurons by pinocytosis, simple diffusion, or receptor-mediated endocytosis. Once incorporated into sensory neurons, they could be transported by slow axonal transport along the axons to the olfactory bulb [38]. From there, pollutants could be transported further into the CNS along mitral cell axons that project from the olfactory bulb to multiple brain regions, including the olfactory cortex, the anterior olfactory nucleus, the piriform cortex, the amygdale, and the hypothalamus.

Accordingly, UFPs have been observed in human olfactory bulb periglomerular neurons and trigeminal ganglia capillaries [10]. Similarly, a decreasing gradient of metal (vanadium and nickel) deposition and accompanying tissue damage from the nose to the brain has been reported in the canine nervous system, confirming the importance of the nasal route for the entry of air pollutants into the CNS [39]. Controlled exposures of rats to UFPs and metals also demonstrated their accumulation in the olfactory bulb [40–42]. Taken together, these findings suggest that NPs can be taken up directly by the olfactory mucosa and enter the CNS or the cerebrospinal fluid by bypassing the circulatory system [12]. Uptake through the nose might even be enhanced by additional pollutant-induced systemic inflammation by deteriorating the olfactory mucosal barrier, which would result in increased neuropathology.

Additional direct neuronal entry routes for NPs have been described that involve the retrograde and anterograde transport in axons and dendrites such as the transport of inhaled NPs to the CNS via sensory nerve fibers that innervate the airway epithelia [12]. Ground-level ozone exposure activates the CNS through the vagal nerves without the involvement of the thoracic spinal nerves [43]. PM-related LPS is likely to play an important role in these pathways, as shown by vagal upregulation of CD14 [44].

Even though the translocation rate of NPs from their site of entry to secondary organs might be rather low, continuous or chronic exposure to NPs may result in their accumulations in the brain as a secondary target organ in significant amounts [12]. Thus, it is also important to obtain data on the retention characteristics of NPs in both primary and secondary target organs, including associated elimination and clearance pathways [12]. With regard to the CNS, no data on NP elimination are available yet. It is conceivable, however, that CSF circulation provides an excretory pathway for NPs that enter via neuronal uptake. Usually, the CSF serves as a fluid cushion for the brain, but also distributes substances to all brain regions and acts as an elimination route for metabolic waste products [45]. NPs could be eliminated from the CSF through the same mechanisms: uptake of CSF by the blood circulatory system through arachnoid vili or via the nasal lymphatic system. The exact details of NP clearance from the brain, however, await future investigation [12].

4. Air Pollution and Neurological Disease

Results about the direct effects of air pollutants and airborne particles on neuronal cells have been reported from experimental studies *in vitro*, using cell culture systems and *in vivo*, using inhalation and instillation paradigms in rodents as well as from epidemiological and controlled clinical studies in humans.

4.1. Experimental Studies

4.1.1. In Vitro Studies. A variety of *in vitro* studies assessed the potential toxic effects of air pollutants (Table 1), by measuring changes in cell viability, alterations of apoptosis, the dysfunction of mitochondria, the production of reactive oxygen species (ROS), or the production of pro-inflammatory cytokines as sensitive identifiers [1]. Varying degrees of proinflammatory- and oxidative stress-related cellular responses and decreased cell viability were reported upon stimulation with laboratory-generated or filter-collected ambient air particles in different cell culture systems [42]. Of particular interest are studies utilizing neuronal and microglial cell lines or primary cultures of those cells that were exposed to concentrated ambient air particles (CAPs), diesel exhaust particles (DEPs), toxic gases, such as ozone, bacterial endotoxins, such as LPS, or toxic elements, such as manganese. All investigated neuronal, glial or cerebral endothelial cell types were shown to be targets of the toxic effects of air pollutants [46–48]. However, the underlying mechanisms could be rather complex, and some insight into the interaction of different cell types was derived from coculture systems. For instance, it was shown that the neurotoxic effects of DEPs on dopaminergic neurons could be either direct or indirect via the release of inflammatory mediators and ROS from activated microglial cells [46, 49]. Interestingly, pretreatment of neuron-glia cocultures with LPS increased the vulnerability of the cells to the toxic effects of DEP, while DEPs alone were not harmful [49].

An important aspect of *in vitro* toxicity studies is the establishment of dose-response relationships. For instance, low concentrations (20–40 μg/mL of gas per mL of complete medium) of oxygen-ozone were not toxic to astroglial cells, while higher concentrations (60 μg/mL) severely decreases cell viability [48]. Transcriptomic and proteomic profiling of cultured cells upon exposure to CAPs may provide insights into alterations of gene and protein expression. One such study demonstrated the upregulation of inflammatory and innate immunity pathway components in mouse immortalized BV2 cells when exposed to CAPs [50]. Likewise,

Table 1: The effects of air pollutants on neuronal and glial cells *in vitro*.

Pollutants	Species	Cell type	Assays	Key findings	References
PMs					
DEPs	Rat	VM Neuron-glia	TH immunostaining	DA neurotoxicity	[46]
			OX-42 immunostaining	Microglial activation	
	Mouse ($PHOX^{-/-}$)	Microglia	DCFH-DA	Increased microglial ROS	
		Microglia	DA uptake	No DEP neurotoxicity	
DEPs + LPS	Rat	VM Neuron-glia	Griess reaction	Increased NO production	[49]
	Rat	HAPI microglial cell line	TH immunostaining	DA neurotoxicity	
			ELISA	Increased TNFα release	
DEPs	Rat	Brain capillaries	CM-H_2DCFDA	Increased ROS production	[47]
			ELISA	Increased TNFα release	
CAPs	Mouse	BV2 microglial cell line	ELISA	Increased TNFα, IL6 release	[50]
				Increased P-glycoprotein	
			Western blotting microarray	Upregulated inflammatory genes	
Ozone	Rat	Astrocyte	MDA	Increased lipid peroxidation	[48]
			LDH	Decreased cell viability	

Abbreviations: concentrated ambient particles (CAPs), 2′,7′-dichlorfluorescein-diacetate (DCFH-DA), dopaminergic (DA), diesel exhaust particles (DEPs), enzyme-linked immunosorbent assay (ELISA), interleukin-6 (IL-6), lactate dehydrogenase (LDH), malondialdehyde (MDA) nitric oxide (NO), reactive oxygen species (ROS), tyrosine hydroxylase (TH), tumor necrosis factor alpha (TNFα), ventral mesencephalic (VM).

the expression profiles of microRNAs, which emerged as crucial mediators of posttranscriptional gene regulation, might change during exposure to air pollutants [51]. Indeed, hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), a common environmental contaminant and explosive nitroamine that is widely used in military ammunition, has been shown to change brain microRNA expression in exposed mice [52].

The rapidly growing number of engineered nanoparticles (ENPs) and nanomaterials (NMs) might also contribute to air pollution as new nanotechnologies are constantly developed, and NMs are used increasingly in daily life through the advent of new products. In addition, ENPs are extensively tested for their usefulness in medical diagnostic and therapeutic applications. Although no human ailments have been directly attributed to NMs so far, preliminary experimental studies indicate that NMs could initiate adverse biological responses and that NPs could have toxicological properties [53]. Thus, ENPs constitute a novel neurotoxic risk and several *in vitro* studies could demonstrate adverse effects of ENPs on CNS cells (not included in Table 1). For instance, titanium dioxide, aluminum oxide, and nanosized silica particles were shown to decrease cell viability and to increase apoptosis in neuronal and endothelial cell cultures [54–58]. These substances also increased the amount of ROS, which resulted in concomitant activation of microglia [54–59]. An important point in *in vitro* nanoneurotoxicity studies is therefore the necessity to accurately characterize particle size, as particles of different size might exert different effects or similar effects to different degrees. In addition, a controlled investigation of the physicochemical properties of the NPs over time and their interactions with culture media should also be considered [60, 61]. Although NPs in environmental air samples might be much more heterogeneous, epidemiological and toxicological studies with airborne ultrafine particles can be viewed as the basis for the expanding field of nanotoxicology [42].

In vitro studies bear several distinct advantages for studying neurotoxic effects of air pollutants because the technology is cheap, the cultured cells grow rapidly, and the assays provide reproducible results. However, many times immortalized cell lines are used, which might not correctly reflect the more complex responses of native CNS cells or of neurons in their natural complex environment. Unfortunately, long-term and large-scale cultures of primary CNS cells are still challenging and thus might not be useful for high-throughput screening of toxicological effects. The emerging field of induced pluripotent stem cells, which can be easily derived from somatic cells such as dermal fibroblasts and keratinocytes, may provide a solution to this problem and induced pluripotent stem cells could soon emerge as a novel experimental paradigm for human neurotoxicity studies [62, 63].

Despite their advantages, *in vitro* studies have also important limitations, some of which are methodological. The interpretation and cross-comparison of results from different research groups might be hampered because of the use of particles with different chemical compositions or different culture cells. The duration of exposure and concentrations might differ across laboratories. More importantly, however, responses of cultured cells might not faithfully reflect the responses of the entire body system or target organ. In general, ultraphysiological doses of air pollutants are used in cell cultures studies and the long-term study of the effect of chronic exposure to low doses of potentially toxic material is not feasible. Organotypic cell cultures and tissue explant cultures might be more useful in this regard since the integrity of tissue of interest is fully or partially preserved. Because systemic effects and biodistribution of air pollutants cannot

be investigated in *in vitro* assays, *in vivo* studies provide additional and important information on the adverse effects of air pollutants.

4.1.2. In Vivo Studies. The confirmation of *in vitro* results through realistic *in vivo* studies is mandatory to validate hypotheses generated from *in vitro* studies [12]. *In vivo* studies are invaluable tools for the examination of bio-distribution, the biokinetic properties, and the pathophysiological effects of air pollution on the whole body system. They also provide an opportunity to study neurobehavioral effects of air pollution in intact living animals. Novel noninvasive imaging techniques can be used to visualize neuroinflammation, microglia activation, brain redox-status, and BBB integrity in live animals [64, 65]. Importantly, *in vivo* studies allow the use of experimental conditions, routes of administration, and exposure regimes that are not available in cell culture systems. For instance, they enable a comparison of the effects of acute, subchronic, and chronic exposure of the whole animal. Likewise, pollutants can be administered through different natural and artificial routes such as inhalation, nasal and intratracheal instillation, or intraperitoneal injection (Table 2). Like cell culture studies, whole animal studies are amenable to investigate alterations in gene and protein expression, and activation of signaling pathways upon exposure to air pollutants. Finally, prevention strategies and therapeutic approaches can be tested in a preclinical setting.

To investigate the effect of certain gene products on the susceptibility to damage by air pollutants, genetically modified animals can be used. For instance, one study used Apolipoprotein E (ApoE) knockout ($ApoE^{-/-}$) mice and could show that ApoE deficiency enhances air pollutant-induced neurotoxicity [66]. Exposure to UFPs activates NFκB and AP-1 transcription factors via JNK-activation in $ApoE^{-/-}$ mice in a dose- and duration-dependent manner [67]. In a more recent study, these findings were confirmed, providing evidence that air pollution can produce neuropathological damage in individuals that are susceptible to oxidative stress [68].

Tin-Tin-Win-Shwe et al. used wild-type male BALB/c mice and instilled carbon black (CB) intranasally [74]. Six hours after instillation, the mice were intraperitoneally injected with the bacteria cell wall component lipoteichoic acid (LTA) and the authors could show that LTAtreatment potentiates CB-induced neurological effects. CB modulates the levels of extracellular amino acid neurotransmitter and proinflammatory cytokine IL-1β mRNA expression synergistically with LTA in the mouse olfactory bulb. In a recent study by Zanchi et al., rats were exposed to residual oil fly ash (ROFA), one of the residues generated by combustion, by intranasal instillation and were treated with the antioxidant N-acetylcysteine (NAC) intraperitoneally for 30 days [73]. ROFA instillation alone induced an increase in lipid peroxidation levels in the striatum and the cerebellum, whereas NAC treatment had preventive effects.

Ozone is by far the most important air pollutant in terms of its concentration, its persistence, and its ubiquitous occurrence. A list of preclinical studies that investigated the neurotoxic effects of ozone inhalation using different experimental paradigms is given in Table 2. For instance, Pereyra-Muñoz et al. showed that chronic (4 h daily for 15 or 30 days) and low-dose (0.25 ppm) exposure induces oxidative damage to neurons in the striatum and substantia nigra [75]. Angoa-Pérez et al. exposed ovariectomized rats to air loaded with ozone for 7, 15, 30, or 60 days (0.25 ppm, 4 h per day) [76]. A second experimental group of ovariectomized rats were treated with 17[beta]-estradiol 2 h after ozone exposure in an otherwise identical exposure regime. The data suggest that chronic ozone inhalation produces oxidative stress and loss of dopaminergic neurons in the substantia nigra and that the effects can be reduced by treatment with 17[beta]-estradiol [71, 76]. Neural mechanisms underlying adaptive responses to acute ozone exposure were also studied in adult rats that were subjected to 0.5 ppm ozone exposure for 3 h and were then allowed to recover for 3 h before examination. In this paradigm, acute ozone exposure had an effect primarily on glial cells in the CNS [79]. The protein expression levels of vascular endothelial growth factor (VEGF) were upregulated in central respiratory areas, such as the nucleus tractus solitarius (NTS) and the ventrolateral medulla (VLM). Persistent VEGF upregulation following ozone exposure may contribute to brain repair and consecutive functional adaptations. Rats that inhaled 0.5 or 2 ppm ± 10% of ozone for 1.5–120 h suffered from lung inflammation that induced the activation of NTS neurons through the vagus nerve. It also promoted neuronal activation in other, stress-responsive regions of the CNS as could be demonstrated by up-regulated levels of the immediate early-gene product c-Fos [43].

As exemplified above, *in vivo* studies offer a unique possibility to test the potential of neuroprotective agents such as hormones and antioxidants against air pollutants [71, 73, 76, 78]. Selective inhibitors of the cyclooxygenase-2 (COX-2) enzyme have been tested in young healthy dogs which were residents of highly air polluted urban regions. Inhibition of COX-2 showed beneficial effects probably by reducing frontal lobe IL-1β expression [80]. Interestingly, treatment with dark chocolate has also been found to be neuroprotective against long-term air pollution in mice [44].

Despite the clear advantages of *in vivo* studies that were summarized here (studying pathophysiological mechanisms or neurobehavioral responses and testing preclinical preventive and treatment strategies), a long list of confounding parameters experimentally may obscure the results. Methodological details such as sex, age, strain, dose, and the particular assay that was used to measure the outcome should be considered carefully when comparing results across different studies. In particular body size, age, gender, species, and strain are known to have dosimetric effects in air pollution research [81]. Although there is growing epidemiologic evidence that associations between air pollution and respiratory health differ between females and males, comparative studies or studies on female rodents in general are limited [72, 82].

Likewise, only a single study evaluated the influence of age on air pollution-induced CNS injury [78]. In this study, ozone inhalation resulted in high-lipid peroxidation in the frontal cortex of old rats, which is in contrast to findings in young rats, where oxidative stress injury occurred

Table 2: The effects of air pollutants on the central nervous system *in vivo*.

Pollutants	Species	Route of administration	Assays	Key findings and outcome	References
PMs					
	Mouse ($ApoE^{-/-}$)	Inhalation	TH immunostaining	DA neurotoxicity Astrogliosis	[66]
CAPs	Mouse ($ApoE^{-/-}$)	Inhalation	EMSA Western blotting	NFκB and AP-1 activation JNK activation	[67]
	Mouse	Inhalation	EMSA ELISA	NFκB activation	
				Increased TNFα and IL-1 α levels	[68]
	Rat	Inhalation	IHC, RT-PCR Western blotting	Increased HO-1 and COX2 mRNA and protein expression	[69]
DEPs	Mouse	Inhalation (w/wo i.p. LTA injection)	Microdialysis/HPLC RT-PCR	Increased glutamate levels Inreased NMDA receptor subunits (NR1, NR2A, and NR2B), and CaMKIV mRNA	[70]
	Inhalation (nasal)		EMSA ELISA, RT-PCR	NFκB and AP-1 activation Increased TNFα and IL-1 α levels and mRNA expression	[71]
Rat	Mice	Inhalation	Open-field test	Decreased locomotor activity	[72]
	Rat	Inhalation/Intratracheal	IBA-1 immunostaining	Microglial activation	
			ELISA	Increased TNFα, IL-1β, IL-6, and MIP-1α levels	[49]
			qRT-PCR	Increased TNFα, MIP-1α mRNA expression	
ROFA	Rat	In instillation	TBARs	Increased lipid peroxidation	
			Open-field test	Decreased exploratory behavior	[73]
NSCB	Mouse	in instillation (w/wo ip ITA injection)	RT-PCR Microdialysis/HPLC	Increased TNFα, IL-1β, and chemokine mRNA expression Increased glutamate glycine levels	[74]
	Rat	Inhalation (temporal)	Motor activity test Lipid peroxidation assay TH immunostaining	Decreased motor activity Increased lipid peroxidation Loss of DA neurons (SN)	[75]
	Rat (ovariectomized)	Inhalation	TH immunostaining	Loss of DA neurons (SN)	[76]
	Rat	Inhalation	Behavioral tests	Increased freezing behavior Decreased exploratory behavior	[77]
			Lipid peroxidation assay	Increased lipid peroxidation	
				Neurodegeneration	
			Electron microscopy Microdialysis/HPLC	Changes in neurotransmitter levels	
Ozone	Rat(ovariectomized)	Inhalation	Behavioral tests Lipid peroxidation assay	Impaired olfactory perception and social recognition memory Increased lipid peroxidation	[71]
	Rat	Inhalation	Behavioral tests Lipid peroxidation assay	Impaired memory Increased lipid peroxidation	[78]
	Rat	Inhalation	IHC	Increased VEGF, IL-6 and TNFα	[79]

Table 2: Continued.

Pollutants	Species	Route of administration	Assays	Key findings and outcome	References
	Rat	Inhalation	IHC	Increased c-Fos expression in different brain regions including NTS	[43]

Abbreviations: apolipoprotein E (ApoE), calcium/calmodulin-dependent protein kinase type IV(CaMKIV), concentrated ambient particles (CAPs), cyclooxygenase-2 (COX-2), dopaminergic (DA), diesel exhaust particles (DEPs), electrophoretic mobility shift assay (EMSA), enzyme-linked immunosorbent assay (ELISA), heme oxygenase (HO), high-performance liquid chromatography (HPLC), allograft inflammatory factor 1(IBA1), immunohistochemistry (IHC), interleukin-1 alpha (IL-1α), interleukin-1beta (IL-1β), interleukin-6 (IL-6), c-Jun N-terminal kinases (JNK), macrophage inflammatory proteins (MIPs), nanosized carbon black (NSCB), lipoteichoic acid (LTA), nuclear factor kappa B (NFκB), nucleus tractus solitarius (NTS), residual oil fly ash (ROFA), reverse transcription polymerase chain reaction (RT-PCR), substantia nigra (SN), thiobarbituric acid-reactive substances (TBARS), tyrosine hydroxylase (TH), tumor necrosis factor alpha (TNFα), and vascular endothelial growth factor (VEGF).

in the hippocampus. Region specific inflammation and alterations in gene expression were also seen after DEPs exposure, suggesting a selective vulnerability of specific neuronal subpopulations similarly to the selective loss of specific neurons that is typical for certain neurodegenerative diseases [69, 83]. Although strain difference is an important variable in a variety of lung injury studies, it is a widely neglected parameter in air pollution-induced CNS injury research [84, 85].

Variations in the geographic location of sample collection, and seasonal climate variations during the collection of ambient air samples are neglected oftenly as well. However, these parameters have a crucial impact on the results and should be clearly described in all studies. Use of filtered ambient air samples may, on one hand, simulate real-world exposure conditions, on the other hand, the samples also contain unidentified or unmeasurable components. Thus, the inherent heterogeneities of *in vivo* experimental paradigms show a need for standardization of test parameters that enables a more reliable comparison between studies from different laboratories. The lack of such a standardized system also hampers the translation of data from preclinical studies to humans. In particular, the anatomy of the respiratory tract and the nasal cavity, the breathing pattern (nasal breathing is obligatory for rodents), and brain anatomy differ greatly across species and impede generalization of the results. For instance, while the olfactory mucosa lines more than 50% of the surface of the nasal cavities in rodents, the human olfactory tissue is restricted to a mere 3–5%. The use of nonhuman primates would provide results more relevant to humans, but poses great ethical concerns.

4.2. Epidemiological, Postmortem, and Clinical Studies

4.2.1. Stroke. While cardiorespiratory effects of air pollution have been extensively investigated [3], only preliminary findings are available on the effects of airborne pollutants on the CNS. Stroke is one of the most prevalent CNS disorders which can be caused by air pollution. A relationship between air pollution and stroke was first reported after the Great London fog [8], but similar results were obtained from different geographic regions that include Canada, Japan, Italy, Sweden, USA, UK, France, Taiwan, and Korea [86–95]. However, a one-to-one comparison of these studies is difficult because each study measured different pollutants, investigated populations with different genetic background, or people exposed to different environmental conditions, in addition to evaluating different stroke-related parameters. Despite the experimental differences, a large number of studies demonstrated a positive correlation between stroke mortality rates, hospital admission, and outdoor pollution [87–90, 92–95], although contradictory results were reported as well [91, 96]. Interestingly, a Canadian study showed that only a specific subgroup of patients, those suffering from diabetes mellitus, was at high risk for ischemic stroke [91]. Age and gender may also differentially affect the risk of air pollution-related ischemic stroke. Elderly people and women appear to be more sensitive to the effect of air pollutants [87]. It also appears that the air pollution-related ischemic stroke risk is higher than the risk for hemorrhagic stroke [8, 86]. Hemorrhagic and ischemic strokes have distinct pathogenesis and also differ in terms of other risk factors.

Mechanistically, the correlation between air pollution and stroke might be due to the observation that fine PM and UFPs exert procoagulant effects *in vivo* [97, 98]. Yet, the stroke risk increases with both, short-term and long-term exposure to outdoor air pollution [90, 99], although the effects of long-term exposure on stroke risk are less prominent [99]. In addition to these epidemiological findings, a limited number of *in vivo* studies also support a close correlation between air pollution and stroke. For instance, SO_2 inhalation caused cerebral changes similar to the alterations resulting from middle cerebral artery occlusion (MCAO) and aggravated histological changes in ischemic brain regions [100].

Air pollution will continue to become a major health problem, especially in developing countries and rapidly growing economies. Unfortunately, booming economic development increases air pollution and related disease including stroke. Thus, there is a great demand to organize population-based and prospective studies to evaluate and to develop preventive measures against the unfavorable effect of air pollution on severe cerebrovascular diseases, such as ischemic stroke.

4.2.2. Neurodegenerative Diseases. Concomitant with a general increase in life expectancies worldwide, the incidence and prevalence of common neurodegenerative diseases grow as well, thereby increasing the financial and social burden on individuals and society. Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is characterized by extracellular deposition of amyloid-beta ($A\beta$) peptide

fibrils known as amyloid plaques and intracellular protein aggregates called neurofibrillary tangles (NFTs) [101]. AD is the most common cause of dementia in aged people, affecting 27 million people globally. Parkinson's disease (PD), the second common neurodegenerative disorder, is caused by the degeneration of dopaminergic neurons in the substantia nigra and a progressive loss of dopaminergic neurotransmission in the caudate and putamen of the neostriatum [102]. This severe movement disorder affects 1-2% of the population above the age of 50. Most AD and PD cases are sporadic, and age is the leading risk factor. The etiologies of the diseases, however, are multifactorial, and the risk factors include environmental factors and genetic predisposition. Environmental exposures to metals, air pollution, and pesticides as well as nutritional factors are common risk factors for neurodegenerative diseases [103]. Although different neurodegenerative diseases have distinct pathologies and clinical presentations, they often share common mechanisms such as protein aggregation, oxidative stress injury, neuroinflammation, microglial activation, apoptosis, and mitochondrial dysfunction, which ultimately result in the loss of specific neurons [101, 102]. Accumulating evidence suggest that exposure to air pollution can trigger these common denominators of neurodegenerative diseases and lead to neuropathology.

The first histopathological evidence for a link between air pollution and neuropathology came from studies that were carried out on animal populations that are naturally exposed to polluted urban environments in Mexico City [1]. Using light and electron microscopy, Calderón-Garcidueñas et al. reported significant inflammatory and neurodegenerative changes in the olfactory mucosa, the olfactory bulb as well as in subcortical and cortical structures in otherwise healthy mongrel canines, whereas similar changes were not evident in control groups inhabiting less-polluted rural areas [104]. Breakdown of nasal and olfactory barriers, alterations in the BBB, and degeneration of cortical neurons were observed even in animals that were younger than 1 year of age. With growing age, and therefore extended exposure, the dogs exhibited reactive astrogliosis, white matter glial cell apoptosis, ApoE immunoreactivity in vascular cells, and nonneuritic plaques and NFTs. These findings suggest an accelerated AD-like neuropathology in chronically exposed animals. Feral dogs naturally exposed to urban air pollution also showed DNA damage in olfactory and hippocampal genomic DNA [39]. Cerebral inflammatory responses were associated with the neurohistological findings as demonstrated by nuclear translocation of the neuronal NFκB p65 subunit, increased inducible nitric oxide synthase (iNOS) immunoreactivity in endothelial, glial and neuronal cells, and increased endothelial and glial COX-2 immunoreactivity [39, 104]. Animals from polluted areas exhibited deposits of diffuse amyloid plaques a decade earlier than control animals from less-polluted regions [39, 104]. Although most animals do not develop the full human pathology of AD, aged dogs are known to suffer from cognitive dysfunctions that resemble key aspects of AD [105]. The decline in executive functions and the impairment of learning and memory represent a spectrum that comprises normal aging, mild cognitive impairment, and early/mild AD in humans [106]. However, dense core neuritic plaques and NFTs could not be observed consistently in the dogs. Because of the numerous atmospheric contaminants found in the highly polluted air of Mexico City, postmortem studies on resident feral dogs could only link the neuropathology to the complex mixture of ozone, PM, LPS, and unmeasurable air pollutants [14]. Thus, whether airborne UFPs are causatively involved in the observed CNS change remain to be determined [5, 16]. However, the oil-combustion PM-associated metals nickel and vanadium, as well as UFPs were detected in the dogs brains, indicating that brain uptake of metals and UFPs may occur in natural exposure settings [11, 39].

Similar findings were recently observed in postmortem examinations of human samples and in laboratory animals [1, 14]. Adult human residents of highly polluted urban areas of Mexico City exhibit significantly higher COX-2 expression in the olfactory bulb, the hippocampus, and the frontal cortex, and greater neuronal astrocytic accumulation of $A\beta_{42}$ when compared to age-, gender-, and education-matched subjects from cities with low pollution levels [9, 13]. Based on evaluation of the clinical medical records and information from relatives and coworkers by 2 physicians, each subject was considered cognitively and neurologically fit when alive [9]. The neuropathology, however, could be observed in subjects as early as in the second decade, suggesting that neuropathologies induced by chronic exposure to high levels of air pollution share similarities with the pathology of AD [107]. Although NFTs or $A\beta$ neuritic plaques could not be observed because of the relative young age of the subjects, neuroinflamation and intraneuronal $A\beta_{42}$ accumulation in target brain areas may be compatible with a premature accelerated process preceding AD neurodegeneration. Most interestingly, a recent postmortem study on children and young adults who died suddenly has shown that lifelong exposure to air pollution is associated with neuroinflammation, altered innate immune responses, disruption of the BBB, endothelial activation, and accumulation of disease proteins ($A\beta_{42}$ and α-synuclein) in the CNS [10]. Moreover, $A\beta_{42}$-immunoreactivity was higher in brain tissue derived from carriers of the ApoE ε4 allele than those of ApoE ε3 carriers suggesting that a specific genotype constitutes a higher risk for developing AD in a polluted environment. The ApoE ε4 allele is known to contribute to a genetic predisposition for late-onset AD, although the mechanisms by which ApoE ε4 influences onset and progression of the disease are not well understood [101, 108].

The accumulation of α-synuclein in the brain of young people that were exposed to air pollution lifelong is noteworthy [10]. α-synuclein is a major component of Lewy bodies, a pathological hallmark of PD [102]. Dopaminergic neurons were found to be selectively vulnerable to DEPs both *in vitro* and *in vivo* [46, 49]. However, a recent epidemiological study from Canada did not support a direct link between the markers of traffic-generated air pollution and PD, although an association between ambient manganese pollution and the risk of physician-diagnosed PD was reported [109].

A further interesting similarity between air pollution-induced neuropathologies and neurodegenerative disorders

is the early involvement of the olfactory bulb [110]. Olfactory dysfunction, especially in ApoE ε4 carriers, can be seen from childhood in individuals that grew up in highly polluted environments. Yet, olfactory dysfunction is also among the first clinical signs of AD and PD [111]. In sporadic PD, olfactory impairment precedes motor symptoms by years and is independent of the loss of dopaminergic neurons. In AD, however, olfactory dysfunction and disease progression correlate [112].

Recent epidemiological studies combined with psychological tests support an association between chronic exposure to traffic-related air pollution and decreased cognitive function in both genders [113, 114]. Altogether, these findings warrant further and more extensive epidemiological, forensic, and toxicological studies that aim to understand the association between chronic exposure and the risk of neurodegenerative diseases development. Such efforts may lead to the development of preventative strategies for these devastating diseases in certain risk groups.

4.3. Implications for Neurodevelopment and Mental Health. Normal brain development is a complicated process that involves controlled cell proliferation, neuronal migration from their place of birth to their final location, and the establishment of specific connections between neurons and target tissues [115]. All of these processes are tightly controlled, but are also influenced by environmental conditions. Air pollutants can affect the brain at any age, but the developing brain is particularly vulnerable because of its high neuronal proliferation and differentiation rates and its immature metabolism and imperfect BBB [116]. Disturbances of developmental processes in the brain can lead to permanent abnormalities that translate into later life.

In developing embryos, the placenta serves as a barrier against many environmentally hazardous substances, but it might not be protective against all components of air pollution. Among documented hazards that affect neurodevelopment are certain industrial chemicals, maternal smoking, alcohol, certain drugs, noise, diet as well as maternal stress [117]. This section, however, only focuses on the effects of air pollutants on neurodevelopment.

Ozone is one of the best studied substances in preclinical examinations that assess the effects of exposure to an air pollutant during the prenatal period. Prenatal ozone exposure leads to permanent damage of the cerebellum [118] and disruption of the cerebellar monoaminergic system [119]. In addition, prolonged prenatal ozone exposure altered the levels neurotrophic factor in the brain. CD-1 rats showed reduced nerve growth factor levels in the hippocampus and increased brain-derived neurotrophic factor levels in the striatum when exposed to ozone [120]. Changes in neuronal responses and neuronal injury were also evaluated by immunohistochemistry in rats using c-Fos immunolabeling as a marker for neuronal activity and tyrosine hydroxylase labeling to highlight catecholaminergic neuron injury. Ozone exposure during the prenatal period induced long-lasting changes in the nucleus tractus solitarius (NTS), important respiratory control center [121].

In vivo studies have shown that prenatal exposure to DEPs can also affect brain development [122, 123]. *In utero* administration of a low dose of DEPs (1.0 mg DEP/m^3) reduced locomotor activity and dopamine turnover in the striatum [122] and affected monoamine metabolisms in a variety of brain regions generally [123]. Other air pollutants can also adversely affect the brain during development. For instance, when silica and titanium dioxide NPs were injected intravenously to pregnant mice, they could be detected in the fetal brain [124]. This suggests that NPs can cross the maternal-fetal barrier in the placenta and could cause neurotoxicity in the offspring. Using an *ex vivo* human placental perfusion model, Wick et al. found that nanosized material can cross the placenta without affecting the viability of the placental explant *per se* [125]. However, the ability of ambient air pollutants to cross the placenta needs further evaluation to understand the full spectrum of possible effects.

Epidemiological and clinical studies demonstrating a negative impact of air pollution on neural development in humans were performed in children living in Mexico City [10, 11, 107]. 181 children of African-American and Dominican origin from New York City, who had valid prenatal polycyclic aromatic hydrocarbons (PAHs) monitoring data, were evaluated for mental and psychomotor development at age 3 [126]. Prenatal exposure to high concentration of PAHs was found to be associated with a lower mental development index at age 3. A second study from Boston, examined the relation between CB and cognition [127]. Long-term exposure to CB particles was associated with a decrease in cognitive testscores, even after adjustment for socioeconomic status, birth weight, smoking, and blood lead level. These studies, however, have certain limitations, such as limited monitoring of pollutants levels and significant reduction in the sample from the original cohort over time. Moreover, the presence of confounding factors was not addressed in these studies. A third study showed that early-life exposure to emissions from indoor gas appliances is negatively correlated with neuropsychological development through the first 4 years of life. Children that carried the glutathione-S-transferase gene Val-105 allele were particularly susceptible to the effects [128]. Electrophysiological examinations confirmed disturbances in brain development as a result of exposure to polluted air. Brainstem auditory-evoked potentials (BAEPs) were compared across children from highly and lowly polluted cities [129]. Children from the highly polluted environments displayed significant delays in the central conduction time of BAEPs, suggesting that exposure to air pollution may be a risk for auditory and vestibular impairment.

Prenatal exposure to air pollutants may also constitute a risk factor for neurodevelopmental disorders such as autism and neuropsychiatric diseases such as schizophrenia. Schizophrenia is a chronic disease of the brain that is characterized by positive and negative psychiatric symptoms as well as cognitive dysfunction. The incidence of schizophrenia in the population is about 1% [130]. Schizophrenia is caused through a combination of genetic factors and environmental insults, for instance prenatal infection [131]. An increased risk for schizophrenia is evident in people inhabiting urban regions [132]. The exact reasons remain unclear, but

exposures to infectious agents or toxins from the urban environment have been suggested as possible causes. An important feature of airborne PM is that they may interact with other pathogens to serve as transporters for viruses, bacteria or molecules with infectious or antigenic properties, for instance, bacteria cell wall components [133]. Contrary results, however, were reported in a study from Finland, showing a correlation between living in rural regions and increased risk for schizophrenia [134]. The authors suggested that nontraffic source of air pollution, such as firewood, could have been a possible risk factor [134].

Autism on the other hand is a neurodevelopmental disorder that is characterized by impairments in social interaction, verbal and nonverbal communication, and repetitive behavior [135]. The prevalence for autism in the general population has been reported to range from 0.2 to 0.6% with an increasing trend over the recent years. Although, the exact etiology of autism is still unclear, genetic, environmental, and social factors may contribute to the development of the disease [136]. Maternal exposure to air pollution during the prenatal period may also be a risk factor. 284 autistic children and 657 healthy controls were examined in a San Francisco study that evaluated the possible effects of air pollution on autism development [137]. An association was found between the estimated concentrations of metals and solvents in the ambient air around the birth residence and autism. An association was also found between autism and residential proximity to freeways during the third trimester [138]. These alerting results suggest that subtle health effects, such as functional delays in brain maturation and impairment of neurobehavioral competences, should be included in studies of chronic effects of urban air pollution [116].

As derived from studies on the aged population, air pollution also has adverse effects on mental health during adulthood [113, 114]. A study by Chen and Schwartz demonstrated that neurobehavioral effects are associated with long-term exposure to ambient PM and ozone in adults [139]. Further longitudinal studies are urgently needed to fully explore the relationship between long-term exposure and neurobehavioral changes and subsequent development of neurocognitive impairment, such as cognitive decline and dementia. Ten human volunteers were exposed to dilute amounts of DEPs (300 $\mu g/m^3$), and brain activity was monitored by quantitative electroencephalography (EEG) showing a significant increase in the EEGs median power frequency and fast wave activity [140]. Additional studies need to determine whether other types of air pollutants elicit comparable effects on brain activity. The use of recent and more sophisticated technology, such as functional MRI and recording of event related potentials, in future studies will contribute to a better understanding of the relationship between air pollution and mental health.

5. Cellular and Molecular Mechanisms of Neuronal Injury Induced by Air Pollution

Air pollution can produce its adverse effects in the CNS through a variety of cellular and molecular mechanisms (Figure 1). Given the complex nature of polluted ambient air, CNS pathology is probably a result of the synergistic interaction of multiple pathways and mechanisms [1]. Although the exact mechanisms that are responsible for air pollution-induced neurotoxicity are poorly understood, postmortem and experimental studies suggest that air pollution causes oxidative stress, neuroinflammation, cerebrovascular damage, and cell death, which are also common features of neurodegenerative disorders. Genetic and epigenetic mechanisms might also be involved.

5.1. The Interaction of Air Pollutants with Cells and Cellular Organelles. Possible mechanisms by which air pollutants can interact with biological tissue depend on the size, the structure, and the composition of the components in the polluted air, determining their spectrum of molecular activity and entry routes. PMs can be taken up by mammalian cells in different ways, including phagocytosis, pinocytosis, passive diffusion, receptor-mediated endocytosis, direct penetration of the cell membrane, or transcytosis. Which route is taken largely depends on the physicochemical properties of the toxic components. PM that cannot enter cells directly could still interact with surface proteins and change cellular signaling and behavior.

There is a particular relationship between the particle size and the ways by which it can be taken up by cells. While the uptake of fine particles (0.1–2.5 μm diameter) by macrophages is a specific receptor-mediated process (phagocytosis) the uptake of ultrafine particles (<0.1 μm diameter) can occur by other, nonspecific mechanisms. These mechanisms may include electrostatic, van der Waals, and steric interactions and are subsumed under the term adhesive interaction, although the exact mechanisms remain to be determined [13, 33]. As mentioned before, ultrafine PMs can cross red blood cell membranes rapidly and easily; a process that appears to be mediated by an unidentified non-phagocytic mechanism [33]. Particles smaller than 100 nm could be observed in intraluminal erythrocytes that were collected from frontal lobe and trigeminal ganglia capillaries from postmortem brain tissue [10]. UFPs have a very large surface-to-volume ratio and are not enclosed by membranous organelles, which allow them to directly interact with intracellular proteins, organelles, or DNA. Such particles may reach specific organelles, such as mitochondria, lysosomes, and nuclei, where they could induce an oxidative burst within their membranes by interfering with NADPH-oxidase activity. They may also induce the release of inflammatory mediators and cytokines by the cell [13]. A recent study has shown that exposure to airborne UPMs is associated with mitochondrial damage, as reflected by an increase in the copy number of mitochondrial DNA (mtDNA) [141]. Damaged mitochondria may then contribute to increased oxidative-stress through altered ROS production and subsequently overloading the cell with ROSs, or by interfering with cellular antioxidant defense mechanisms.

Interaction of airborne PM with cellular proteins can also result in protein degradation and protein denaturation. Loss of enzyme activity and formation of autoantigens are possible consequences [142]. Environmental NPs can also significantly increase the rate of protein fibrillation, which provides

a possible link between air pollution and neurodegenerative disorders [143, 144]. If these findings can be confirmed under realistic *in vivo* conditions, it would have far-reaching consequences with respect to the mechanisms underlying neurodegenerative diseases [12]. Other key molecular pathways that are affected in neurodegenerative diseases lead to misfolding, aggregation, and accumulation of proteins in the brain [145, 146]. PMs that have the capability to enter nerve cells could contribute to these processes, so could oxidative stress that is induced by the air pollutants.

Cellular responses to oxidative stress can lead to changes in mitochondria and other organelles, notably the endoplasmic reticulum (ER), and eventually triggers the cell to enter a cell death pathway [147, 148]. Mitochondria, as regulators of cellular energy metabolism and apoptosis, are critical organelles in switching between different cellular responses leading to death or survival of the cell. Perturbed ER calcium homeostasis may also contribute to neuronal dysfunction and degeneration in neurodegenerative disorders [149]. The ER is critical for early protein biosynthesis steps of secreted and membrane proteins, which occurs in the lumen of the ER, where the ER machinery assists in their folding.

Loss of ER homeostasis triggers stress responses, which are a hallmark of many inflammatory and neurodegenerative diseases [150]. Recent studies have shown that exposure to airborne PM causes ER stress in lung tissue [151, 152]. Neurodegenerative disorders are often characterized by the aggregation and accumulation of misfolded proteins [153]. Protein folding stress in the ER may lead to activation of the unfolded protein response (UPR). Organic DEP chemicals induce an UPR and proinflammatory effects in human bronchial epithelial cell line [154]. However, the possible relationship between ER stress and exposure to air pollution has not been studied in the context of CNS cells. The interesting crosstalk between innate immune pathways and ER-signaling that regulates the intensity and duration of innate immune responses should also be considered in neuroinflammation-induced by air pollution [150].

5.2. Neuronal and Glial Cell Death. Air pollution-induced loss of neurons is a consistent finding in postmortem and experimental studies, and neuronal cell death may be direct or indirect via microglia activation. It is noteworthy that several different types of NPs, including ambient UFPs, target mitochondria directly [42, 142]. This can lead to disruption of the mitochondrial electron transport chain, which leads to increased superoxide radical production. Furthermore, ambient UFPs perturb the permeability of the mitochondrial transition pore, resulting in the release of proapoptotic factors and ultimately programmed cell death [142]. It has also been suggested that presynaptic terminals are a target for NP-mediated changes in glutamatergic neurotransmission, which can result in neuronal damage and finally neurodegeneration [155].

In addition to neurons, other CNS cells may also be target of air pollution. Indeed, astroglial cell death has been reported upon exposure to high dose of ozone *in vitro* [48]. As suggested by MRI studies in dogs and children of Mexico City, oligodendroglial cells may be affected by air pollution [11, 80], and prefrontal white matter hyperintense lesions were observed in these studies. However, any experimental study specifically focusing on the effects of air pollution on oligodendrocytes and myelin has not been reported so far. Brain endothelial cells and pericytes are other candidate target cells. Exposure to DEPs resulted in endothelial activation and dysfunction in rat brain capillaries, but cell viability was not assessed in the study [47].

Besides apoptosis and necrosis, additional cell death mechanisms may also contribute to air pollution-induced CNS injury. Increased levels of autophagic vacuoles were observed upon exposure of cells to NMs *in vitro* [156]. Autophagy is a cellular process for the disposal of damaged organelles or denatured proteins through a lysosomal degradation pathway. The interaction of NMs with the autophagy pathway may be disruptive to neurons, leading to severe structural changes and ultimately cell death. Impaired autophagy is also implicated in the pathogenesis of neurodegenerative disorders [157]. However, the exact role of autophagy in CNS injury induced by air pollutants remains to be identified.

5.3. Oxidative Stress, DNA Damage, and Genotoxicity. Oxidative stress refers to an imbalance between the production of ROS and the cells ability to detoxify reactive intermediates or to repair cellular damage caused by ROS. They are highly reactive molecules because of their unpaired electrons and form as natural byproducts of a cell normal oxygen metabolism. They also fulfill important roles in cell signaling and homeostasis. However, during times of environmental stress such as air pollution, ROS levels can increase dramatically, resulting in significant damage to cellular components, including proteins, lipids, and DNA. Disturbances in the normal redox-state of tissues can cause toxic effects through the production of peroxides and free radicals (e.g., chemical species that contains one or more unpaired electrons). The two most important oxygen-derived free radicals are superoxide and hydroxyl radicals. Free radicals are important for a number of biological processes, such as the elimination of bacteria by phagocytic cells. Excessive ROS accumulation, however, poses a challenge for cell survival, and cells have developed defense mechanisms against excessive amounts of ROS that include antioxidant enzymes (superoxide dismutase, catalase, and glutathione reductase, glutathione peroxides) and antioxidant molecules (glutathione, taurine, selenium, vitamins E and C).

Under normal conditions, ROS are generated at low concentrations and are easily neutralized by cellular antioxidant defenses such as glutathione (GSH) and antioxidant enzymes [142]. However, under conditions of excess ROS production, antioxidant and detoxification enzymes (phase II enzymes) are induced. The expression of genes that encode these enzymes contain antioxidant response elements (ARE) in their promoter regions, which contains a binding site for the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription factor [158]. At moderate levels of oxidative stress, the Nrf2 protective response pathway is activated; resulting in mitogen-activated protein kinase- (MAPK)

and NFκB- (a redox-sensitive transcription factor) induced proinflammatory responses [142]. Increased intracellular calcium levels also mediate the activation of these signaling pathways. At high levels of oxidative stress, perturbation of the mitochondrial permeability transition pore and the electron transfer chain cause apoptotic and necrotic cell death. Nrf2 regulates the expression of numerous cytoprotective genes that function to detoxify reactive species produced during ambient air pollutant metabolic reactions, highlighting the important role of Nrf2 in the defense against air pollutant-induced toxicity [158]. Dysfunction of Nrf2 may also be a risk factor for neurodegenerative diseases such as PD [159]. However, the possible role of Nrf2 in air pollution-induced injury has not yet been studied in the context of CNS.

The brain is especially vulnerable to oxidative stress injury because of its high metabolic activity, its low activity of antioxidant enzymes (superoxide dismutase and catalase), its low content of endogenous radical scavengers, such as vitamin C, its high cellular content of lipids and proteins, and its high amounts of redox metals such as iron and copper which can act as a potent catalyst for ROS production [103, 160]. Oxidative stress has been consistently linked to aging-related neurodegenerative diseases leading to the generation of lipid peroxides, carbonyl proteins, and oxidative DNA damage in tissue samples from affected brains [103, 161]. Metals, pesticides, and air pollutants, all of which have been associated with neurodegeneration share a common feature, namely, their capacity to lead to increased production of reactive oxygen and nitrogen species. Although each pollutant has its own mechanism of toxicity, several air pollutants, like ozone, sulfur dioxide, volatile organic compounds, and PM, are oxidants that can act directly on cellular components and disturb physiological functions [17, 162–164]. Some of these pollutants go through a series of metabolic reactions catalyzed by phase II enzymes, in order to be detoxified and excreted. These reactions involve chemical modifications, like oxidation, to increase the solubility of the original compound so that it can be excreted. During these metabolic reactions, many reactive intermediates, particularly ROS, are produced [158]. Both postmortem and *in vivo* studies have recently revealed a link between oxidative stress and air pollution-induced CNS injury [10, 47, 71, 73, 78]. For toxicological screening studies, more refined approaches, for example, the use of nanosensors to detect ROS generation by NPs will emerge with time [32, 142].

Exposure to combustion particles is consistently associated with oxidative damage to DNA and lipids in humans detected from leukocytes, plasma, urine, and exhaled breath [165, 166]. The evaluation of apurinic/apyrimidinic sites in nasal and brain genomic DNA in healthy dogs naturally exposed to urban pollution in Mexico City showed DNA damage suggesting a link to air pollution [39]. DNA damage is also crucial in aging and in age-related disorders, such as AD. The processes involved in particle-induced genotoxicity remain poorly understood, because the particles are uniquely complex and of diverse physicochemical characteristics [16]. Interestingly, a recent study evaluating the link between gaseous air pollutants and brain cancer mortality did not provide evidence for an increased risk of mortality due to air pollution [167].

5.4. Microglial Activation. Microglia, the macrophage-like cells of CNS, are the principal players in the brain's innate immune response. They are the immunocompetent cells of the brain that continuously survey their environment with highly motile extensions [168]. Microglial cells normally provide tissue maintenance and immune surveillance to the brain and exert a neuroprotective role by their ability to phagocytose aggregated disease proteins and pathogens and to secrete neurotrophic factors. Microglia cells rapidly change their cell morphology in response to any disturbance of nervous system homeostasis and are then referred to as activated on the basis of morphological changes and expression of cell surface antigens [168]. Microglial activation is the main cellular event during neuroinflammation. The activation of microglia results in the production and release of a myriad of inflammatory cascade mediators, including Nitric oxide (NO), chemokines, proinflammatory cytokines, ROS, and reactive nitrogen species (RNS) those are deleterious to the CNS [169]. Microglial activation and inflammation are also associated with progressive neuronal apoptosis in human neurodegenerative diseases [170–172]. However, it is not clear whether activation of microglia and the inflammatory responses play a role in the cause of the disease or whether cell activation is a response to the early changes associated with the disease process.

Microglia are also activated in response to aggregated disease proteins (Aβ and α-synuclein), bacterial endotoxins (LPS), proinflammatory cytokines, MMP-3 released from apoptotic neurons, and environmental neurotoxins [1, 173]. An important molecular component of microglial responses is the toll-like receptor 4 (TLR4), a pathogen-receptor known to initiates an inflammatory cascade in response to various CNS stimuli [174]. LPS, as the prototypical endotoxin, binds to a CD14/TLR4/MD2 receptor complex and enables TLR4 signaling. Human autopsy studies showed evidence for increased CD14 expression in response to chronic exposure to high levels of air pollution, indicating an activation of either infiltrating monocytes or the resident microglial cells [112]. Similar findings were observed in brain tissue of young healthy dogs exposed to air pollution [80]. As demonstrated by morphological changes and increased superoxide production in a neuron-glia cell culture system, DEPs can also activate microglia *in vitro* [46]. Furthermore, neuron-glia cocultures treated with DEP showed selective dopaminergic neurotoxicity that only occurred in the presence of microglia, indicating that activated microglia cells mediate the neuronal damage. Neuron-glia co-cultures derived from mice lacking functional NADPH oxidase, the enzyme responsible for extracellular superoxide production, were insensitive to DEP-induced neurotoxicity, indicating that microglia-derived ROS mediate DEP-induced dopaminergic neurotoxicity [1, 46]. Interestingly, cytochalasin D, a phagocytosis inhibitor, reduced DEP-induced superoxide production in enriched-microglia cultures, implying that DEP is phagocytized by microglia to trigger the production of superoxide [46], whereas UFPs themselves can inhibit phagocytosis in

alveolar macrophages [175]. This difference may result from the differences in cell or particle type. A very recent *in vivo* study could also demonstrate DEP-induced microglial activation, neuroinflammation, and dopaminergic neurotoxicity [49].

Metals associated with air pollution are also able to activate microglia. Manganese, a component of industrial-derived air pollution, is able to activate rat microglia *in vitro* [176]. Microglial activation by manganese chloride also induces dopaminergic neurotoxicity *in vitro* and application of antioxidants, such as superoxide dismutase/catalase, glutathione, NAC, or inhibitors of NO biosynthesis significantly protected dopaminergic neurons against damage [177]. LPS on the other hand amplifies neurotoxicity induced by activated microglia in response to manganese chloride [178]. Interestingly, the responses of microglia and astroglia to these activators differ, although both cell types are regarded as cellular components of the brain's innate immune system.

5.5. Neuroinflammation and Inflammasome Activation. Neuroinflammation is a complex and innate response of neural tissue against harmful stimuli such as pathogens, damaged cells, and other irritants within the CNS. A crucial component of innate immunity in the CNs involves the production of proinflammatory cytokines mediated by inflammasome signaling [179]. The innate immune cells in the CNS, microglia and astrocytes, express pattern-recognition receptors (PRRs), for example, TLR4, which participate in the assembly and activation of the inflammasome [179]. The inflammasome itself is a multiprotein complex that consists of caspase 1, PYCARD, NALP (a NOD-like receptor serving as a PRR), and sometimes caspase 5 or caspase 11 [180]. Nucleotide-binding domain, leucine-rich repeat, pyrin domain containing 3 (NLRP3) are a key component of the inflammasome complex, which also includes ASC (apoptotic speck-containing protein with a card) and procaspase-1 [181]. The exact composition of the inflammasome depends on the activator which initiates its assembly, that is, dsRNA will trigger one inflammasome composition, whereas asbestos will induce the assembly of a different variant. The inflammasome promotes the maturation of inflammatory cytokines such as IL-1β and interleukin 18 (IL-18). It has also been shown to induce cell pyroptosis, a process of programmed cell death that is distinct from apoptosis [181]. The inflammasome orchestrates the activation of caspase precursors, which in turn, cleave the precursor forms of the cytokines as IL-1β, IL-18 and interleukin-33 (IL-33), which triggers an inflammatory response, or the release of toxins from glial and endothelial cells [179].

Inflammasome activation was recently shown to be induced in acute brain injury as well, thus the NLRP1 inflammasome may constitute an important component of the CNSs' response to traumatic brain injury [182]. An inflammasome complex also forms after experimental focal brain ischemia as could be demonstrated by immunohistochemical analysis of inflammasome proteins in neurons, astrocytes, microglia, and macrophages [183]. The NLRP3 inflammasome also plays an important role in an experimental model of MS, which is mediated by caspase-1 and IL-18 [184]. Although it has recently been shown that the NALP3 inflammasome is involved in the innate immune response to Aβ in microglia [185], the specific pathophysiologic role of the inflammasome in neurodegenerative disorders still remains to be clarified [186].

The organic substances adsorbed onto airborne Asian sand dust activate the NALP3 inflammasome in macrophage cell lines and murine lung [187]. Exposure of macrophages to CB induces inflammasome activation and pyroptosis [188]. The identification of pyroptosis as a cellular response to carbon NP exposure is novel and has important consequences for environmental and health-related issues. Another study showed that TiO_2 and SiO_2 NPs activate the NLRP3 inflammasome in cultured keratinocytes, murine lung, and dendritic cells [189, 190]. Whether air pollutants induce inflammasome activation in CNS and neuroglial cells remains to be identified.

5.6. Reactive Astrogliosis. Astrocytes are characteristic star-shaped glial cells that outnumber neurons in the brain about fivefold. They perform many functions, including biochemical support of cerebral endothelial cells that form the BBB, provision of nutrients to the nervous tissue, maintenance of extracellular ion balance, buffering of excess neurotransmitters, secretion of neurotrophic factors, control of cerebral blood flow, supporting neurogenesis as well as repair of injured brain and spinal cord [191]. Reactive astrogliosis is a ubiquitous feature of CNS pathologies [192]. At later stages of CNS disorders, astrocytes become activated and contribute to neuroinflammation and neurodegeneration. Astroglia were reported to be activated in humans that were chronically exposed to high levels of air pollution, as evidenced by enhanced glial fibrillary acidic protein (GFAP) expression [9, 10]. Animal studies investigating ozone exposure showed that astroglial cells that are located close to brain capillaries have enhanced expression of IL-6 and TNFα [79] or are increased in number [193]. However, it is unclear whether the astroglia respond to components of air pollution, to the inflammation, and oxidative stress produced from other cell types or to cellular damage [1].

5.7. Impacts on the Blood-Brain Barrier. The BBB is the major site of controlled blood-CNS exchange. This physical barrier protects the CNS from potential toxins and pathogenic agents. An intact BBB is important for the proper functioning of the CNS by actively controlling cellular and molecular trafficking between the systemic circulation and the brain parenchyma [194]. Cerebral endothelial cells have luminal tight junctions that form the physical barrier of the inter-endothelial cleft. Endothelial cell are covered on the outside by a basement membrane, which also surrounds pericytes. Around these structures end-feet processes from nearby astrocytes can be found which seal the BBB additionally [195]. The BBB integrity is impaired in many common CNS disorders such as AD, PD, and stroke [196]. Activation or damage of the various cellular components of the BBB facilitates leukocyte infiltration leading to CNS injury. Systemic inflammation induced by inhaled air pollutants can disturb

the integrity of the BBB through the effects of circulating proinflammatory cytokines and LPS on cerebral endothelial cells [1]. Furthermore, an increase in ROS is a common trigger for many downstream pathways that directly mediate BBB compromise such as oxidative damage, tight junction modification and matrix metalloproteinases (MMP) activation [197]. Air-borne particulate matter has been identified both in human brain capillaries and in the brain parenchyma, although the exact transport mechanisms are unclear [10]. Additionally, increased expression of intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) was observed in cerebral vasculature suggesting endothelial activation. As demonstrated by an *ex vivo* study, DEPs induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation in the rat brain capillaries [47]. These findings suggest that the BBB is an important target for air pollutants. Therapeutic strategies that aim to change BBB permeability may combat neurotoxic effects of air pollutant on the CNS.

5.8. Gene-Air Pollution Interaction and Epigenetic Mechanisms. Individual differences that were observed upon exposure to the same polluted ambient air suggest that genetic susceptibility is likely to play a role in response to air pollution [198]. Gene-air pollution interaction was extensively studied in pulmonary and cardiac disorders [198, 199]. There are, however, only a limited number of studies that address gene-air pollution interaction in CNS injury. The Apo ε4 allele shows an amplifier effect on brain injury caused by exposure to air pollution [107]. Air pollution-induced olfactory dysfunction, also an early indicator for neurodegeneration, was higher in Apo ε4 carriers [110] and experimental *in vivo* studies showed that APOE$^{-/-}$ mice were more vulnerable to neuropathology induced by air pollution [66–68].

Another susceptibility gene for the effects of air pollution in the brain may be the glutathione-S-transferase gene (GSTP1) because of its important role as radical scavenger [128]. Adverse effects of exposure to nitrogen dioxide on cognitive function are more significant in children with any GSTP1 Val-105 allele. Since oxidative stress, and inflammatory processes are common denominators of air pollution-induced neuropathology, oxidative stress and inflammatory pathway genes including Glutathione S-transferase Mu 1(GSTM1), GSTP1, NAD(P)H dehydrogenase quinone 1(NQO1), TNF, and TLR4 are further logical candidates for the study of the association with the susceptibility to air pollutants [200].

Air pollutants can change gene expression through a broad array of gene regulatory mechanisms. Epigenetics is a posttranscriptional control mechanism in gene regulation. Changes in DNA methylation and histone acetylation leads to imprinting, gene silencing, and suppression of gene expression without altering the sequence of the silenced genes [201]. Epigenetic alternations are often involved in the pathogenesis of neurological disorders [202, 203]. Air pollution related neurological damage may occur via epigenetic effects and could be demonstrated [204, 205]. Nano and microsized SiO_2 exposure significantly decreased genomic DNA methylation and levels of the related methyl transferase in normal HaCaT epithelial cells line [205]. DEP exposure induces Cox-2 gene expression by increasing histone H4 acetylation and histone deacetylase 1 (HDAC1) degradation in bronchial epithelial cells [204]. Similar results were also obtained from *in vivo* studies [206]. Exposure of inbred mice to particulate air pollution caused hypermethylation in spermatogonial stem cells. Human studies showed that either short- or long-term exposure to air pollution in elderly can cause hypomethylation in peripheral lymphocytes [207, 208]. In addition, higher exposure to traffic-related air pollution is associated with shorter leukocyte telomeres, which is a sign of biological aging [209]. Further studies are necessary to clarify in how much epigenetic changes contribute to neurological symptoms caused by air pollution.

6. Conclusions and Future Prospects

Air pollutants have been, and continue to be, major contributing factors to chronic diseases and mortality, thereby dramatically impacting public health. Air pollution is a global problem and has become one of the major issues of public health as well as climate and environmental protection. The effects of air pollutants are thus at a high level of interest for scientific, governmental, and public communities. An increasing number of people are exposed to a complex mixture of inhalable NPs and toxic chemicals occupationally or as a result of man made and natural disasters, such as war, fires, and volcanic eruptions [210, 211]. Air pollution is increasingly recognized as an important and modifiable determinant of cardiovascular and respiratory diseases in urban communities [3, 16]. Although adverse cardiopulmonary outcomes have been the focus of many studies, air pollution-related damage to the CNS has been widely neglected. However, there is mounting evidence that air pollution also contributes to CNS damage or increased progression of neurodegenerative disorders.

The data discussed as part of this critical update highlight that UFPs rapidly translocate from the lungs into the cells and into the blood circulation. There is good evidence that oxidative stress occurs in other organs, such as the heart and the brain. The breadth, strength, and consistency of the preclinical and clinical evidence provide a compelling argument that air pollution, especially traffic-derived pollution, causes CNS damage and that there is a clear link between air pollution and neurological diseases. Airborne particles cause neuropathology, which seem to be mediated by direct or indirect proinflammatory and oxidative responses. Both, the physical characteristics of the particle itself and toxic compounds adsorbed on the particle may be responsible for the damage. The time of exposure has a key role in damage. Minimum doses of pollution can be handled by the organism when this exposure is acute, but the same doses administered chronically lead to an oxidative stress state that can produce neurodegeneration. Astroglia, cerebral endothelial cells, and microglia in particular respond to components of air pollution with chronic activation, inflammation, and oxidative

stress [1]. CNS effects can be chronic, can begin in early childhood, and may accumulate with age [1].

Given the enormous complexity of the CNS and the complex nature of air pollution, the resulting CNS pathology can have many underlying causes and pathways and could be due to synergistic interaction of multiple pathways and mechanisms making it difficult to pinpoint a clear stimulus-response relationship. While epidemiological data link increased risk for stroke, MS, and PD to the exposure to specific air pollutants, further experimental and mechanistic studies aiming at the association between the components of air pollution and the development of CNS diseases are of pressing importance for mental health [1]. The adverse effects of the complex mixtures of polluted air components are poorly understood. For instance, the contribution of direct effects of airborne UFPs to CNS injury remains to be worked out in detail, and data on the presence of UFPs in the human CNS are still lacking to date. The biological studies can be strengthened by the use of recent discovery tools and platforms, such as proteomics and genomics, to develop biomarkers for toxicity screening [142]. The main problems that are encountered in testing air pollutants toxicity in humans are dosimetry, the lack of appropriate standardized protocols, and good quantitative descriptions of real-world exposure conditions [60, 142]. Novel detection methods need to be developed for exposure assessment and dosimetry calculation.

Our current knowledge provides a basis for much more extensive epidemiological, forensic, and toxicological studies aimed at identifying the underlying mechanisms of neural damage, and strengthening of the association between chronic exposure to air pollutants, and the risk of developing neurological diseases. However, epidemiologic and observational data are limited by imprecise measurements of pollution exposure, the potential of environmental, and social factors to confound the apparent associations. Since genetic susceptibility is likely to play a role in response to air pollution, gene-environment interaction studies can be a tool to explore the mechanisms and the importance of molecular pathways for the association between air pollution and CNS damage [198]. Inconsistencies between studies sometimes prevent us from drawing firm conclusions. The limited sample size of most studies, difficulty in quantifying exposure, providing a qualitative description of active components from complex environmental air samples, method of ascertainment, time of measurement, and collinearity between pollutants make difficult to use for the study of gene by gene interactions [200]. More studies and more intensive collaborationsare needed to generate larger and more diverse cohorts and standardized data that would allow us to draw stronger conclusions [198]. The roles of gene-air pollution interactions and epigenetic mechanisms need to be considered [200]. Better understanding of the mediators and mechanisms of CNS injury due to air pollution will help to develop preventive and treatment strategies for the protection of individuals at risk. Improving air quality standards, minimizing personal exposures, and the redesign of engine and fuel technologies will also reduce air pollution and its consequences for neurological morbidity and mortality.

Abbreviations

Aβ:	Amyloid-beta
AD:	Alzheimer's disease
ARE:	Antioxidant response element
ApoE:	Apolipoprotein E
ASC:	Apoptosis-associated speck-like protein containing a CARD
BAEPs:	Brainstem auditory evoked potentials
BBB:	Blood-brain barrier
CB:	Carbon black
CNS:	Central nervous system
CAPs:	Concentrated ambient air particles
COX-2:	Cyclooxygenase-2
DEPs:	Diesel exhaust particles
EEG:	Electroencephalography
ER:	Endoplasmic reticulum
ENPs:	Engineered nanoparticles
GFAP:	Enhanced glial fibrillary acidic protein
GSH:	Glutathione
GSTP1:	Glutathione-S-transferase gene
GSTM1:	Glutathione S-transferase Mu 1
HDAC1:	Histone deacetylase 1
iNOS:	Inducible nitric oxide synthase
IL-6:	Interleukin-6
IL-1β:	Interleukin-1beta
IL-18:	Interleukin 18
ICAM:	Intercellular adhesion molecule
LTA:	Lipoteichoic acid
MMP:	Matrix metalloproteinases
MCAO:	Middle cerebral artery occlusion
mtDNA:	Mitochondrial DNA
MAP:	Mitogen-activated protein
MAPK:	Mitogen-activated protein kinase-
MS:	Multiple sclerosis
LPS:	Lipopolysaccharide
NQO1:	NAD(P)H dehydrogenase quinone 1
NMs:	Nanomaterials
NP:	Nano-sized particulate
NAC:	N-acetylcysteine
NFTs:	Neurofibrillary tangles
NO:	Nitric oxide
NFκB:	Nuclear factor kappa B
Nrf2:	Nuclear factor (erythroid-derived 2)-like 2
NLRP3:	Nucleotide-binding domain, leucine-rich repeat, pyrin domain containing 3
NTS:	Nucleus tractus solitarius
PRRs:	Pattern Recognition Receptors
PD:	Parkinson's disease
PM:	Particulate matter
PAHs:	Polycyclic aromatic hydrocarbons
RNS:	Reactive nitrogen species
ROS:	Reactive oxygen species
ROFA:	Residual oil fly ash
WHO:	World Health Organization
TLR4:	Toll-like receptor 4
TNFα:	Tumor necrosis factor alpha
UFPs:	Ultrafine
UPR:	Unfolded protein response

VEGF: Vascular endothelial growth factor
VCAM: Vascular cell adhesion molecule
VLM: Ventrolateral medulla.

References

[1] M. L. Block and L. Calderón-Garcidueñas, "Air pollution: mechanisms of neuroinflammation and CNS disease," *Trends in Neurosciences*, vol. 32, no. 9, pp. 506–516, 2009.

[2] K. M. Narayan, M. K. Ali, and J. P. Koplan, "Global noncommunicable diseases—were worlds meet," *The New England Journal of Medicine*, vol. 363, no. 13, pp. 1196–1198, 2010.

[3] N. L. Mills, K. Donaldson, P. W. Hadoke et al., "Adverse cardiovascular effects of air pollution," *Nature Clinical Practice Cardiovascular Medicine*, vol. 6, no. 1, pp. 36–44, 2009.

[4] H. Chen, M. S. Goldberg, and P. J. Villeneuve, "A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases," *Reviews on Environmental Health*, vol. 23, no. 4, pp. 243–297, 2008.

[5] G. Oberdörster and M. J. Utell, "Ultrafine particles in the urban air: to the respiratory tract—and beyond?" *Environmental Health Perspectives*, vol. 110, no. 8, pp. A440–A441, 2002.

[6] A. Elbaz and F. Moisan, "Update in the epidemiology of Parkinson's disease," *Current Opinion in Neurology*, vol. 21, no. 4, pp. 454–460, 2008.

[7] K. Lauer, "Environmental risk factors in multiple sclerosis," *Expert Review of Neurotherapeutics*, vol. 10, no. 3, pp. 421–440, 2010.

[8] F. J. Mateen and R. D. Brook, "Air pollution as an emerging global risk factor for stroke," *Journal of the American Medical Association*, vol. 305, no. 12, pp. 1240–1241, 2011.

[9] L. Calderón-Garcidueñas, W. Reed, R. R. Maronpot et al., "Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution," *Toxicologic Pathology*, vol. 32, no. 6, pp. 650–658, 2004.

[10] L. Calderón-Garcidueñas, A. C. Solt, C. Henríquez-Roldán et al., "Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults," *Toxicologic Pathology*, vol. 36, no. 2, pp. 289–310, 2008.

[11] L. Calderón-Garcidueñas, A. Mora-Tiscareño, E. Ontiveros et al., "Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs," *Brain and Cognition*, vol. 68, no. 2, pp. 117–127, 2008.

[12] G. Oberdörster, A. Elder, and A. Rinderknecht, "Nanoparticles and the brain: cause for concern?" *Journal of Nanoscience and Nanotechnology*, vol. 9, no. 8, pp. 4996–5007, 2009.

[13] A. Peters, B. Veronesi, L. Calderón-Garcidueñas et al., "Translocation and potential neurological effects of fine and ultrafine particles a critical update," *Particle and Fibre Toxicology*, vol. 3, article 13, 2006.

[14] S. M. MohanKumar, A. Campbell, M. Block, and B. Veronesi, "Particulate matter, oxidative stress and neurotoxicity.," *Neurotoxicology*, vol. 29, no. 3, pp. 479–488, 2008.

[15] L. Craig, J. R. Brook, Q. Chiotti et al., "Air pollution and public health: a guidance document for risk managers," *Journal of Toxicology and Environmental Health A*, vol. 71, no. 9-10, pp. 588–698, 2008.

[16] C. Terzano, F. Di Stefano, V. Conti, E. Graziani, and A. Petroianni, "Air pollution ultrafine particles: toxicity beyond the lung," *European Review for Medical and Pharmacological Sciences*, vol. 14, no. 10, pp. 809–821, 2010.

[17] F. Mazzoli-Rocha, S. Fernandes, M. Einicker-Lamas, and W. A. Zin, "Roles of oxidative stress in signaling and inflammation induced by particulate matter," *Cell Biology and Toxicology*, vol. 26, no. 5, pp. 481–498, 2010.

[18] P. T. Scheepers and R. P. Bos, "Combustion of diesel fuel from a toxicological perspective I. Origin of incomplete combustion products," *International Archives of Occupational and Environmental Health*, vol. 64, no. 3, pp. 149–161, 1992.

[19] J. J. de Hartog, G. Hoek, A. Peters et al., "Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study," *American Journal of Epidemiology*, vol. 157, no. 7, pp. 613–623, 2003.

[20] H. E. Wichmann, C. Spix, T. Tuch et al., "Daily mortality and fine and ultrafine particles in Erfurt, Germany part I: role of particle number and particle mass," *Research Reports*, no. 98, pp. 5–86, 2000.

[21] G. Oberdorster, R. M. Gelein, J. Ferin, and B. Weiss, "Association of particulate air pollution and acute mortality: involvement of ultrafine particles?" *Inhalation Toxicology*, vol. 7, no. 1, pp. 111–124, 1995.

[22] A. Peters, H. E. Wichmann, T. Tuch, J. Heinrich, and J. Heyder, "Respiratory effects are associated with the number of ultrafine particles," *American Journal of Respiratory and Critical Care Medicine*, vol. 155, no. 4, pp. 1376–1383, 1997.

[23] A. Furuyama, S. Kanno, T. Kobayashi, and S. Hirano, "Extrapulmonary translocation of intratracheally instilled fine and ultrafine particles via direct and alveolar macrophage-associated routes," *Archives of Toxicology*, vol. 83, no. 5, pp. 429–437, 2009.

[24] A. Nemmar, P. H. M. Hoet, B. Vanquickenborne et al., "Passage of inhaled particles into the blood circulation in humans," *Circulation*, vol. 105, no. 4, pp. 411–414, 2002.

[25] C. Cunningham, S. Campion, K. Lunnon et al., "Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease," *Biological Psychiatry*, vol. 65, no. 4, pp. 304–312, 2009.

[26] J. L. Teeling and V. H. Perry, "Systemic infection and inflammation in acute CNS injury and chronic neurodegeneration: underlying mechanisms," *Neuroscience*, vol. 158, no. 3, pp. 1062–1073, 2009.

[27] R. Dantzer, J. C. O'Connor, G. G. Freund, R. W. Johnson, and K. W. Kelley, "From inflammation to sickness and depression: when the immune system subjugates the brain," *Nature Reviews Neuroscience*, vol. 9, no. 1, pp. 46–56, 2008.

[28] K. J. Tracey, "Reflex control of immunity," *Nature Reviews Immunology*, vol. 9, no. 6, pp. 418–428, 2009.

[29] K. Genc, K. U. Tufekci, and S. Genc, "The endotoxin-induced neuroinflammation model of Parkinson's disease," *Parkinson's Disease*, vol. 2011, Article ID 487450, 25 pages, 2011.

[30] W. A. Banks and S. M. Robinson, "Minimal penetration of lipopolysaccharide across the murine blood-brain barrier," *Brain, Behavior, and Immunity*, vol. 24, no. 1, pp. 102–109, 2010.

[31] S. Sisó, M. Jeffrey, and L. González, "Sensory circumventricular organs in health and disease," *Acta Neuropathologica*, vol. 120, no. 6, pp. 689–705, 2010.

[32] A. Valavanidis, K. Fiotakis, and T. Vlachogianni, "Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms," *Journal of*

Environmental Science and Health C, vol. 26, no. 4, pp. 339–362, 2008.

[33] M. Geiser, B. Rothen-Rutishauser, N. Kapp et al., "Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells," *Environmental Health Perspectives*, vol. 113, no. 11, pp. 1555–1560, 2005.

[34] B. M. Rothen-Rutishauser, S. Schürch, B. Haenni, N. Kapp, and P. Gehr, "Interaction of fine particles and nanoparticles with red blood cells visualized with advanced microscopic techniques," *Environmental Science & Technology*, vol. 40, no. 14, pp. 4353–4359, 2006.

[35] J. Lewis, G. Bench, O. Myers et al., "Trigeminal uptake and clearance of inhaled manganese chloride in rats and mice," *NeuroToxicology*, vol. 26, no. 1, pp. 113–123, 2005.

[36] J. Wang, Y. Liu, F. Jiao et al., "Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO_2 nanoparticles," *Toxicology*, vol. 254, no. 1-2, pp. 82–90, 2008.

[37] B. Wang, W. Y. Feng, M. Wang et al., "Transport of intranasally instilled fine Fe_2O_3 particles into the brain: microdistribution, chemical states, and histopathological observation," *Biological Trace Element Research*, vol. 118, no. 3, pp. 233–243, 2007.

[38] L. Illum, "Is nose-to-brain transport of drugs in man a reality?" *Journal of Pharmacy and Pharmacology*, vol. 56, no. 1, pp. 3–17, 2004.

[39] L. Calderón-Garcidueñas, R. R. Maronpot, R. Torres-Jardon et al., "DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration," *Toxicologic Pathology*, vol. 31, no. 5, pp. 524–538, 2003.

[40] D. C. Dorman, K. A. Brenneman, A. M. McElveen, S. E. Lynch, K. C. Roberts, and B. A. Wong, "Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain," *Journal of Toxicology and Environmental Health A*, vol. 65, no. 20, pp. 1493–1511, 2002.

[41] A. Elder, R. Gelein, V. Silva et al., "Translocation of inhaled ultrafine manganese oxide particles to the central nervous system," *Environmental Health Perspectives*, vol. 114, no. 8, pp. 1172–1178, 2006.

[42] G. Oberdörster, E. Oberdörster, and J. Oberdörster, "Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles," *Environmental Health Perspectives*, vol. 113, no. 7, pp. 823–839, 2005.

[43] F. Gackière, L. Saliba, A. Baude, O. Bosler, and C. Strube, "Ozone inhalation activates stress-responsive regions of the CNS," *Journal of Neurochemistry*, vol. 117, no. 6, pp. 961–972, 2011.

[44] R. Villarreal-Calderon, R. Torres-Jardón, J. Palacios-Moreno et al., "Urban air pollution targets the dorsal vagal complex and dark chocolate offers neuroprotection," *International Journal of Toxicology*, vol. 29, no. 6, pp. 604–615, 2010.

[45] M. B. Segal, "The choroid plexuses and the barriers between the blood and the cerebrospinal fluid," *Cellular and Molecular Neurobiology*, vol. 20, no. 2, pp. 183–196, 2000.

[46] M. L. Block, X. Wu, Z. Pei et al., "Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase," *The FASEB Journal*, vol. 18, no. 13, pp. 1618–1620, 2004.

[47] A. M. Hartz, B. Bauer, M. L. Block, J.-S. Hong, and D. S. Miller, "Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier," *The FASEB Journal*, vol. 22, no. 8, pp. 2723–2733, 2008.

[48] N. B. Zhou, Z. J. Fu, and T. Sun, "Effects of different concentrations of oxygen - ozone on rats' astrocytes in vitro," *Neuroscience Letters*, vol. 441, no. 2, pp. 178–182, 2008.

[49] S. Levesque, T. Taetzsch, M. E. Lull et al., "Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity," *Environmental Health Perspectives*, vol. 119, no. 8, pp. 1149–1155, 2011.

[50] P. Sama, T. C. Long, S. Hester et al., "The cellular and genomic response of an immortalized microglia cell line (BV2) to concentrated ambient particulate matter," *Inhalation Toxicology*, vol. 19, no. 13, pp. 1079–1087, 2007.

[51] M. J. Jardim, "microRNAs: implications for air pollution research," *Mutation Research*, vol. 717, no. 1-2, pp. 38–45, 2011.

[52] B. Zhang and X. Pan, "RDX induces aberrant expression of MicroRNAs in mouse brain and liver," *Environmental Health Perspectives*, vol. 117, no. 2, pp. 231–240, 2009.

[53] T. Xia, N. Li, and A. E. Nel, "Potential health impact of nanoparticles," *Annual Review of Public Health*, vol. 30, pp. 137–150, 2009.

[54] L. Chen, R. A. Yokel, B. Hennig, and M. Toborek, "Manufactured aluminum oxide nanoparticles decrease expression of tight junction proteins in brain vasculature," *Journal of Neuroimmune Pharmacology*, vol. 3, no. 4, pp. 286–295, 2008.

[55] S. Liu, L. Xu, T. Zhang, G. Ren, and Z. Yang, "Oxidative stress and apoptosis induced by nanosized titanium dioxide in PC12 cells," *Toxicology*, vol. 267, no. 1–3, pp. 172–177, 2010.

[56] T. C. Long, J. Tajuba, P. Sama et al., "Nanosize titanium dioxide stimulates reactive oxygen species in brain microglia and damages neurons in vitro," *Environmental Health Perspectives*, vol. 115, no. 11, pp. 1631–1637, 2007.

[57] J. Wu, J. Sun, and Y. Xue, "Involvement of JNK and P53 activation in G2/M cell cycle arrest and apoptosis induced by titanium dioxide nanoparticles in neuron cells," *Toxicology Letters*, vol. 199, no. 3, pp. 269–276, 2010.

[58] J. Wu, C. Wang, J. Sun, and Y. Xue, "Neurotoxicity of silica nanoparticles: brain localization and dopaminergic neurons damage pathways," *ACS Nano*, vol. 5, no. 6, pp. 4476–4489, 2011.

[59] A. Gramowski, J. Flossdorf, K. Bhattacharya et al., "Nanoparticles induce changes of the electrical activity of neuronal networks on microelectrode array neurochips," *Environmental Health Perspectives*, vol. 118, no. 10, pp. 1363–1369, 2010.

[60] M. Dusinska, M. Dusinska, L. M. Fjellsbø et al., "Testing strategies for the safety of nanoparticles used in medical applications," *Nanomedicine*, vol. 4, no. 6, pp. 605–607, 2009.

[61] H. T. Wiogo, M. Lim, V. Bulmus, J. Yun, and R. Amal, "Stabilization of magnetic iron oxide nanoparticles in biological media by fetal bovine serum (FBS)," *Langmuir*, vol. 27, no. 2, pp. 843–850, 2011.

[62] B. D. Anson, K. L. Kolaja, and T. J. Kamp, "Opportunities for use of human iPS cells in predictive toxicology," *Clinical Pharmacology and Therapeutics*, vol. 89, no. 5, pp. 754–758, 2011.

[63] S. Durnaoglu, S. Genc, and K. Genc, "Patient-specific pluripotent stem cells in neurological diseases," *Stem Cells International*, vol. 2011, Article ID 212487, 17 pages, 2011.

[64] K. Matsumoto, F. Hyodo, K. Anzai, H. Utsumi, J. B. Mitchell, and M. C. Krishna, "Brain redox imaging," *Methods in Molecular Biology*, vol. 711, pp. 397–419, 2011.

[65] A. Winkeler, R. Boisgard, A. Martin, and B. Tavitian, "Radioisotopic imaging of neuroinflammation," *Journal of Nuclear Medicine*, vol. 51, no. 1, pp. 1–4, 2010.

[66] B. Veronesi, O. Makwana, M. Pooler, and L. C. Chen, "Effects of subchronic exposure to concentrated ambient particles: VII. Degeneration of dopaminergic neurons in Apo $E^{-/-}$ mice," *Inhalation Toxicology*, vol. 17, no. 4-5, pp. 235–241, 2005.

[67] M. T. Kleinman, J. A. Araujo, A. Nel et al., "Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways," *Toxicology Letters*, vol. 178, no. 2, pp. 127–130, 2008.

[68] A. Campbell, J. A. Araujo, H. Li, C. Sioutas, and M. Kleinman, "Particulate matter induced enhancement of inflammatory markers in the brains of apolipoprotein E knockout mice," *Journal of nanoscience and nanotechnology*, vol. 9, no. 8, pp. 5099–5104, 2009.

[69] D. Van Berlo, C. Albrecht, A. M. Knaapen et al., "Comparative evaluation of the effects of short-term inhalation exposure to diesel engine exhaust on rat lung and brain," *Archives of Toxicology*, vol. 84, no. 7, pp. 553–562, 2010.

[70] T. T. Win-Shwe, D. Mitsushima, S. Yamamoto et al., "Extracellular glutamate level and NMDA receptor subunit expression in mouse olfactory bulb following nanoparticle-rich diesel exhaust exposure," *Inhalation Toxicology*, vol. 21, no. 10, pp. 828–836, 2009.

[71] R. Guevara-Guzmán, V. Arriaga, K. M. Kendrick et al., "Estradiol prevents ozone-induced increases in brain lipid peroxidation and impaired social recognition memory in female rats," *Neuroscience*, vol. 159, no. 3, pp. 940–950, 2009.

[72] K. S. Hougaard, A. T. Saber, K. A. Jensen, U. Vogel, and H. Wallin, "Diesel exhaust particles: effects on neurofunction in female mice," *Basic & Clinical Pharmacology & Toxicology*, vol. 105, no. 2, pp. 139–143, 2009.

[73] A. C. Zanchi, C. D. Venturini, M. Saiki, P. H. Nascimento Saldiva, H. M. Tannhauser Barros, and C. R. Rhoden, "Chronic nasal instillation of residual-oil fly ash (ROFA) induces brain lipid peroxidation and behavioral changes in rats," *Inhalation Toxicology*, vol. 20, no. 9, pp. 795–800, 2008.

[74] Tin-Tin-Win-Shwe, D. Mitsushima, S. Yamamoto et al., "Changes in neurotransmitter levels and proinflammatory cytokine mRNA expressions in the mice olfactory bulb following nanoparticle exposure," *Toxicology and Applied Pharmacology*, vol. 226, no. 2, pp. 192–198, 2008.

[75] N. Pereyra-Muñoz, C. Rugerio-Vargas, M. Angoa-Pérez, G. Borgonio-Pérez, and S. Rivas-Arancibia, "Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone," *Journal of Chemical Neuroanatomy*, vol. 31, no. 2, pp. 114–123, 2006.

[76] M. Angoa-Pérez, H. Jiang, A. I. Rodríguez, C. Lemini, R. A. Levine, and S. Rivas-Arancibia, "Estrogen counteracts ozone-induced oxidative stress and nigral neuronal death," *NeuroReport*, vol. 17, no. 6, pp. 629–633, 2006.

[77] S. Rivas-Arancibia, C. Dorado-Martínez, L. Colín-Barenque, K. M. Kendrick, C. de La Riva, and R. Guevara-Guzmán, "Effect of acute ozone exposure on locomotor behavior and striatal function," *Pharmacology Biochemistry and Behavior*, vol. 74, no. 4, pp. 891–900, 2003.

[78] S. Rivas-Arancibia, C. Dorado-Martínez, G. Borgonio-Pérez et al., "Effects of taurine on ozone-induced memory deficits and lipid peroxidation levels in brains of young, mature, and old rats," *Environmental Research A*, vol. 82, no. 1, pp. 7–17, 2000.

[79] S. Araneda, L. Commin, M. Atlagich et al., "VEGF overexpression in the astroglial cells of rat brainstem following ozone exposure," *NeuroToxicology*, vol. 29, no. 6, pp. 920–927, 2008.

[80] L. Alderón-Garcidueñas, A. Mora-Tiscareño, G. Gómez-Garza et al., "Effects of a cyclooxygenase-2 preferential inhibitor in young healthy dogs exposed to air pollution: a pilot study," *Toxicologic Pathology*, vol. 37, no. 5, pp. 644–660, 2009.

[81] R. F. Phalen, L. B. Mendez, and M. J. Oldham, "New developments in aerosol dosimetry," *Inhalation Toxicology*, vol. 22, no. 2, pp. 6–14, 2010.

[82] J. E. Clougherty, "A growing role for gender analysis in air pollution epidemiology," *Environmental Health Perspectives*, vol. 118, no. 2, pp. 167–176, 2010.

[83] M. E. Gerlofs-Nijland, D. van Berlo, F. R. Cassee, R. P. Schins, K. Wang, and A. Campbell, "Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain," *Particle and Fibre Toxicology*, vol. 7, article 12, 2010.

[84] A. C. P. Elder, R. Gelein, M. Azadniv, M. Frampton, J. Finkelstein, and G. Oberdörster, "Systemic effects of inhaled ultrafine particles in two compromised, aged rat strains," *Inhalation Toxicology*, vol. 16, no. 6-7, pp. 461–471, 2004.

[85] D. R. Prows, H. G. Shertzer, M. J. Daly, C. L. Sidman, and G. D. Leikauf, "Genetic analysis of ozone-induced acute lung injury in sensitive and resistant strains of mice," *Nature Genetics*, vol. 17, no. 4, pp. 471–474, 1997.

[86] J. B. Henrotin, J. P. Besancenot, Y. Bejot, and M. Giroud, "Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France," *Occupational and Environmental Medicine*, vol. 64, no. 7, pp. 439–445, 2007.

[87] Y. C. Hong, J. T. Lee, H. Kim, and H. J. Kwon, "Air pollution: a new risk factor in ischemic stroke mortality," *Stroke*, vol. 33, no. 9, pp. 2165–2169, 2002.

[88] L. D. Lisabeth, J. D. Escobar, J. T. Dvonch et al., "Ambient air pollution and risk for ischemic stroke and transient ischemic attack," *Annals of Neurology*, vol. 64, no. 1, pp. 53–59, 2008.

[89] R. Maheswaran, R. P. Haining, P. Brindley et al., "Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study," *Stroke*, vol. 36, no. 2, pp. 239–243, 2005.

[90] K. A. Miller, D. S. Siscovick, L. Sheppard et al., "Long-term exposure to air pollution and incidence of cardiovascular events in women," *The New England Journal of Medicine*, vol. 356, no. 5, pp. 447–458, 2007.

[91] M. J. O'Donnell, J. Fang, M. A. Mittleman, M. K. Kapral, and G. A. Wellenius, "Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke," *Epidemiology*, vol. 22, no. 3, pp. 422–431, 2011.

[92] A. Oudin, U. Strömberg, K. Jakobsson, E. Stroh, and J. Björk, "Estimation of short-term effects of air pollution on stroke hospital admissions in Southern Sweden," *Neuroepidemiology*, vol. 34, no. 3, pp. 131–142, 2010.

[93] S. S. Tsai, W. B. Goggins, H. F. Chiu, and C. Y. Yang, "Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan," *Stroke*, vol. 34, no. 11, pp. 2612–2616, 2003.

[94] S. Vidale, A. Bonanomi, M. Guidotti, M. Arnaboldi, and R. Sterzi, "Air pollution positively correlates with daily stroke admission and in hospital mortality: a study in the urban area of Como, Italy," *Neurological Sciences*, vol. 31, no. 2, pp. 179–182, 2010.

[95] T. Yorifuji, I. Kawachi, T. Sakamoto, and H. Doi, "Associations of outdoor air pollution with hemorrhagic stroke mortality," *Journal of Occupational and Environmental Medicine*, vol. 53, no. 2, pp. 124–126, 2011.

[66] B. Veronesi, O. Makwana, M. Pooler, and L. C. Chen, "Effects of subchronic exposure to concentrated ambient particles: VII. Degeneration of dopaminergic neurons in Apo $E^{-/-}$ mice," *Inhalation Toxicology*, vol. 17, no. 4-5, pp. 235–241, 2005.

[67] M. T. Kleinman, J. A. Araujo, A. Nel et al., "Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways," *Toxicology Letters*, vol. 178, no. 2, pp. 127–130, 2008.

[68] A. Campbell, J. A. Araujo, H. Li, C. Sioutas, and M. Kleinman, "Particulate matter induced enhancement of inflammatory markers in the brains of apolipoprotein E knockout mice," *Journal of nanoscience and nanotechnology*, vol. 9, no. 8, pp. 5099–5104, 2009.

[69] D. Van Berlo, C. Albrecht, A. M. Knaapen et al., "Comparative evaluation of the effects of short-term inhalation exposure to diesel engine exhaust on rat lung and brain," *Archives of Toxicology*, vol. 84, no. 7, pp. 553–562, 2010.

[70] T. T. Win-Shwe, D. Mitsushima, S. Yamamoto et al., "Extracellular glutamate level and NMDA receptor subunit expression in mouse olfactory bulb following nanoparticle-rich diesel exhaust exposure," *Inhalation Toxicology*, vol. 21, no. 10, pp. 828–836, 2009.

[71] R. Guevara-Guzmán, V. Arriaga, K. M. Kendrick et al., "Estradiol prevents ozone-induced increases in brain lipid peroxidation and impaired social recognition memory in female rats," *Neuroscience*, vol. 159, no. 3, pp. 940–950, 2009.

[72] K. S. Hougaard, A. T. Saber, K. A. Jensen, U. Vogel, and H. Wallin, "Diesel exhaust particles: effects on neurofunction in female mice," *Basic & Clinical Pharmacology & Toxicology*, vol. 105, no. 2, pp. 139–143, 2009.

[73] A. C. Zanchi, C. D. Venturini, M. Saiki, P. H. Nascimento Saldiva, H. M. Tannhauser Barros, and C. R. Rhoden, "Chronic nasal instillation of residual-oil fly ash (ROFA) induces brain lipid peroxidation and behavioral changes in rats," *Inhalation Toxicology*, vol. 20, no. 9, pp. 795–800, 2008.

[74] Tin-Tin-Win-Shwe, D. Mitsushima, S. Yamamoto et al., "Changes in neurotransmitter levels and proinflammatory cytokine mRNA expressions in the mice olfactory bulb following nanoparticle exposure," *Toxicology and Applied Pharmacology*, vol. 226, no. 2, pp. 192–198, 2008.

[75] N. Pereyra-Muñoz, C. Rugerio-Vargas, M. Angoa-Pérez, G. Borgonio-Pérez, and S. Rivas-Arancibia, "Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone," *Journal of Chemical Neuroanatomy*, vol. 31, no. 2, pp. 114–123, 2006.

[76] M. Angoa-Pérez, H. Jiang, A. I. Rodríguez, C. Lemini, R. A. Levine, and S. Rivas-Arancibia, "Estrogen counteracts ozone-induced oxidative stress and nigral neuronal death," *NeuroReport*, vol. 17, no. 6, pp. 629–633, 2006.

[77] S. Rivas-Arancibia, C. Dorado-Martínez, L. Colín-Barenque, K. M. Kendrick, C. de La Riva, and R. Guevara-Guzmán, "Effect of acute ozone exposure on locomotor behavior and striatal function," *Pharmacology Biochemistry and Behavior*, vol. 74, no. 4, pp. 891–900, 2003.

[78] S. Rivas-Arancibia, C. Dorado-Martínez, G. Borgonio-Pérez et al., "Effects of taurine on ozone-induced memory deficits and lipid peroxidation levels in brains of young, mature, and old rats," *Environmental Research A*, vol. 82, no. 1, pp. 7–17, 2000.

[79] S. Araneda, L. Commin, M. Atlagich et al., "VEGF overexpression in the astroglial cells of rat brainstem following ozone exposure," *NeuroToxicology*, vol. 29, no. 6, pp. 920–927, 2008.

[80] L. Alderón-Garcidueñas, A. Mora-Tiscareño, G. Gómez-Garza et al., "Effects of a cyclooxygenase-2 preferential inhibitor in young healthy dogs exposed to air pollution: a pilot study," *Toxicologic Pathology*, vol. 37, no. 5, pp. 644–660, 2009.

[81] R. F. Phalen, L. B. Mendez, and M. J. Oldham, "New developments in aerosol dosimetry," *Inhalation Toxicology*, vol. 22, no. 2, pp. 6–14, 2010.

[82] J. E. Clougherty, "A growing role for gender analysis in air pollution epidemiology," *Environmental Health Perspectives*, vol. 118, no. 2, pp. 167–176, 2010.

[83] M. E. Gerlofs-Nijland, D. van Berlo, F. R. Cassee, R. P. Schins, K. Wang, and A. Campbell, "Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain," *Particle and Fibre Toxicology*, vol. 7, article 12, 2010.

[84] A. C. P. Elder, R. Gelein, M. Azadniv, M. Frampton, J. Finkelstein, and G. Oberdörster, "Systemic effects of inhaled ultrafine particles in two compromised, aged rat strains," *Inhalation Toxicology*, vol. 16, no. 6-7, pp. 461–471, 2004.

[85] D. R. Prows, H. G. Shertzer, M. J. Daly, C. L. Sidman, and G. D. Leikauf, "Genetic analysis of ozone-induced acute lung injury in sensitive and resistant strains of mice," *Nature Genetics*, vol. 17, no. 4, pp. 471–474, 1997.

[86] J. B. Henrotin, J. P. Besancenot, Y. Bejot, and M. Giroud, "Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France," *Occupational and Environmental Medicine*, vol. 64, no. 7, pp. 439–445, 2007.

[87] Y. C. Hong, J. T. Lee, H. Kim, and H. J. Kwon, "Air pollution: a new risk factor in ischemic stroke mortality," *Stroke*, vol. 33, no. 9, pp. 2165–2169, 2002.

[88] L. D. Lisabeth, J. D. Escobar, J. T. Dvonch et al., "Ambient air pollution and risk for ischemic stroke and transient ischemic attack," *Annals of Neurology*, vol. 64, no. 1, pp. 53–59, 2008.

[89] R. Maheswaran, R. P. Haining, P. Brindley et al., "Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study," *Stroke*, vol. 36, no. 2, pp. 239–243, 2005.

[90] K. A. Miller, D. S. Siscovick, L. Sheppard et al., "Long-term exposure to air pollution and incidence of cardiovascular events in women," *The New England Journal of Medicine*, vol. 356, no. 5, pp. 447–458, 2007.

[91] M. J. O'Donnell, J. Fang, M. A. Mittleman, M. K. Kapral, and G. A. Wellenius, "Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke," *Epidemiology*, vol. 22, no. 3, pp. 422–431, 2011.

[92] A. Oudin, U. Strömberg, K. Jakobsson, E. Stroh, and J. Björk, "Estimation of short-term effects of air pollution on stroke hospital admissions in Southern Sweden," *Neuroepidemiology*, vol. 34, no. 3, pp. 131–142, 2010.

[93] S. S. Tsai, W. B. Goggins, H. F. Chiu, and C. Y. Yang, "Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan," *Stroke*, vol. 34, no. 11, pp. 2612–2616, 2003.

[94] S. Vidale, A. Bonanomi, M. Guidotti, M. Arnaboldi, and R. Sterzi, "Air pollution positively correlates with daily stroke admission and in hospital mortality: a study in the urban area of Como, Italy," *Neurological Sciences*, vol. 31, no. 2, pp. 179–182, 2010.

[95] T. Yorifuji, I. Kawachi, T. Sakamoto, and H. Doi, "Associations of outdoor air pollution with hemorrhagic stroke mortality," *Journal of Occupational and Environmental Medicine*, vol. 53, no. 2, pp. 124–126, 2011.

[96] A. Le Tertre, S. Medina, E. Samoli et al., "Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities," *Journal of Epidemiology & Community Health*, vol. 56, no. 10, pp. 773–779, 2002.

[97] E. Kilinç, H. Schulz, G. J. Kuiper et al., "The procoagulant effects of fine particulate matter in vivo," *Particle and Fibre Toxicology*, vol. 8, article 12, 2011.

[98] A. Nemmar, M. F. Hoylaerts, and B. Nemery, "Effects of particulate air pollution on hemostasis," *Clinics in Occupational and Environmental Medicine*, vol. 5, no. 4, pp. 865–881, 2005.

[99] J. Y. Johnson, B. H. Rowe, and P. J. Villeneuve, "Ecological analysis of long-term exposure to ambient air pollution and the incidence of stroke in Edmonton, Alberta, Canada," *Stroke*, vol. 41, no. 7, pp. 1319–1325, 2010.

[100] N. Sang, Y. Yun, H. Li, L. Hou, M. Han, and G. Li, "SO_2 Inhalation contributes to the development and progression of ischemic stroke in the brain," *Toxicological Sciences*, vol. 114, no. 2, pp. 226–236, 2010.

[101] C. Ballard, S. Gauthier, A. Corbett, C. Brayne, D. Aarsland, and E. Jones, "Alzheimer's disease," *The Lancet*, vol. 377, no. 9770, pp. 1019–1031, 2011.

[102] J. M. Shulman, P. L. de Jager, and M. B. Feany, "Parkinson's disease: genetics and pathogenesis," *Annual Review of Pathology*, vol. 6, pp. 193–222, 2011.

[103] L. Migliore and F. Coppedè, "Environmental-induced oxidative stress in neurodegenerative disorders and aging," *Mutation Research*, vol. 674, no. 1-2, pp. 73–84, 2009.

[104] L. Calderón-Garcidueñas, B. Azzarelli, H. Acuna et al., "Air pollution and brain damage," *Toxicologic Pathology*, vol. 30, no. 3, pp. 373–389, 2002.

[105] M. Sarasa and P. Pesini, "Natural non-trasgenic animal models for research in Alzheimer's disease," *Current Alzheimer Research*, vol. 6, no. 2, pp. 171–178, 2009.

[106] C. W. Cotman and E. Head, "The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches," *Journal of Alzheimer's Disease*, vol. 15, no. 4, pp. 685–707, 2008.

[107] L. Calderón-Garcidueñas, M. Franco-Lira, R. Torres-Jardón et al., "Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology," *Toxicologic Pathology*, vol. 35, no. 1, pp. 154–162, 2007.

[108] J. Kim, J. M. Basak, and D. M. Holtzman, "The role of apolipoprotein E in Alzheimer's disease," *Neuron*, vol. 63, no. 3, pp. 287–303, 2009.

[109] M. M. Finkelstein and M. Jerrett, "A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities," *Environmental Research*, vol. 104, no. 3, pp. 420–432, 2007.

[110] L. Calderón-Garcidueñas, M. Franco-Lira, C. Henríquez-Roldán et al., "Urban air pollution: influences on olfactory function and pathology in exposed children and young adults," *Experimental and Toxicologic Pathology*, vol. 62, no. 1, pp. 91–102, 2010.

[111] R. L. Doty, "The olfactory system and its disorders," *Seminars in Neurology*, vol. 29, no. 1, pp. 74–81, 2009.

[112] A. Welge-Lüssen, "Ageing, neurodegeneration, and olfactory and gustatory loss," *B-ENT*, vol. 5, pp. 129–132, 2009.

[113] M. C. Power, M. G. Weisskopf, S. E. Alexeeff, B. A. Coull, A. Spiro, and J. Schwartz, "Traffic-related air pollution and cognitive function in a cohort of older men," *Environmental Health Perspectives*, vol. 119, no. 5, pp. 682–687, 2011.

[114] U. Ranft, T. Schikowski, D. Sugiri, J. Krutmann, and U. Krämer, "Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly," *Environmental Research A*, vol. 109, no. 8, pp. 1004–1011, 2009.

[115] P. J. Grandjean and P. Landrigan, "Developmental neurotoxicity of industrial chemicals," *The Lancet*, vol. 368, no. 9553, pp. 2167–2178, 2006.

[116] J. Sunyer, "The neurological effects of air pollution in children," *European Respiratory Journal*, vol. 32, no. 3, pp. 535–537, 2008.

[117] J. Julvez and P. Grandjean, "Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy," *Industrial Health*, vol. 47, no. 5, pp. 459–468, 2009.

[118] P. Rivas-Manzano and C. Paz, "Cerebellar morphological alterations in rats induced by prenatal ozone exposure," *Neuroscience Letters*, vol. 276, no. 1, pp. 37–40, 1999.

[119] R. Gonzalez-Pina, C. Escalante-Membrillo, A. Alfaro-Rodriguez, and A. Gonzalez-Maciel, "Prenatal exposure to ozone disrupts cerebellar monoamine contents in newborn rats," *Neurochemical Research*, vol. 33, no. 5, pp. 912–918, 2008.

[120] D. Santucci, A. Sorace, N. Francia, L. Aloe, and E. Alleva, "Prolonged prenatal exposure to low-level ozone affects aggressive behaviour as well as NGF and BDNF levels in the central nervous system of CD-1 mice," *Behavioural Brain Research*, vol. 166, no. 1, pp. 124–130, 2006.

[121] A. Boussouar, S. Araneda, C. Hamelin, C. Soulage, K. Kitahama, and Y. Dalmaz, "Prenatal ozone exposure abolishes stress activation of Fos and tyrosine hydroxylase in the nucleus tractus solitarius of adult rat," *Neuroscience Letters*, vol. 452, no. 1, pp. 75–78, 2009.

[122] S. Yokota, K. Mizuo, N. Moriya, S. Oshio, I. Sugawara, and K. Takeda, "Effect of prenatal exposure to diesel exhaust on dopaminergic system in mice," *Neuroscience Letters*, vol. 449, no. 1, pp. 38–41, 2009.

[123] T. Suzuki, S. Oshio, M. Iwata et al., "In utero exposure to a low concentration of diesel exhaust affects spontaneous locomotor activity and monoaminergic system in male mice," *Particle and Fibre Toxicology*, vol. 7, article 7, 2010.

[124] K. Yamashita, Y. Yoshioka, K. Higashisaka et al., "Silica and titanium dioxide nanoparticles cause pregnancy complications in mice," *Nature Nanotechnology*, vol. 6, no. 5, pp. 321–328, 2011.

[125] P. Wick, A. Malek, P. Manser et al., "Barrier capacity of human placenta for nanosized materials," *Environmental Health Perspectives*, vol. 118, no. 3, pp. 432–436, 2010.

[126] F. P. Perera, V. Rauh, R. M. Whyatt et al., "Effect of prenatal exposure to airborne polycyclic aromatic hydocarbons on neurodevelopment in the first 3 years of life among inner-city children," *Environmental Health Perspectives*, vol. 114, no. 8, pp. 1287–1292, 2006.

[127] S. F. Suglia, R. O. Wright, J. Schwartz, and R. J. Wright, "Association between lung function and cognition among children in a prospective birth cohort study," *Psychosomatic Medicine*, vol. 70, no. 3, pp. 356–362, 2008.

[128] E. Morales, J. Julvez, M. Torrent et al., "Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers," *American Journal of Epidemiology*, vol. 169, no. 11, pp. 1327–1336, 2009.

[129] L. Calderón-Garcidueñas, A. D'Angiulli, R. J. Kulesza et al., "Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials," *International Journal of Developmental Neuroscience*, vol. 29, no. 4, pp. 365–375, 2011.

[130] D. A. Lewis and J. A. Lieberman, "Catching up on schizophrenia: natural history and neurobiology," *Neuron*, vol. 28, no. 2, pp. 325–334, 2000.

[131] A. S. Brown and E. J. Derkits, "Prenatal infection and schizophrenia: a review of epidemiologic and translational studies," *The American Journal of Psychiatry*, vol. 167, no. 3, pp. 261–280, 2010.

[132] B. D. Kelly, E. O'Callaghan, J. L. Waddington et al., "Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland," *Schizophrenia Research*, vol. 116, no. 1, pp. 75–89, 2010.

[133] L. H. Tonelli and T. T. Postolache, "Airborne inflammatory factors: 'from the nose to the brain'," *Frontiers in Bioscience*, vol. 2, pp. 135–152, 2010.

[134] J. Perälä, S. I. Saarni, A. Ostamo et al., "Geographic variation and sociodemographic characteristics of psychotic disorders in Finland," *Schizophrenia Research*, vol. 106, no. 2-3, pp. 337–347, 2008.

[135] P. H. Patterson, "Maternal infection and immune involvement in autism," *Trends in Molecular Medicine*, vol. 17, no. 7, pp. 389–394, 2011.

[136] P. J. Landrigan, "What causes autism? Exploring the environmental contribution," *Current Opinion in Pediatrics*, vol. 22, no. 2, pp. 219–225, 2010.

[137] G. C. Windham, L. Zhang, R. Gunier, L. A. Croen, and J. K. Grether, "Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area," *Environmental Health Perspectives*, vol. 114, no. 9, pp. 1438–1444, 2006.

[138] H. E. Volk, I. Hertz-Picciotto, L. Delwiche, F. Lurmann, and R. McConnell, "Residential proximity to freeways and autism in the CHARGE study," *Environmental Health Perspectives*, vol. 119, no. 6, pp. 873–877, 2011.

[139] J. C. Chen and J. Schwartz, "Neurobehavioral effects of ambient air pollution on cognitive performance in US adults," *NeuroToxicology*, vol. 30, no. 2, pp. 231–239, 2009.

[140] B. Crüts, L. van Etten, H. Törnqvist et al., "Exposure to diesel exhaust induces changes in EEG in human volunteers," *Particle and Fibre Toxicology*, vol. 5, article 11, 2008.

[141] L. Hou, Z.-Z. Zhu, X. Zhang et al., "Airborne particulate matter and mitochondrial damage: a cross-sectional study," *Environmental Health A*, vol. 9, article 48, 2010.

[142] A. Nel, T. Xia, L. Mädler, and N. Li, "Toxic potential of materials at the nanolevel," *Science*, vol. 311, no. 5761, pp. 622–627, 2006.

[143] V. L. Colvin and K. M. Kulinowski, "Nanoparticles as catalysts for protein fibrillation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 21, pp. 8679–8680, 2007.

[144] S. Linse, C. Cabaleiro-Lago, W. F. Xue et al., "Nucleation of protein fibrillation by nanoparticles," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 21, pp. 8691–8696, 2007.

[145] A. M. Cuervo, E. S. Wong, and M. Martinez-Vicente, "Protein degradation, aggregation, and misfolding," *Movement Disorders*, vol. 25, supplement 1, pp. S49–S54, 2010.

[146] T. Nakamura and S. A. Lipton, "Cell death: protein misfolding and neurodegenerative diseases," *Apoptosis*, vol. 14, no. 4, pp. 455–468, 2009.

[147] G. C. Higgins, P. M. Beart, Y. S. Shin, M. J. Chen, N. S. Cheung, and P. Nagley, "Oxidative stress: emerging mitochondrial and cellular themes and variations in neuronal injury," *Journal of Alzheimer's Disease*, vol. 20, no. 2, pp. 453–473, 2010.

[148] S. Orrenius, P. Nicotera, and B. Zhivotovsky, "Cell death mechanisms and their implications in toxicology," *Toxicological Sciences*, vol. 119, no. 1, pp. 3–19, 2011.

[149] M. P. Mattson, "ER calcium and Alzheimer's disease: in a state of flux," *Science Signaling*, vol. 3, no. 114, Article ID pe10, 2010.

[150] F. Martinon and L. H. Glimcher, "Regulation of innate immunity by signaling pathways emerging from the endoplasmic reticulum," *Current Opinion in Immunology*, vol. 23, no. 1, pp. 35–40, 2010.

[151] S. Laing, G. Wang, T. Briazova et al., "Airborne particulate matter selectively activates endoplasmic reticulum stress response in the lung and liver tissues," *American Journal of Physiology*, vol. 299, no. 4, pp. C736–C749, 2010.

[152] T. L. Watterson, B. Hamilton, R. Martin, and R. A. Coulombe Jr., "Urban particulate matter causes ER stress and the unfolded protein response in human lung cells," *Toxicological Sciences*, vol. 112, no. 1, pp. 111–122, 2009.

[153] J. M. Tan, E. S. P. Wong, and K. L. Lim, "Protein misfolding and aggregation in Parkinson's disease," *Antioxidants & Redox Signaling*, vol. 11, no. 9, pp. 2119–2134, 2009.

[154] E. J. Jung, N. K. Avliyakulov, P. Boontheung, J. A. Loo, and A. E. Nel, "Pro-oxidative DEP chemicals induce heat shock proteins and an unfolding protein response in a bronchial epithelial cell line as determined by DIGE analysis," *Proteomics*, vol. 7, no. 21, pp. 3906–3918, 2007.

[155] S. V. Fedorovich, A. V. Alekseenko, and T. V. Waseem, "Are synapses targets of nanoparticles?" *Biochemical Society Transactions*, vol. 38, no. 2, pp. 536–538, 2010.

[156] S. T. Stern and D. N. Johnson, "Role for nanomaterial-autophagy interaction in neurodegenerative disease," *Autophagy*, vol. 4, no. 8, pp. 1097–1100, 2008.

[157] M. Xilouri and L. Stefanis, "Autophagy in the central nervous system: implications for neurodegenerative disorders," *CNS and Neurological Disorders Drug Targets*, vol. 9, no. 6, pp. 701–719, 2010.

[158] V. Rubio, M. Valverde, and E. Rojas, "Effects of atmospheric pollutants on the Nrf2 survival pathway," *Environmental Science and Pollution Research*, vol. 17, no. 2, pp. 369–382, 2010.

[159] K. U. Tufekci, E. Civi Bayin, S. Genc, and K. Genc, "The Nrf2/ARE pathway: a promising target to counteract mitochondrial dysfunction in Parkinson's disease," *Parkinson's Disease*, vol. 2011, Article ID 314082, 14 pages, 2011.

[160] K. Jomova, D. Vondrakova, M. Lawson, and M. Valko, "Metals, oxidative stress and neurodegenerative disorders," *Molecular and Cellular Biochemistry*, vol. 345, no. 1-2, pp. 91–104, 2010.

[161] J. C. Fernández-Checa, A. Fernández, A. Morales, M. Marí, C. R. García-Ruiz, and A. Colell, "Oxidative stress and altered mitochondrial function in neurodegenerative diseases: lessons from mouse models," *CNS and Neurological Disorders Drug Targets*, vol. 9, no. 4, pp. 439–454, 2010.

[162] S. Bolognin, L. Messori, and P. Zatta, "Metal ion physiopathology in neurodegenerative disorders," *NeuroMolecular Medicine*, vol. 11, no. 4, pp. 223–238, 2009.

[163] R. Singh, B. Kaur, I. Kalina et al., "Effects of environmental air pollution on endogenous oxidative DNA damage in humans," *Mutation Research*, vol. 620, no. 1-2, pp. 71–82, 2007.

[164] W. Yang and S. T. Omaye, "Air pollutants, oxidative stress and human health," *Mutation Research*, vol. 674, no. 1-2, pp. 45–54, 2009.

[165] P. Møller, N. R. Jacobsen, J. K. Folkmann et al., "Role of oxidative damage in toxicity of particulate," *Free Radical Research*, vol. 44, no. 1, pp. 1–46, 2010.

[166] P. MØller and S. Loft, "Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution," *Environmental Health Perspectives*, vol. 118, no. 8, pp. 1126–1136, 2010.

[167] R. McKean-Cowdin, E. E. Calle, J. M. Peters et al., "Ambient air pollution and brain cancer mortality," *Cancer Causes and Control*, vol. 20, no. 9, pp. 1645–1651, 2009.

[168] R. M. Ransohoff and A. E. Cardona, "The myeloid cells of the central nervous system parenchyma," *Nature*, vol. 468, no. 7321, pp. 253–262, 2010.

[169] M. A. Lynch, "The multifaceted profile of activated microglia," *Molecular Neurobiology*, vol. 40, no. 2, pp. 139–156, 2009.

[170] B. Cameron and G. E. Landreth, "Inflammation, microglia, and Alzheimer's disease," *Neurobiology of Disease*, vol. 37, no. 3, pp. 503–509, 2010.

[171] C. M. Long-Smith, A. M. Sullivan, and Y. M. Nolan, "The influence of microglia on the pathogenesis of Parkinson's disease," *Progress in Neurobiology*, vol. 89, no. 3, pp. 277–287, 2009.

[172] S. Mandrekar-Colucci and G. E. Landreth, "Microglia and inflammation in Alzheimer's disease," *CNS and Neurological Disorders Drug Targets*, vol. 9, no. 2, pp. 156–167, 2010.

[173] Y. S. Kim, S. S. Kim, J. J. Cho et al., "Matrix metalloproteinase-3: a novel signaling proteinase from apoptotic neuronal cells that activates microglia," *The Journal of Neuroscience*, vol. 25, no. 14, pp. 3701–3711, 2005.

[174] M. M. Buchanan, M. Hutchinson, L. R. Watkins, and H. Yin, "Toll-like receptor 4 in CNS pathologies," *Journal of Neurochemistry*, vol. 114, no. 1, pp. 13–27, 2010.

[175] W. Möller, D. M. Brown, W. G. Kreyling, and V. Stone, "Ultrafine particles cause cytoskeletal dysfunctions in macrophages: role of intracellular calcium," *Particle and Fibre Toxicology*, vol. 2, article 7, 2005.

[176] P. Zhang, A. Hatter, and B. Liu, "Manganese chloride stimulates rat microglia to release hydrogen peroxide," *Toxicology Letters*, vol. 173, no. 2, pp. 88–100, 2007.

[177] P. Zhang, T. A. Wong, K. M. Lokuta, D. E. Turner, K. Vujisic, and B. Liu, "Microglia enhance manganese chloride-induced dopaminergic neurodegeneration: role of free radical generation," *Experimental Neurology*, vol. 217, no. 1, pp. 219–230, 2009.

[178] P. Zhang, K. M. Lokuta, D. E. Turner, and B. Liu, "Synergistic dopaminergic neurotoxicity of manganese and lipopolysaccharide: differential involvement of microglia and astroglia," *Journal of Neurochemistry*, vol. 112, no. 2, pp. 434–443, 2010.

[179] S. Chakraborty, D. K. Kaushik, M. Gupta, and A. Basu, "Inflammasome signaling at the heart of central nervous system pathology," *Journal of Neuroscience Research*, vol. 88, no. 8, pp. 1615–1631, 2010.

[180] K. Schroder and J. Tschopp, "The Inflammasomes," *Cell*, vol. 140, no. 6, pp. 821–832, 2010.

[181] F. Bauernfeind, A. Ablasser, E. Bartok et al., "Inflammasomes: current understanding and open questions," *Cellular and Molecular Life Sciences*, vol. 68, no. 5, pp. 765–783, 2011.

[182] J. P. de Rivero Vaccari, G. Lotocki, O. F. Alonso, H. M. Bramlett, W. D. Dietrich, and R. W. Keane, "Therapeutic neutralization of the NLRP1 inflammasome reduces the innate immune response and improves histopathology after traumatic brain injury," *Journal of Cerebral Blood Flow and Metabolism*, vol. 29, no. 7, pp. 1251–1261, 2009.

[183] D. P. Abulafia, J. P. de Rivero Vaccari, J. D. Lozano, G. Lotocki, R. W. Keane, and W. D. Dietrich, "Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice," *Journal of Cerebral Blood Flow and Metabolism*, vol. 29, no. 3, pp. 534–544, 2009.

[184] S. Jha, S. Y. Srivastava, W. J. Brickey et al., "The inflammasome sensor, NLRP3, regulates CNS inflammation and demyelination via caspase-1 and interleukin-18," *The Journal of Neuroscience*, vol. 30, no. 47, pp. 15811–15820, 2010.

[185] A. Halle, V. Hornung, G. C. Petzold et al., "The NALP3 inflammasome is involved in the innate immune response to amyloid-β," *Nature Immunology*, vol. 9, no. 8, pp. 857–865, 2008.

[186] G. Trendelenburg, "Acute neurodegeneration and the inflammasome: central processor for danger signals and the inflammatory response?" *Journal of Cerebral Blood Flow and Metabolism*, vol. 28, no. 5, pp. 867–881, 2008.

[187] M. He, T. Ichinose, S. Yoshida et al., "Airborne Asian sand dust enhances murine lung eosinophilia," *Inhalation Toxicology*, vol. 22, no. 12, pp. 1012–1025, 2010.

[188] A. C. Reisetter, L. V. Stebounova, J. Baltrusaitis et al., "Induction of inflammasome-dependent pyroptosis by carbon black nanoparticles," *The Journal of Biological Chemistry*, vol. 286, no. 24, pp. 21844–21852, 2011.

[189] M. Winter, H.-D. Beer, V. Hornung, U. Krämer, R. P. Schins, and I. Förster, "Activation of the inflammasome by amorphous silica and TiO_2 nanoparticles in murine dendritic cells," *Nanotoxicology*, vol. 5, no. 3, pp. 326–340, 2011.

[190] A. S. Yazdi, G. Guarda, N. Riteau et al., "Nanoparticles activate the NLR pyrin domain containing 3 (Nlrp3) inflammasome and cause pulmonary inflammation through release of IL-1α and IL-1β," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 45, pp. 19449–19454, 2010.

[191] M. V. Sofroniew and H. V. Vinters, "Astrocytes: biology and pathology," *Acta Neuropathologica*, vol. 119, no. 1, pp. 7–35, 2010.

[192] M. E. Hamby and M. V. Sofroniew, "Reactive astrocytes as therapeutic targets for CNS disorders," *Neurotherapeutics*, vol. 7, no. 4, pp. 494–506, 2010.

[193] S. Rivas-Arancibia, R. Guevara-Guzmán, Y. López-Vidal et al., "Oxidative stress caused by ozone exposure induces loss of brain repair in the hippocampus of adult rats," *Toxicological Sciences*, vol. 113, no. 1, pp. 187–197, 2010.

[194] N. J. Abbott, A. A. K. Patabendige, D. E. M. Dolman, S. R. Yusof, and D. J. Begley, "Structure and function of the blood-brain barrier," *Neurobiology of Disease*, vol. 37, no. 1, pp. 13–25, 2010.

[195] E. A. Neuwelt, B. Bauer, C. Fahlke et al., "Engaging neuroscience to advance translational research in brain barrier biology," *Nature Reviews Neuroscience*, vol. 12, no. 3, pp. 169–182, 2011.

[196] A. M. Palmer, "The role of the blood-CNS barrier in CNS disorders and their treatment," *Neurobiology of Disease*, vol. 37, no. 1, pp. 3–12, 2010.

[197] P. B. L. Pun, J. Lu, and S. Moochhala, "Involvement of ROS in BBB dysfunction," *Free Radical Research*, vol. 43, no. 4, pp. 348–364, 2009.

[198] A. Zanobetti, A. Baccarelli, and J. Schwartz, "Gene-air pollution interaction and cardiovascular disease: a review," *Progress in Cardiovascular Diseases*, vol. 53, no. 5, pp. 344–352, 2011.

[199] I. A. Yang, K. M. Fong, P. V. Zimmerman, S. T. Holgate, and J. W. Holloway, "Genetic susceptibility to the respiratory effects of air pollution," *Thorax*, vol. 63, no. 6, pp. 555–563, 2008.

[200] I. Romieu, H. Moreno-Macias, and S. J. London, "Gene by environment interaction and ambient air pollution," *Proceedings of the American Thoracic Society*, vol. 7, no. 2, pp. 116–122, 2010.

[201] Q. Lu, X. Qiu, N. Hu, H. Wen, Y. Su, and B. C. Richardson, "Epigenetics, disease, and therapeutic interventions," *Ageing Research Reviews*, vol. 5, no. 4, pp. 449–467, 2006.

[202] L. Chouliaras, B. P. F. Rutten, G. Kenis et al., "Epigenetic regulation in the pathophysiology of Alzheimer's disease," *Progress in Neurobiology*, vol. 90, no. 4, pp. 498–510, 2010.

[203] S. C. F. Marques, C. R. Oliveira, C. M. F. Pereira, and T. F. Outeiro, "Epigenetics in neurodegeneration: a new layer of complexity," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 35, no. 2, 348355 pages, 2011.

[204] D. Cao, P. A. Bromberg, and J. M. Samet, "COX-2 expression induced by diesel particles involves chromatin modification and degradation of HDAC1," *American Journal of Respiratory Cell and Molecular Biology*, vol. 37, no. 2, pp. 232–239, 2007.

[205] C. Gong, G. Tao, L. Yang, J. Liu, Q. Liu, and Z. Zhuang, "SiO_2 nanoparticles induce global genomic hypomethylation in HaCaT cells," *Biochemical and Biophysical Research Communications*, vol. 397, no. 3, pp. 397–400, 2010.

[206] C. Yauk, A. Polyzos, A. Rowan-Carroll et al., "Germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 2, pp. 605–610, 2008.

[207] J. Madrigano, A. Baccarelli, M. A. Mittleman et al., "Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men," *Environmental Health Perspectives*, vol. 119, no. 7, pp. 977–982, 2011.

[208] A. Baccarelli, R. O. Wright, V. Bollati et al., "Rapid DNA methylation changes after exposure to traffic particles," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 7, pp. 572–578, 2009.

[209] J. Mccracken, A. Baccarelli, M. Hoxha et al., "Annual ambient black carbon associated with shorter telomeres in elderly men: veterans affairs normative aging study," *Environmental Health Perspectives*, vol. 118, no. 11, pp. 1564–1570, 2010.

[210] K. W. Altman, S. C. Desai, J. Moline et al., "Odor identification ability and self-reported upper respiratory symptoms in workers at the post-9/11 World Trade Center site," *International Archives of Occupational and Environmental Health*, vol. 84, no. 2, pp. 131–137, 2011.

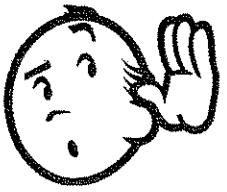
[211] S. R. Gislason, T. Hassenkam, S. Nedel et al., "Characterization of Eyjafjallajökull volcanic ash particles and a protocol for rapid risk assessment," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 18, pp. 7307–7312, 2011.

Exhibit 10

Noise Pollution

What is Noise Pollution?

- Noise pollution is unpleasant noise created by people or machines that can be annoying, distracting, intrusive, and/or physically painful.[i]
- Noise pollution can come from sources such as "...road traffic, jet planes, garbage trucks, construction equipment, manufacturing processes, lawn mowers, leaf blowers, and boom boxes."[ii]



- Noise or sound is measured in decibels (dB). An increase of about 10 dB is approximately double the increase in loudness.[iii]
- A person's hearing can be damaged if exposed to noise levels over 75 dB over a prolonged period of time. The World Health Organization recommends that the sound level indoors should be less than 30 dB.

What are the health concerns related to Noise Pollution?

- The World Health Organization (WHO) and the U.S. Environmental Protection Agency (EPA) recognize the harmful health effects of noise pollution.[iv],[v]
- According to the CDC, noise pollution is "an increasing public health problem" that can lead to a variety of adverse health effects.[vi]
- Problems related to noise include hearing loss, stress, high blood pressure, interference with speech, headaches, disturbance of rest and sleep, productivity and mental-health effects, and a general reduction in one's quality of life.[ii]

Noise Pollution and Children in the Child Care Setting

- Studies show that children in classrooms who are exposed to noise pollution experience reading delays.[vii]
- Children exposed to noise pollution learn to tune out not only noise but also the teacher's voice, which can harm their reading and language skills.[viii]
- Children have more difficulty understanding spoken language and distinguishing the sounds of speech when learning in a noisy environment.[viii]
- Children from noisier areas have higher resting blood pressure and higher stress levels.[iv]
- Children develop better concentration skills in a quiet environment.[ix]

What you can do:

Consider possible sources of noise pollution in the child care setting and identify effective ways to reduce harmful impacts:

- Try to use acoustical tile ceilings, wall coverings, and bookshelves to absorb sound.[vii]
- Close windows and doors to shut out noise from road and plane traffic.
- Place noisy activities next to each other, away from areas needing quiet for concentration on quiet, learning activities.

J. Building Acoustics 10(2), 97-106, 2003

THE EFFECTS OF NOISE ON CHILDREN AT SCHOOL: A REVIEW

Bridget M Shield[1] and Julie E Dockrell[2]

[1]*Division of Building Services, Faculty of Engineering Science and Technology, South Bank University, London SE1 0AA* shieldbm@sbu.ac.uk

[2]*Psychology and Human Development, Institute of Education, London University, 25 Woburn Square, London WC1H 0AA* j.dockrell@ioe.ac.uk

ABSTRACT

This paper reviews research on issues relating to the effects of noise on children at school. Areas covered include factors affecting speech intelligibility in the classroom; the effects of environmental and classroom noise on children's academic performance; children's annoyance due to noise; and surveys of classroom noise levels. Consistencies and discrepancies between the results of various studies are highlighted. The paper concludes by outlining some current acoustic standards for classrooms.

1. INTRODUCTION

There has been a great deal of research in the past 30 years into the effects of noise on children's learning and performance at school. This has been mainly concerned with the primary school age range (5 to 11 years), and has included studies of the effects of chronic exposure to different kinds of environmental noise and of other kinds of classroom noise. Many of these studies have examined the effects of noise on children's cognitive processing in a range of tasks and on their academic performance at school. In addition to the examination of the effects of noise on children's performance, a limited number of surveys have investigated the annoyance experienced by children in relation to their noise exposure at school.

A major effect of noise in the classroom is the reduction of speech intelligibility, and the hearing and understanding of speech by children of different ages in various noise and acoustic conditions is a related important research field.

In parallel with studies of the effects of noise at school, there have been several surveys of classroom noise and acoustics, and investigations into the way in which the acoustics of classrooms may be improved. Concern about the effects of noise on children's learning, and how they may be mitigated, is reflected in current work towards improving standards for classroom acoustics.

2. GENERAL EFFECTS OF NOISE ON CHILDREN

In the past 30 years there have been many investigations examining the relationship between noise exposure of school children and their performance in various cognitive tasks. The earlier studies were concerned mainly with external environmental noise exposure of schools, but more recently the effects of internal classroom noise have been investigated. It is generally accepted that noise has a detrimental effect upon the learning and attainments of primary school children [1,2]. At the beginning of the 1990s there were two major reviews of previous work to date in this area [3,4], both of which concluded that chronic noise exposure of young children has a particularly detrimental effect upon their reading ability. More recently Picard and Bradley [5]

have published a major review of issues related to speech intelligibility in classrooms, which covers many aspects of noise and acoustics in the classroom.

In investigating the effects of environmental noise on children a wide range of attainments and performance factors have been considered. These include literacy [6-11], attention [12-17], mathematics [7,11], and memory [18-21]. Tasks that involve language, such as reading, and those that have high cognitive processing demands involving attention, problem solving and memory appear to be those most affected by exposure to noise [4, 11, 20, 22] although such effects are not always evident [6, 7, 23-25].

In summary, it appears from this body of work that the general effects of chronic noise exposure on children are deficits in sustained attention and visual attention; poorer auditory discrimination and speech perception; poorer memory for tasks that require high processing demands of semantic material; and poorer reading ability and school performance on national standardised tests.

The types of noise which have been considered in these studies include aircraft noise [6, 7, 9, 22, 26, 27]; train noise [19, 28, 29], traffic and street noise [30, 31]. Many of these studies have focused on the effects of noise from a single source, although noise exposure in the classroom is likely to be due to a combination of internal and external sources. Despite this, there have been few studies in which the effects of irrelevant noise in the classroom have been considered. One such study is the large scale investigation by Shield and Dockrell [11] which examined, separately and in combination, the effects of environmental and classroom noise on children's perceptions of noise and performance.

3. SOURCES OF NOISE IN THE CLASSROOM

The noise in a classroom is made up of external noise which is transmitted through the building envelope, plus internally generated noise, so that children in school may be exposed to noise from a wide variety of sources. External noise is likely to consist of a range of environmental noise including noise from transportation sources, industrial noise, plant noise and the noise of people outside the school. An additional source of noise which is reputed to cause significant disturbance to teaching is the noise of rain falling on lightweight school roofs [32,33].

The predominant external noise source, particularly in urban areas, is likely to be road traffic [34,35] although aircraft noise may also affect many schools, with fewer schools exposed to railway noise.

A survey in 2000 by Shield and Dockrell [36] of noise sources outside schools in London found that the predominant sources were cars (outside 86% of schools), aircraft (54%), lorries (35%) and buses (24%), with 11% of schools exposed to railway noise. This distribution of sources agrees closely with the occurrence of sources recorded outside dwellings around the UK during the 2000/2001 National Noise Incidence Survey (NNIS) [34] (for example NNIS found 87% of dwellings exposed to road traffic noise, and 12% of dwellings exposed to railway noise.) It can therefore be assumed that these figures are likely to reflect the typical noise exposure of schools in industrial societies.

Studies of annoyance caused by noise heard in schools by Dockrell *et al* [37-39] suggest that certain occasional noise events such as overflying aircraft, trains or sirens may affect children and teachers disproportionately to their contribution to the overall noise environment of a school.

In addition to external noise transmitted through the building façade to a classroom, noise inside a classroom may include noise from teaching equipment (computers, projectors and so on), noise from building services in the classroom, and noise transmitted through the walls, floor and ceiling from other parts of the school. Shield *et al* [11, 36], however, in a survey of 140 primary school classrooms, found that the dominant source of noise in a primary school classroom is the noise generated by the pupils themselves as they take part in a range of classroom activities.

4. SPEECH INTELLIGIBILITY

A major effect of noise and poor acoustics in the classroom is the reduction of speech intelligibility. If children are unable to understand the teacher then the major function of a classroom in providing an environment that enables the transfer of information from teacher to pupil is impaired. In addition it is important, both for learning and for social interaction, that children are able to hear and understand their peers in the classroom.

4.1 Children's understanding of speech

There have been many studies of children's understanding of speech in different noise and reverberant conditions, some of which have paid particular attention to the acoustic conditions of classrooms. These studies have shown that young children are far more susceptible to poor acoustic conditions than adults. Nelson [40], in describing the development of the 2002 ANSI standard on classroom acoustics [41], gives a brief review of recent work in this area. It has been shown through research with children of differing ages that a child's understanding of speech in noise and reverberation does not reach an adult level until the late teenage years. Before this time, the younger the child the greater the detrimental effect of noise and reverberation [42-45], with children under about 13 years of age being particularly susceptible.

Children and adults who are hearing impaired are more seriously affected by noise and reverberation than those with normal hearing. It is estimated that at any one time up to 40% of children in a primary school class in the UK or USA may have some form of hearing impairment [40,46], due to either permanent damage to their hearing or a temporary condition such as a cold or ear infection. Furthermore, many children with permanent hearing impairments are now educated alongside their mainstream peers, in accordance with the principles of social inclusion and legislation such as the Americans with Disabilities Act [47] and the UK Disability Discrimination Act [48]. It is therefore particularly important to achieve good acoustic conditions in classrooms to meet the needs of these children.

There are other groups of children for whom understanding their teachers and their peers can be difficult in the classroom, for example children who are not being taught in their first language [40, 49], children with disorders such as attention deficit/hyperactivity disorder [50], and children with speech and language difficulties. These children may be easily distracted in poor acoustic conditions or may have

general problems in processing language, which will be exacerbated in classrooms with poor acoustics.

4.2 Acoustic factors affecting speech intelligibility in classrooms

The room acoustic factors that affect speech intelligibility are background noise level and reverberation time. Both Bradley and Hodgson and their colleagues [51-56] have carried out experimental and theoretical studies to investigate the relationship between these factors and speech intelligibility in the classroom. A general conclusion of these studies is that noise is the more critical factor and that criteria for acoustical conditions in the classroom should be based upon speech intelligibility. In work with adults Bradley *et al* [51] found that noise, rather than reverberation, was the most significant factor in understanding speech and that the most important parameter for speech intelligibility is the signal (that is, speech) to noise ratio. As the levels of teachers' voices vary, this means that it is particularly important to reduce the background noise level in a classroom. Bradley [52], in an analysis of measurements of acoustical conditions and speech intelligibility in classrooms for 12 and 13 year old students, concluded that 30 dB(A) was an appropriate background noise level, with optimum reverberation times of 0.4 to 0.5 seconds. There is however some disagreement about the ideal value of the signal to noise ratio for classrooms. Finitzo-Hieber and Tillman [57] in 1978 recommended a signal to noise ratio of 12 dB for both normal hearing and hearing impaired students although others [58, 59] argued that a higher S/N value of 20 to 30 dB is required for the teaching of hearing impaired children. More recently Bistafa and Bradley [53], following a series of theoretical studies, recommended that the speech to noise ratio should be greater than 15 dB throughout a classroom, 25 dB being the ideal value and 20 dB an acceptable value 1 m in front of speaker. These values assume a reverberation time of less than 0.4 to 0.5 seconds. Signal to noise ratios of 15 or 20 dB are recommended for classrooms by the American Speech-Language-Hearing Association [60] and the British Association of Teachers of the Deaf [61] (see section 9).

It is usual to assume that speech intelligibility will increase as reverberation time decreases to zero [62]. Although it is generally accepted that, to maximise speech intelligibility, it is necessary to have a relatively short reverberation time, Hodgson and Nosal [54] argue that, when the noise inside a classroom is taken into account, longer reverberation times are possible without compromising the speech intelligibility. When accounting theoretically for noise of equipment and occupants in a classroom, they predicted that it was possible to achieve high speech intelligibility with reverberation times of up to 1 second, depending on the size of the room. However, the authors concede that their results may not be appropriate in the case of younger and hearing-impaired listeners.

Picard and Bradley, in a major review of research on speech intelligibility in classrooms [5], compared measured noise levels and teachers' voice levels from a range of studies. They estimated that in reality the speech to noise ratio varies from 3 dB in a kindergarten to almost 7 dB in university classrooms.

5. EFFECTS OF ENVIRONMENTAL NOISE

The majority of the research into the effects of noise on children's performance in the classroom has examined the issue in one of two ways. Either the performance of children exposed long term to significant levels of environmental noise has been

compared with that of children with low noise exposure; or the effects of a reduction in environmental noise on children's performance in the classroom have been studied.

Much of the published work on the effects of external noise has concerned pupils in schools exposed to aircraft noise. In the early 1970s Crook and Langdon [63] found that in schools around Heathrow aircraft noise had a significant impact on teaching by interfering with speech and causing changes in teachers' behaviour in the classroom. Two major studies around airports in the 1980s and 1990s involving children aged from 8 to 12 found impaired performance in noise exposed children [4, 6, 7, 64]. In these studies high noise exposure was associated with poor long term memory and reading comprehension, and decreased motivation in school children. Typical levels of aircraft noise to which the schools were exposed were 95 dB L_{peak} [6,7]. A recent study of children in schools affected by aircraft noise from Heathrow Airport, in which children in schools within the 63 dB(A) $L_{Aeq,16hour}$ aircraft noise contour were compared with children in schools outside the 57 dB(A) contour [10, 65, 66] also found that noise affected reading ability for the hardest items.

The effects of chronic exposure to aircraft noise appear to be long term. Cohen *et al* [7] found that reducing the noise inside a school by 16 dB(A) had little effect on children's performance. More recently Hygge [64] found that even when the noise source is removed, as in the closure of an airport, it takes several years for the detrimental effects of noise exposure to cease.

Other studies have examined the effects of school exposure to train and road traffic noise. Bronzaft and McCarthy [29] found that children on the quieter side of a school next to an elevated railway had reading scores higher than children on the side exposed to the train noise, at levels of up to 89 dB(A). A noise abatement programme reduced the train noise inside the school by 6 to 8 dB(A), after which no difference was found between the reading scores on the two sides of the school [67].

In the UK road traffic noise has been found to cause dissatisfaction with the classroom environment among teachers: Sargent *et al* [68] found that there was a greater incidence of complaints about noise at levels above 60 dB(A) L_{A10}. Lukas *et al* [69] found that exposure to traffic noise had a detrimental effect upon children's reading ability. More recently tests in both primary and secondary schools exposed to noise from road traffic have found that noise has a detrimental effect on children's attention [70, 71]. The levels of road traffic noise in these studies were around 70 dB(A) on average.

Hygge [20] investigated the effects of noise from various transportation sources on children aged between 12 and 14. Noise of different sources was played at 66 dB(A) in the classroom. Aircraft and road traffic noise were found to affect long term recall whereas the noise from trains had no effect.

Shield and Dockrell [35] compared external noise levels at over 50 London schools with the schools' scores in standardised assessment tests (SATs) of children aged 7 and 11. There were significant relationships between external noise levels and SATs scores, the relationships being stronger for the older children. The noise parameter that had the highest correlation with SATs results was L_{Amax}, suggesting that it is the noise of individual events, or acute exposure, which may have the most significant

effect. In contrast to other studies, the subjects most affected were mathematics and science. The significant relationships were maintained when the data was corrected for school socio-economic factors such as percentages of children for whom English is not the first language and percentages of children receiving free school meals. Similarly, Haines *et al* [72] found that chronic exposure to aircraft noise was significantly negatively related to performance in the standardised mathematics tests of 11 years olds, although the relationship was not statistically significant when the data was corrected for socio-economic status.

While it appears from all these studies that both chronic and acute exposure to environmental noise may adversely affect children's academic performance, there are many other factors, often unreported, that may influence performance and interact with the effects of noise. These include child based factors such as ability, language or social deprivation. In their study of London schools, Shield and Dockrell [35] found that there was a high correlation between a school's external noise level and the percentage of children having free school meals at the school, the latter being a recognised indicator of social deprivation in an area [73,74]. This suggests that deprived children already living in noisy areas attend schools where their exposure to environmental noise may additionally negatively affect their academic performance.

6. EFFECTS OF CLASSROOM NOISE

There has been less research in the past into the effects on children of noise in the classroom, than of environmental noise. However, research in this area is increasing, several recent studies having investigated the effects of internal noise on children's reading, numeracy and overall academic performance [11, 75-77].

Hetu *et al* [3] found a significant drop in children's performance, particularly in learning to read, when the background noise level interfered with speech. Mackenzie [75] compared the performance of children in primary school classrooms that had been acoustically treated, thereby reducing background noise levels and reverberation times, with children in untreated classrooms. Children performed better in word intelligibility tests in the acoustically treated rooms, the improvement being particularly marked when other pupils were talking in the classrooms. Similar results were obtained by Maxwell and Evans [76] in a study of pre-school children who had been exposed to levels in the classroom of 75 dB(A). Following acoustic treatment to reduce the noise the children's performance improved in letter, number and word recognition. In contrast, in a study of older children, aged 13 and 15, working in levels of 58 to 69 dB(A) during mathematics classes [77] there was poor correlation between sound level and standard of work; however, there was a significant relationship between annoyance and the effect of noise on schoolwork (see section 8 for further discussion of annoyance).

Shield and Dockrell [78] in comparing standardised assessment test scores with internal noise levels in 16 schools found significant relationships between background (L_{A90}) levels in classrooms and test scores for several subjects. The test which showed the strongest association with noise was the English test of the older (age 11)

7. REASONS FOR THE EFFECTS OF NOISE ON CHILDREN

There is a need for further work to examine the reasons for the effects of noise on children's performance, in particular what aspects of their cognitive processing are affected by different types of irrelevant noise. A number of possible explanations have been proposed. These include cognitive coping [23] and level of arousal [4,79]. The cognitive coping hypothesis suggests that children deal with excessive levels of environmental sound by tuning it out. This, it is argued, results in indiscriminate tuning out of all stimuli resulting in generalised poor attention [9]. This explanation would imply that a full range of cognitive tasks would be affected, and this is not what appears to happen. In contrast increased arousal could have the effect of increasing performance on tasks where irrelevant items are screened, but continued high levels of arousal may result in an inability to concentrate. More recently the effects of environmental noise have been conceptualised by Evans *et al* [26] in terms of 'helplessness'. However, both the arousal and the learned helplessness hypotheses fail to make clear predictions about the ways in which environmental noise will differentially affect cognitive skills.

A criticism of studies of the effects of irrelevant noise on adults is that they have mainly involved the performance of simple laboratory tasks in background noise or speech [80]. A marked exception to this is the work of Banbury and Berry [80,81] who examined the disruption of office related tasks by speech and office noise, and confirmed the negative effect of noise exposure on more complex cognitive tasks. However, results obtained with adults cannot necessarily be generalised to children as children's cognitive and linguistic skills are less developed than those of adults. Shield *et al* [11] carried out a series of experimental investigations in schools to examine the ways in which different irrelevant sound sources interfered with children's processing of verbal and non-verbal tasks. They found that children's talk in the classroom had a detrimental effect upon the verbal (reading) task but that the addition of random environmental noise events improved performance on this task. A non-verbal (speed of processing) task was detrimentally affected by both classroom talk and environmental noise individually, the worst performance occurring in a combination of these two sounds.

8. CHILDREN'S PERCEPTIONS OF NOISE AT SCHOOL

The most widespread and well documented subjective response to noise is annoyance. However, while there have been many studies concerned with annoyance caused to adults by different types of noise, including ones which have established dose response relationships between noise and annoyance, children's annoyance due to noise is a relatively under researched area. Yet children's annoyance may be a important factor in determining the effects of noise; indeed Lundquist *et al* [78] found that there was a stronger relationship between school performance and annoyance than between sound level and performance.

Some of the studies of the effects of noise on children already discussed have also considered children's perceptions of sound. Children at school have consistently been found to be annoyed by chronic aircraft noise exposure [22,65]. In their study of the effect of high levels of aircraft noise Haines *et al* [65] demonstrated that annoyance levels due to aircraft noise were significantly higher among children in schools exposed to high levels of aircraft noise compared with schools with lower exposure

levels. In contrast, levels of annoyance due to road traffic noise both at school and at home did not differ significantly across the high and low aircraft noise schools.

Children may be aware of noise without necessarily being annoyed by it. A recent survey by Dockrell and Shield [37-39] of over 2000 London primary school children aged 7 and 11 years, in schools exposed to a range of environmental noise sources, found that children were aware of, and some were annoyed by, specific noise sources. The older children were more aware of the noise, while the younger children found noise more annoying. The most annoying noise sources were trains, motorbikes, lorries and sirens, suggesting that it is intermittent loud noise events which cause most annoyance to children while at school.

9. CLASSROOM NOISE LEVELS

Despite the body of research into the effects of poor speech intelligibility and noise on children in the classroom, there is relatively little published data on typical noise levels in classrooms. Furthermore, owing to changes in instrumentation, measurement techniques and parameters over the past 30 years, the data that is available is limited in scope and often difficult to interpret in terms of current noise parameters and methodologies. The reported levels have on the whole been presented as single figure ratings, either in dB(A) with no explanation of which acoustic parameter was measured, or in terms of L_{Aeq} without reference to time or classroom activity. In a review of classroom noise data published between 1977 and 1991, Hodgson *et al* [82] report that in most cases it is difficult to determine precisely how the measurements were obtained and in what classroom conditions. Picard and Bradley, in a recent large scale review of classroom noise levels also note the lack of detailed data on noise in classrooms [5]. However, with increasing interest world wide in school and classroom acoustics, the rate of publication of classroom and school noise data is increasing. For example, the UK government has recently funded several large scale studies of classroom noise and the effects of noise on children [9,11,83], and similar work is currently being undertaken on a European wide basis [84].

Published data include measurements of teachers' speech levels, background levels in empty classrooms and levels due to student activities in the classroom. However, previous surveys have shown a wide range in noise levels in classrooms, as discussed below.

9.1 Teachers' speech levels

The review by Hodgson *et al* [82] found that data on teachers' speech levels ranged from 40 to 80 dB(A). Picard and Bradley [5] also note the wide range in reported speech levels, the variation being due to different measurement methods and microphone positions. From the published data they estimate that the average speech level in a classroom, 2 metres from the teacher, is 60.1 dB(A).

9.2 Background levels in empty classrooms

In empty classrooms the noise is likely to be due to sources within the classroom such as ventilation system noise, plus noise transmitted from other areas in the school and from external sources. The review by Hodgson *et al* [82] found measured levels of ventilation noise in classrooms ranged from 23 to 55 dB(A).

10.1 WHO Guidelines

The WHO guideline values for schools [94] are summarised in Table 1.

Table 1. WHO guidelines for maximum noise levels and reverberation times in schools

	Noise level, dB L_{Aeq}	Reverberation time, seconds
Classrooms	35	0.6
Halls and cafeterias	-	< 1
Outdoor playgrounds	55	-

The background noise level of 35 dB(A) L_{Aeq} in classrooms is based upon the assumption of 55 dB(A) for a typical teacher's voice level at a distance of 1 m, and of the need for a signal to noise ratio of 15 dB. It is not clear whether the reverberation time requirements apply to occupied or unoccupied rooms. The guidelines state that both background noise level and reverberation time should be lower for hearing impaired children. The maximum noise level of 55 dB(A) in outdoor playgrounds is chosen to be the same value as for outdoor residential areas in daytime, in order to prevent noise annoyance.

10.2 ANSI S12.60-2002

The American National Standard S12.60-2002 'Acoustical Performance Criteria, Design Requirements, and Guidelines for Schools' [41] was published in 2002 and provides design criteria and guidelines for new and refurbished classrooms and other learning spaces. The standard specifies limit values for background noise levels and reverberation times in 'core learning spaces' (that is teaching spaces including classrooms, conference rooms, libraries, music rooms and so on) which are classified according to their volume, see Table 2. The spaces are assumed to be furnished but unoccupied.

Table 2. ANSI S12.60-2002: Maximum background noise levels and reverberation times in learning spaces

Volume of space	Background noise level, dB $L_{Aeq,1hour}$	Reverberation time, seconds
< 283 m^2	35	0.6
> 283 m^2 and ≤ 566 m^2	35	0.7
> 566 m^2	40	-

The standard also includes sound insulation requirements, expressed as STC ratings, between core learning spaces and adjacent areas. For example, the minimum STC between two core learning spaces is 50, between a core learning space and corridor 45, and between a core learning space and cafeteria 60.

The standard includes annexes which give the rationale for the setting of the criteria; advice on noise control, control of reverberation and sound insulation; and recommendations for good practice to verify conformance to the standard.

10.3 Building Bulletin 93

In the UK, although there has been guidance available on the acoustic design of schools since 1975 [95, 976], there have up to now been no legal requirements for compliance with the standards. However from July 2003, the acoustic design of schools is to be regulated under amendments to the Building Regulations. The standards, which will have to be met by both new and refurbished schools, are contained in Building Bulletin 93 'Acoustic Design of Schools', published by the Department for Education and Skills [32].

Building Bulletin 93 replaces Building Bulletin 87 'Guidelines for Environmental Design in Schools' [95] which gave advice on heating, lighting, ventilation and acoustics in schools. James [96] discusses the background to the writing of Building Bulletin 93.

Building Bulletin 93 is a comprehensive document specifying indoor ambient noise levels, reverberation times and sound insulation requirements for over 30 types of teaching and learning spaces in schools. It also includes guidance on noise control, design of rooms for speech and music, the needs of and technology available for hearing impaired children and case studies of good and bad examples of school and classroom design.

Examples of the performance standards for maximum indoor ambient noise levels, in terms of $L_{Aeq,30min}$, and reverberation times are shown in Table 3. Both noise levels and reverberation times are for unoccupied and unfurnished rooms. The reverberation time is the mean of the values at 500 Hz, 1000 Hz and 2000 Hz. Figures in brackets in Table 3 are the corresponding values from Building Bulletin 87, where a direct comparison is possible. (Note that the background noise level in Building Bulletin 87 was expressed as a 1 hour L_{Aeq} and the reverberation time was the mean of the 500 Hz and 1000 Hz values.) In general, the requirements of Building Bulletin 93 are more stringent than those of Building Bulletin 87, to reflect increased awareness of the effects of noise and reverberation on children, and in particular the needs of hearing impaired children.

Table 3. Building Bulletin 93: upper limits for indoor ambient noise levels and reverberation times for a selection of school rooms

	Indoor ambient noise level, dB $L_{Aeq,30min}$	Reverberation time, seconds
Primary school classrooms	35 *(40)*	<0.6 *(0.5-0.8)*
Secondary school classrooms	35 *(40)*	<0.8 *(0.5-0.8)*
Large (> 50 people) lecture room	30 *(35)*	<1.0
Classrooms specifically for hearing impaired pupils	30	<0.4
Library study area	35 *(40)*	<1.0 *(0.5-1.0)*
Assembly halls	35 *(35)*	0.8-1.2
Science lab	40 *(40)*	<0.8 *(0.5-0.8)*
Gymnasium	40	<1.5 *(1.0-1.5)*
Dining rooms	45 *(50)*	<1.0 *(0.5-0.8)*

Values in parentheses are corresponding values from Building Bulletin 87 [96]

Building Bulletin 93 also specifies the required sound insulation between the various different kinds of teaching spaces. The sound insulation requirements are based upon the classifications of the rooms according to their 'activity noise' (low, average, high or very high) and their 'noise tolerance' (very low, low, medium, high). The sound insulation is specified in terms of a weighted standardised level difference $D_{nT(Tmf,max),w}$ where the reference reverberation time is the upper limit of the specified RT for the receiving room. The required values of $D_{nT(Tmf,max),w}$ range from 30 dB for the insulation between a source room with low activity noise (eg study room) and a receiving room with a high tolerance level (eg dining room) to 60 dB between a source room with very high activity noise (eg music classroom) and one with very low tolerance (eg drama studio). The impact sound insulation of floors is specified in terms of the weighted standardised impact sound pressure level $L'_{nT(Tmf,max),w}$, which is is also defined by reference to the maximum RT of the receiving room. The required values of $L'_{nT(Tmf,max),w}$ range from 55 dB for rooms such as music classrooms and large lecture rooms to 65 dB for science laboratories, sports hall, dining rooms and so on.

Building Bulletin 93 also contains standards for open plan spaces, which are specified in terms of the speech transmission index, STI. The performance standard is that any open plan teaching or study areas should be designed so that the STI is greater than 0.6.

10.4 Standards for hearing-impaired pupils

Organisations concerned with the needs of deaf and hearing-impaired people also provide guidance on the acoustic requirements of classrooms. Examples include the position paper on acoustics in educational settings of the American Speech-Language-Hearing Association (ASHA) [60], published in 1995, and the recommended standards for classroom acoustics published in 2001 by the British Association of Teachers of the Deaf (BATOD) [61]. The recommendations of both of these organisations include unoccupied ambient noise levels, reverberation times and signal to noise ratios, as shown in Table 4.

Table 4. Recommendations of ASHA and BATOD for classrooms

	ASHA (1995)	BATOD (2001)
Background noise levels	30 - 35 dB(A)	≤ 35 dB(A)
Reverberation time	≤ 0.4 s	≤ 0.4 s, 125 Hz to 4000 Hz
Signal to Noise ratio	≥15 dB	>20 dB, 125 Hz to 750 Hz >15 dB, 750 Hz to 4000 Hz

In 2002 ASHA published a further report on appropriate facilities for students with speech-language-hearing disorders [97], the major part of which is concerned with the acoustics of classrooms.

11. CONCLUSIONS

The research evidence shows that noise does have an effect on children's performance at school, with older children in the primary school age range appearing to be the most affected by noise. Children are also annoyed by noise at school. Measurement surveys of classrooms show that classroom noise levels can be high, particularly in classrooms without acoustic treatment, and that this is often due to the noise of

classroom activity. One cause of the detrimental effect of noise is the degradation of speech intelligibility in the classroom. The precise nature of the effects of noise upon the cognitive processes of children, however, is as yet not fully understood.

There is increasing awareness among the architectural, educational and acoustical professions about the effects of noise on children and the need to create good acoustic conditions in the classroom. This is being reflected in current national and international standards on classroom acoustics.

12. REFERENCES

1. Berglund, B. and Lindvall, T. (1995) Community Noise. Archives of the Center for Sensory Research, 2(1), 1-195.
2. Institute for Environment and Health (1997) The non-auditory effects of noise. Report R10. http://www.le.ac.uk/ieh/pdf/ExsumR10.pdf
3. Hetu, R., Truchon-Gagnon, C. and Bilodeau, S.A. (1990) Problems of noise in school settings: a review of literature and the results of an exploratory study, Journal of Speech-Language Pathology and Audiology, 14(3), 31-38.
4. Evans, G.W. and Lepore, S.J. (1993) Nonauditory effects of noise on children: a critical review. Children's Environments, 10(1), 31-51.
5. Picard, M. and Bradley, J.S. (2001) Revisiting speech interference in classrooms, Audiology 40, 221-224.
6. Cohen, S., Evans, G.W., Krantz, D.S. and Stokols, D. (1980) Physiological, motivational, and cognitive effects of aircraft noise on children. Moving from the laboratory to the field. American Psychologist, 35(3), 231-243.
7. Cohen, S., Evans, G.W., Krantz, D.S., Stokols, D. and Kelly, S. (1981) Aircraft noise and children: longitudinal and cross-sectional evidence on adaptation to noise and the effectiveness of noise abatement. Journal of Personality and Social Psychology, 40(2), 331-345.
8. Green, K.B., Pasternack, B.S. and Shore, R.E. (1982) Effects of Aircraft Noise on Reading Ability of School-Age Children. Archives of Environmental Health, 37(1), 24-31.
9. Stansfeld, S.A. Haines, M.M., Brentall, S., Head, J., Roberts, R., Berry, B. and Jiggins, M. (2000) West London Schools Study: Aircraft noise at school and child performance and health. Final report for Department of Health and DETR.
10. Haines, M.M., Stansfeld S.A., Job, R.F.S., Berglund, B. and Head, J. (2001) A follow-up study of effects of chronic aircraft noise exposure on child stress responses and cognition, International Journal of Epidemiology, 30, 839-845.
11. Shield, B., Dockrell, J., Asker R. and Tachmatzidis, I. (2002) The effects of noise on the attainments and cognitive development of primary school children. Final report for Department of Health and DETR.
12. Heft, H. (1979) Background and focal environmental conditions of the home and attention in young children. Journal of Applied Social Psychology, 9, 47-69.
13. Kyzar, B.L. (1977) Noise pollution and schools: How much is too much? Council of Educational Facilities Planners Journal, 10-11.
14. Kryter, K.D. (1985) The effects of noise on man. New York: Academic Press.
15. Ko, N.W.M. (1979) Responses of teachers to aircraft noise. Journal of Sound and Vibration, 62, 526-530.
16. Ko, N.W.M. (1981) Responses of teachers to road traffic noise. Journal of Sound and Vibration, 77, 133-136.

17. Moch-Sibony, A. (1984) Study of the effects of noise on personality and certain psychomotor and intellectual aspects of children, after a prolonged exposure. Travail Humane, 47, 155-165.
18. Fenton, T.R., Alley, G.R. and Smith, K. (1974) Effects of white noise on short-term memory of learning disabled boys. Perceptual and Motor Skills, 39, 903-906.
19. Hambrick-Dixon, P.J. (1986) Effects of experimentally imposed noise on task performance of black children attending day care centers near elevated subway trains. Developmental Psychology, 22(2), 259-264.
20. Hygge, S. (1993). Classroom experiments on the effects of aircraft, traffic, train, and verbal noise on long-term recall and recognition in children aged 12-14 years.. Proceedings of the 6th International Congress on Noise as a Public Health Problem, 2, 531-534.
21. Johansson, C.R. (1983) Effects of low intensity, continuous, and intermittent noise on mental performance and writing pressure of children with different intelligence and personality characteristics. Ergonomics, 26(3), 275-288.
22. Evans, G.W., Hygge, S. and Bullinger, M. (1995) Chronic noise and psychological stress. Psychological Science, 6, 333-338.
23. Cohen, S., Evans, G., Krantz, D.S. and Stokols, D. (1986) Behavior, Health, and Environmental Stress. New York: Plenum.
24. Kassinove, H. (1972) Effects of meaningful auditory stimulation on children's scholastic performance. Journal of Educational Psychology, 63(6), 526-530.
25. Slater, R.B. (1968) Effects of noise on pupil performance. Journal of Educational Psychology, 59, 480-514.
26. Evans, G.W., Bullinger, M. and Hygge, S. (1998) Chronic noise exposure and physiological response: a prospective study of children living under environmental stress. Psychological Science, 9, 75-77.
27. Evans, G.W. and Maxwell L. (1997) Chronic noise exposure and reading deficits: the mediating effects of language acquisition. Environment and Behaviour, 29(5), 638-657.
28. Hambrick-Dixon, P.J. (1988) The effect of elevated subway train noise over time on black children's visual vigilance performance. Journal of Environmental Psychology, 8, 299-314.
29. Bronzaft, A.L. and McCarthy, D.P. (1975) The effect of elevated train noise on reading ability. Environment and Behaviour, 7(4), 517-527.
30. Meiss, S. Hygge, S., Lercher, P. Bullinger, M. and Schick A. (2000) The effects of chronic and acute transportation noise on task performance of school children. Proc. Internoise 2000, 347-352.
31. Evans, G.W., Lercher, P., Meis, M., Ising, H. and Kofler, W.W. (2001) Community noise exposure and stress in children. Journal of the Acoustical Society of America 109(3), 1023-1027.
32. Department for Education and Skills (2003), Building Bulletin 93 Acoustic Design of Schools, www.teachernet.gov/acoustics
33. O'Neill,D. (2002) Experience of using Building Bulletin 87: Does Building Bulletin 93 resolve all the difficulties?, presented at School Acoustics meeting, Institute of Acoustics, October 15 2002.
34. BRE. (2002) National Noise Incidence Study 2000/2001 (England and Wales), www.defra.gov.uk/environment/noise/nis0001.
35. Shield, B. and Dockrell, J. (2002), The effects of environmental noise on child academic attainments. Proc. Institute of Acoustics 24(6).

36. Shield, B.M. and Dockrell, J.E. (2003) External and internal noise surveys of London primary schools. Accepted for publication in Journal of the Acoustical Society of America.
37. Dockrell, J.Tachmatzidis, B. Shield and R.Jeffery, (2001) Children's perceptions of noise in schools, Proc. 17th International Congress on Acoustics, Rome.
38. Dockrell, J. and Shield, B. (2002) Children's and teachers' perceptions of environmental noise in classrooms. Proc. Institute of Acoustics 24 (2).
39. Dockrell, J.E. and Shield, B.M. (2003) Children's perception of their acoustic environment at home and at school. Submitted for publication in Journal of the Acoustical Society of America.
40. Nelson, P.B. (2003) Sound in the Classroom - Why Children Need Quiet, ASHRAE journal, February 2003, 22 - 25.
41. American National Standards Institute (2002) Standard S12.60-2002, Acoustical Performance Criteria, Design Requirements, and Guidelines for Schools.
42. Werner, L. and Boike, K.(2001) Infants' sensitivity to broadband noise, Journal of the Acoustical Society of America, 109(5), 2103-2111.
43. Stelmachowitz, P.G. et al. (2000) The relation between stimulus context, speech audibility, and perception for normal-hearing and hearing-impaired children, Journal of Speech, Language and Hearing Research, 43, 902-914.
44. Soli, S.D. and Sullivan, J.A. (1997) Factors affecting children's speech communication in classrooms, Journal of the Acoustical Society of America, 101, S3070.
45. Johnson, C.E.(2000) Children's phoneme identification in reverberation and noise, Journal of Speech, Language and Hearing Research, 43, 144-157.
46. Niskar, A.S., Kieszak, S.M., Holmes, A, Esteban, E, Rubin, C. and Brody, D. (1998) Prevalence of hearing loss among children 6 to 19 years of age. Journal of American Medical Association 279(14), 1071-1075.
47. Americans with Disabilities Act (1990) www.usdoj.gov/crt/ada/
48. Disability Discrimination Act (1995) Part IV www.hmso.gov.uk/acts/acts1995/1995050.
49. Mayo, L., Florentine, M and Buus, S. (1997) Age of secondary language acquisition and perception of speech in noise. Journal of Speech, Language and Hearing Research, 40, 686-693.
50. Breier, J.L. (2002) Dissociation of sensitivity and response bias in children with attention deficit/hyperactivity disorder during central auditory masking. Neuropsychology 16, 28-34.
51. Bradley, J.S., Reich, R.D. and Norcross, S.G. (1999) On the combined effects of signal-to-noise ratio and room acoustics on speech intelligibility. Journal of the Acoustical Society of America, 106, 1820-1829.
52. Bradley, J.S. (1986) Speech intelligibility studies in classrooms. Journal of the Acoustical Society of America, 80(3), 846-854.
53. Bistafa, S.R. and Bradley, J.S. (2000) Reverberation time and maximum background-noise level for classrooms from a comparative study of speech intelligibility metrics. Journal of the Acoustical Society of America, 107, 861-875.
54. Hodgson, M. and Nosal, E. (2002) Effect of noise and occupancy on optimal reverberation times for speech intelligibility in classrooms. Journal of the Acoustical Society of America, 111(2), 931-939.
55. Bradley, J.S. (1986) Predictors of speech intelligibility in rooms. Journal of the Acoustical Society of America, 80, 837-845.

56. Hodgson, M. (2002) Rating, ranking, and understanding acoustical quality in university classrooms. Journal of the Acoustical Society of America, 112(2), 568-575.
57. Finitzo-Hieber, T. and Tillman, T.W. (1978) Room acoustics effects on monosyllabic word discrimination ability for normal and hearing-impaired children, Journal of Speech and Hearing Research 21, 440-458.
58. Ross, M. Classroom amplification. (1986) In Hodgson, W.R. (ed) Hearing Aid Assessment and Use in Audiological Habilitation, Baltimore, Williams and Wilkins, 231-265.
59. Olsen, W.O. (1988) Classroom acoustics for hearing-impaired children. In Bess, F.H. (ed) Hearing Impairment in Children. Parkton, York Press, 266-277.
60. American Speech-Language-Hearing Association (1995) Acoustics in educational settings, ASHA Supplement 14.
61. British Association of Teachers of the Deaf (2001) Classroom acoustics - recommended standards. BATOD Magazine, January 2001.
62. Nabelek, A.K. and Pickett, J.M. (1974) Reception of consonants in a classroom as affected by monaural and binaural listening, noise, reverberation and hearing aids. Journal of the Acoustical Society of America, 56, 628-639.
63. Crook and Langdon (1974) The effects of aircraft noise in schools around London Airport. Journal of Sound and Vibration, 3, 221-232.
64. Hygge, S., Evans, G.W. and Bullinger, M. (1996) The Munich Airport noise study: Cognitive effects on children from before to after the change over of airports. Proceedings of Inter-Noise'96, 2189 - 2192.
65. Haines, M.M., Stansfeld, S.A., Job, R.F.S., Berglund, B. and Head, J. (2001) Chronic aircraft noise exposure, stress responses, mental health and cognitive performance in school children. Psychological Medicine, 31(2), 265-277.
66. Haines, M.M., Stansfeld, S.A., Brentall, S., Head, J., Berry, B., Jiggins, M. and Hygge, S. (2001) West London Schools Study: The effects of chronic aircraft noise exposure on child health. Psychological Medicine, 31, 1385-1396.
67. Bronzaft, A.L. (1981) The Effect of a Noise Abatement Program on Reading Ability. Journal of Environmental Psychology, 1, 215-222.
68. Sargent, J.W., Gidmanm M.I., Humphreys, M.A. and Utley, W.A. (1980) The disturbance caused to school teachers by noise. Journal of Sound and Vibration, 70, 557-572.
69. Lukas, J.S., DuPree, R.B. and Swing, J.W. (1981) Report of a study on the effects of freeway noise on academic achievement of elementary school children, and a recommendation for a criterion level for a school noise abatement program. Learning, Memory and Cognition, 20(6), 1396-1408.
70. Sanz, S., Garcia, A.M. and Garcia, A. (1993) Road traffic noise around schools: a risk for pupils' performance? International Archives of Occupational and Environmental Health, 65, 205-207.
71. Romero, J. and Lliso, D. (1995) Perception and acoustic conditions in secondary Spanish schools. Proceedings of the 15th International Congress on Acoustics, Trondheim, Norway, 271-274.
72. Haines, M.M., Stansfeld, S.A., Head, J. and Job, R.F.S. (2002) Multi-level modelling of aircraft noise on performance tests in schools around Heathrow Airport London. Journal of Epidemiology and Community Health, 56, 139-144.
73. Williamson, W. and Byrne, D.D. (1977) Educational disadvantage in an urban setting. In D.T. Herbert and D.M. Smith (Eds) Social Problems and the City. Oxford: Oxford University Press.

74. Higgs, G., Bellin, W. and Farrell, S. (1997) Educational attainments and social disadvantage: contextualising school league tables. Regional Studies 31, 775-789.
75. MacKenzie, D. (2000) Noise sources and levels in UK schools. Proc. International symposium on Noise Control and Acoustics for Educational Buildings, Proc Turkish Acoustical Society, Istanbul, May 2000, 97-106.
76. Maxwell, L. and Evans, G. (2000) The effects of noise on pre-school children's pre-reading skills. Journal of Environmental Psychology, 20, 91-97.
77. Lundquist, P., Holmberg, K. and Landstrom, U. (2000) Annoyance and effects on work from environmental noise at school. Noise and Health, 2(8), 39-46.
78. Shield, B.M. and Dockrell, J. (2003) The effects of classroom noise on children's academic attainments. To be presented at Euronoise 2003.
79. Poulton, E.C. (1978) A new look at the effects of noise: A rejoinder. Psychological Bulletin, 85, 1068-1079.
80. Banbury, S. and Berry, D.C. (1998) Disruption of office-related tasks by speech and office noise. British Journal of Psychology, 89, 499-517.
81. Banbury, S. and Berry, D.C. (1997) Habituation and Dishabituation to Speech and Office Noise. Journal of Experimental Psychology: Applied, 3(3), 1-16.
82. Hodgson, M., Rempel, R. and Kennedy, S. (1999) Measurement and prediction of typical speech and background noise levels in university classrooms during lectures. Journal of Acoustical Society of America, 105(1), 226-233.
83. MacKenzie, D.J. and Airey, S.L. (1999) Speech intelligibility in classrooms. EPSRC funded research project final report, GR/K3632, EPSRC, Swindon, UK.
84. Matheson, M.P., Asker, R.L., Stansfeld, S.A., Haines, M.M. and Berry, B.F. (2002) The RANCH project: road traffic and aircraft noise exposure and children's cognition and health. Proc. Institute of Acoustics, 24(6).
85. Celik, E. and Karabiber, Z. (2000) A pilot study on the ratio of schools and students affected from noise. Proc. International symposium on Noise Control and Acoustics for Educational Buildings, Proc. Turkish Acoustical Society, Istanbul, May 2000, 119-128.
86. Hay, B. (1995) A pilot study of classroom noise levels and teachers' reactions. Voice, 4, 127-134.
87. Moodley, A. (1989) Acoustic conditions in mainstream classrooms. Journal of British Association of Teachers of the Deaf, 13(2), 48-54.
88. Airey, S. and MacKenzie, D. (1999) Speech intelligibility in classrooms. Proc. Institute of Acoustics 21 (5), 75-79.
89. Hodgson, M. (1994) UBC-classroom acoustical survey. Canadian Acoustics, 22(4), 3-10.
90. Bistafa, S.R. and Bradley, J.S. (2001) Predicting speech metrics in a simulated classroom with varied sound absorption. Journal of Acoustical Society of America, 109(4), 1474-1482.
91. Bradley, J. and Reich, R. (1998) Optimizing classroom acoustics using computer model studies. Canadian Acoustics 26(4), 15-21.
92. Hodgson, M. (1999) Experimental investigation of the acoustical characteristics of university classrooms. Journal of Acoustical Society of America, 106(4), 1810-1819.
93. Vallet, M. (2000) Some European standards on noise n educational buildings. Proc. International symposium on Noise Control and Acoustics for Educational Buildings, Proc. Turkish Acoustical Society, Istanbul, May 2000, 13-20.
94. World Health Organisation. (1999) Guidelines for Community Noise. http://www.who.int/peh/

95. Department for Education and Employment (1997), Building Bulletin 87 Guidelines for Environmental Design of Schools, London: The Stationery Office.
96. James, A. (2002) Acoustic Design of Schools. Acoustics Bulletin 27 (6), 24-29.
97. American Speech-Language-Hearing Association (2002) Appropriate school facilities for students with speech-language-hearing disorders. Technical Report, ASHA Supplement 23.

Starkey Evidence Blog

Impact of Classroom Noise on Children's Listening

Listening Effort at Signal-to-Noise Ratios that are Typical of the School Classroom

Howard, C. S., Munro, K. & Plack, C. J. (2010). Listening effort at signal-to-noise ratios that are typical of the school classroom. *International Journal of Audiology*, 49, 928-932.

This editorial discusses the clinical implications of an independent research study. The original work was not associated with Starkey Laboratories and does not reflect the opinions of the authors.

Everyday activities often require attention to more than one concurrent task. The ability to do this successfully depends on a number of factors; including distractions, the difficulty of the tasks and

the perceived importance of the tasks. In a classroom, children regularly have to attend to multiple tasks at the same time. For instance, they may be taking notes and reading information on a board or a computer screen, while also listening to the teacher and comments or questions from other students. To complicate matters, these tasks are often carried out in the presence of varying levels of background noise.

Classroom noise has a detrimental effect on learning (Shield & Dockrell, 2003). Completing more than one task at a time in a noisy place may adversely affect learning because it requires greater listening effort on behalf of the student. In other words, in the presence of background noise and when attending to multiple tasks, greater cognitive resources must be dedicated to understanding speech. This means that performance on one or more of the tasks, including comprehension of the spoken lesson, can deteriorate. Classroom signal to noise ratios (SNRs) have been measured in the range of -7dB to +5dB (Arnold & Canning, 1999; Crandell & Smaldino, 1995, 2000). Low SNRs are known to have a particularly detrimental effect on speech perception for hearing-impaired listeners, especially children (Blandy & Lutman, 2005; Jamieson et al. 2004). Therefore, the effect of SNR on listening effort and classroom multi-tasking are of special concern for hearing-impaired students.

Listening effort can be measured in adults with self-report ratings, in children it is usually measured with dual-task paradigms. Hicks and Tharpe (2002) compared the performance of children with mild hearing loss to that of normal hearing children in a dual-task study. The primary task was word recognition at 70dB in quiet and in multi-talker babble at SNRs of +10dB to +20dB. The secondary task measured visual reaction time to randomly presented lights. The authors found that reaction time was longer

for the hearing-impaired children than for the normal-hearing children, suggesting that the hearing-impaired children required more listening effort, therefore devoting fewer cognitive resources to the secondary task. Interestingly, there was no significant effect of SNR on listening effort.

McFadden & Pittman (2008) conducted a dual-task experiment with hearing-impaired and normal-hearing 8-12 year olds. The primary task was to categorize words, presented in quiet and in noise at SNRs or 0dB and +6dB. The secondary task involved completion of a dot-to-dot puzzle. Performance on the secondary task decreased when both tasks were performed together, though there was no significant effect of hearing loss or SNR.

The authors of the current study surmised that the SNRs used in previous studies were too favorable and did not represent typical classroom SNRs. SNR may indeed have a detrimental effect on multi-tasking, but the SNRs used in previous experiments might not have been sufficiently challenging to yield an effect. The study summarized in this blog post aimed to measure listening effort in a dual task paradigm using SNRs that were more typical of classroom environments. The authors hypothesized that as SNR decreased, listening effort would increase, yielding poorer performance on the secondary task. Thirty-one normal-hearing children, age 9-12 years, participated in the study. None of the subjects had any history of hearing loss or communication or learning disabilities.

The primary task was a word recognition test using consonant-vowel-consonant monosyllables (Boothroyd, 1968). Words were spoken by a male speaker at 65dB and presented binaurally via headphones. Each set of words was mixed with multi-speaker babble which had been recorded from children's background chatter (Hamilton, 2008), which

the authors deemed most similar to typical classroom background noise. The level of babble was adjusted to create four SNR conditions: quiet, +4dB, 0dB and -4dB. The secondary task involved rehearsing sets of 5 visually-presented digits and reciting them at a later time. Each task was presented alone and together in a dual-task condition. In the dual-task condition, the string of 5 digits was presented for 3 seconds. Then, a set of 5 words was presented and scored before the subjects were asked to recall the rehearsed digits.

For performance on the primary task, the authors found a significant effect of SNR and task combination, as well as a significant interaction between SNR and task combination. In other words, performance on the word recognition task deteriorated when combined with the digit recall task, and also deteriorated with decreasing SNR. Even more deterioration in performance was noted in the dual task condition when SNR decreased.

For performance on the secondary task, there was less of an effect of SNR in the single task condition, suggesting that subjects were able to ignore the background noise successfully as they completed the visual recall task. For the dual task condition, digit recall performance decreased significantly, especially for lower SNRs. There was a strong, significant interaction between SNR and task combination, showing that performance decreased more substantially in the dual task condition when SNRs were lower.

As expected, mean performance on the word recognition test decreased with lower SNRs. In general, the dual task condition yielded similar word recognition performance, but for lower SNRs, performance on the secondary task deteriorated, supporting the hypothesis that increased listening effort was required for multi-tasking in the presence of

increasing background noise. This is consistent with results found for adult subjects, in which decreased performance on a secondary reaction-time task was found when noise was added to the primary listening task (Downs & Crum, 1978).

All test stimuli used in the current experiment were presented under headphones. This test condition removes acoustic cues that would be experienced in the classroom where there is spatial separation between primary and secondary speech stimuli. Future work with hearing-impaired children listening in a spatially distributed sound field would more closely approximate a classroom environment. Additionally, the use of hearing aids with directional microphones and FM systems may reduce some deleterious effects of SNR. Further research is needed to illuminate the interactions among these variables.

The current study showed a clear deterioration in secondary task performance as the SNR decreased, suggesting that increased listening effort was required in conditions with poorer SNRs. This has important implications for classroom environments, in which children are regularly required to listen and perform secondary tasks such as taking notes and reading visual materials. As classroom background noise increases, children are likely to have fewer cognitive resources available to attend to the spoken lesson, take notes and participate in discussions. Decreases in classroom noise levels may be achieved in many ways, including classroom architecture and design, the use of acoustic damping and noise reduction materials and organization of students' workstations.

These observations have particular importance for hearing-impaired students, who are more likely to suffer deleterious effects of classroom background noise. Although this study did not include hearing-impaired listeners, the findings support the

continued recommendation of preferential seating, FM systems and other efforts to improve signal to noise ratio in the classroom.

References

Arnold, P. & Canning, D. (1999). Does classroom amplification aid comprehension? *British Journal of Audiology,* 33, 171-178.

Blandy, S. & Lutman, M. (2005). Hearing threshold levels and speech recognition in noise in 7-year-olds. *International Journal of Audiology,* 44, 435-443.

Boothroyd, A. (1968). Developments in speech audiometry. *British Journal of Audiology,* 2, 3-10.

Crandell, C.C. & Smaldino, J.J. (1995). Speech perception in the classroom. In: C. Crandell, J. Smaldino & C. Flexer (eds.), *Sound-field FM Amplification: Theory and Practical Applications*. San Diego, California: Singular Publication Group.

Crandell, C.C. & Smaldino, J.J. (2000). Classroom acoustics for children with normal hearing and with hearing impairment. *Language, Speech and Hearing Services in Schools,* 31, 362-370.

Downs, D.W. & Crum, M.A. (1978). Processing demands during auditory learning under degraded listening conditions. *Journal of Speech and Hearing Research,* 21, 702-714.

Hamilton, G. (2008). *Compressed Babble for Speech-in-Noise Testing.* Available from: The Ewing Foundation in association with the University of Manchester. www.ewing-foundation.org.uk/.

Hicks, C.B. & Tharpe, A.M. (2002). Listening effort and fatigue in school-age children with and without hearing loss. *Journal of Speech, Language and*

Hearing Research, 45, 573-584.

Howard, C. S., Munro, K. & Plack, C. J. (2010). Listening effort at signal-to-noise ratios that are typical of the school classroom. *International Journal of Audiology,* 49, 928-932.

Jamieson, D.G., Kranjc, G., Yu, K. (2004). Speech intelligibility of young school-aged children in the presence of real-life classroom noise. *Journal of the American Academy of Audiology,* 15, 508-517.

McFadden, B. & Pittman, A. (2008). Effect of minimal hearing loss on children's ability to multitask in quiet and in noise. *Language, Speech and Hearing Services in Schools,* 39, 342-351.

Shield, B.M. & Dockrell, J.E. (2003). The effects of noise on children at school: A review. *Journal of Building Acoustics,* 10, 97-106.

Post Comment

Name *

Email *

Website (optional)

Comment