Submission for Deadline 5 - Comments on material received to deadline 4

Air pollution and Manston Airport

The applicant appears to have little care for the populations who will be impacted should their flawed application be successful. In particular, as a resident of Ramsgate I have had absolutely no direct contact from the applicant regarding the effects on my and my family's well-being consequent on the low level overflying by large freight aircraft many times each day and night. Nor do the applicant's mitigation and compensation plans take any account of the effects of extensive noise and atmospheric pollution on the many thousands of local residents who will be impacted.

I have noted a number of very strong submissions on noise, but the effects on health from air pollution resulting from the creation of a new airport at Manston appear to be less well represented.

A new airport at Manston will have a major adverse impact on air quality, not only from engine exhaust and non exhaust emissions from aircraft, but also emissions from the units providing power to the aircraft on the ground, the traffic due to the airport ground service, maintenance work, heating facilities, fugitive vapours from refuelling operations, kitchens and restaurants for crew (and passengers at a later date) and operators, intermodal transportation systems, and road traffic for transporting people and goods in and out to the airport[1]. Of particular concern are ultra-fine particles (UFPs). UFPs are emitted by aircraft engines during near-surface level operations including taxi, takeoff, climb, descent and landing, as well as idling at gates and on taxiways. Other sources of UFPs include ground support equipment operating around the terminal areas. Exposure to UFPs, even if components are not very toxic, may cause oxidative stress[2], inflammatory mediator release, and could induce heart disease, lung disease, and other systemic effects[3][4].

One study [5] showed that airplane exhaust could be harming communities up to 10 miles from the airport, but the applicant does not appear to consider effects beyond a very close proximity to the airport.

I have no confidence in our elected representatives to take up this subject; most of Thanet District Council are UKIP affiliated and their manifesto is to expand regional airports: "UKIP will encourage investment in regional airports. The current Heathrow plan will destroy many villages and listed buildings as well as add to pollution in the locality." [6] - they don't appear to realise that investing in Manston will destroy many villages and listed buildings as well as add to pollution in the locality!

I urge the Examining Authority to seek whether the applicant plans sufficient remediation and compensation to cover the very large number of people who will be adversely affected by the development of this new airport. I also urge the Examining Authority to consider whether the applicant has irrefutably demonstrated pressing public need sufficient to permit the Government to show proportionality / public interest to justify infringement of our human rights (in particular articles 8 and 13 of the Human Rights Convention).

Yours faithfully

Dr Philip Shotton, MA Natural Sciences (Cantab) PhD Pharmacology (Cantab)
Resident of Ramsgate, directly under the planned flight path, 2 miles E of the runway.

References (attached file name in brackets)

[1] AIRCRAFT ENGINE EXHAUST EMISSIONS AND OTHER AIRPORT-RELATED CONTRIBUTIONS TO AMBIENT AIR POLLUTION: A REVIEW. Mauro Masiol and Roy M. Harrison (Aircraft_Engine_Exhaust_Emissions_V3_PostProof.pdf)
[2] Air pollution, oxidative stress and dietary supplementation: a review I. Romieu, F. Castro-Giner, N. Kunzli, and J. Sunyerb (oxidative_stress_ufp.pdf)
[3] Particulate Matter Air Pollution and Cardiovascular Disease An Update to the Scientific Statement From the American Heart Association(cvd_ufps.pdf)
[4] 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 (neuroinflammation.pdf)
[5] Emissions from an International Airport Increase Particle Number Concentrations 4‑fold at 10 km Downwind (downwind_emissions.pdf)
[6] UKIP Interim Manifesto - Policies for the People (UKIP_Manifesto_Sept_2018.pdf)

AHA Scientific Statement

Particulate Matter Air Pollution and Cardiovascular Disease

An Update to the Scientific Statement From the American Heart Association

Robert D. Brook, MD, Chair; Sanjay Rajagopalan, MD; C. Arden Pope III, PhD; Jeffrey R. Brook, PhD; Aruni Bhatnagar, PhD, FAHA; Ana V. Diez-Roux, MD, PhD, MPH; Fernando Holguin, MD; Yuling Hong, MD, PhD, FAHA; Russell V. Luepker, MD, MS, FAHA; Murray A. Mittleman, MD, DrPH, FAHA; Annette Peters, PhD; David Siscovick, MD, MPH, FAHA; Sidney C. Smith, Jr, MD, FAHA; Laurie Whitsel, PhD; Joel D. Kaufman, MD, MPH; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Abstract**—**In 2004, the first American Heart Association scientific statement on "Air Pollution and Cardiovascular Disease" concluded that exposure to particulate matter (PM) air pollution contributes to cardiovascular morbidity and mortality. In the interim, numerous studies have expanded our understanding of this association and further elucidated the physiological and molecular mechanisms involved. The main objective of this updated American Heart Association scientific statement is to provide a comprehensive review of the new evidence linking PM exposure with cardiovascular disease, with a specific focus on highlighting the clinical implications for researchers and healthcare providers. The writing group also sought to provide expert consensus opinions on many aspects of the current state of science and updated suggestions for areas of future research. On the basis of the findings of this review, several new conclusions were reached, including the following: Exposure to PM $<2.5\ \mu m$ in diameter ($PM_{2.5}$) over a few hours to weeks can trigger cardiovascular disease–related mortality and nonfatal events; longer-term exposure (eg, a few years) increases the risk for cardiovascular mortality to an even greater extent than exposures over a few days and reduces life expectancy within more highly exposed segments of the population by several months to a few years; reductions in PM levels are associated with decreases in cardiovascular mortality within a time frame as short as a few years; and many credible pathological mechanisms have been elucidated that lend biological plausibility to these findings. It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality. This body of evidence has grown and been strengthened substantially since the first American Heart Association scientific statement was published. Finally, $PM_{2.5}$ exposure is deemed a modifiable factor that contributes to cardiovascular morbidity and mortality. **(*Circulation*. 2010;121:2331-2378.)**

Key Words: AHA Scientific Statements ■ atherosclerosis ■ epidemiology ■ prevention ■ air pollution ■ public policy

In 2004, the American Heart Association (AHA) published its first scientific statement regarding air pollution and cardiovascular disease (CVD).[1] The rationale was to provide researchers, healthcare providers, and regulatory agencies with a comprehensive review of the evidence linking air pollution exposure with cardiovascular morbidity and mor-

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on February 22, 2010. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0038). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier=3023366.

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e3181dbece1**

tality. There was also an explicit aim to educate clinicians about the importance of this issue, because the cardiovascular health consequences of air pollution generally equal or exceed those due to pulmonary diseases.[1–4] Finally, a list of key remaining scientific questions and strategic avenues for investigation were provided to help foster and guide future research.

The first AHA writing group concluded that short-term exposure to particulate matter (PM) air pollution contributes to acute cardiovascular morbidity and mortality[1] and that exposure to elevated PM levels over the long term can reduce life expectancy by a few years. Although some mechanistic details remained incompletely described, the existing science was deemed adequate to substantiate several plausible biological pathways whereby PM could instigate acute cardiovascular events and promote chronic disease.

There is mounting evidence from a rapid growth of published data since the previous statement related to the harmful cardiovascular effects of air pollution.[3,4] Most, but not all, epidemiological studies corroborate the elevated risk for cardiovascular events associated with exposure to fine PM <2.5 μm in aerodynamic diameter ($PM_{2.5}$). $PM_{2.5}$ generally has been associated with increased risks of myocardial infarction (MI), stroke, arrhythmia, and heart failure exacerbation within hours to days of exposure in susceptible individuals. Several new studies have also demonstrated that residing in locations with higher long-term average PM levels elevates the risk for cardiovascular morbidity and mortality. Some recent evidence also implicates other size fractions, such as ultrafine particles (UFPs) <0.1 μm, gaseous copollutants (eg, ozone and nitrogen oxides [NO_x]), and specific sources of pollution (eg, traffic). In addition, there have been many insights into the mechanisms whereby PM could prove capable of promoting CVDs.[2–4] Air pollutants have been linked with endothelial dysfunction and vasoconstriction, increased blood pressure (BP), prothrombotic and coagulant changes, systemic inflammatory and oxidative stress responses, autonomic imbalance and arrhythmias, and the progression of atherosclerosis. In the interim, the US Environmental Protection Agency (EPA) completed its updated "Air Quality Criteria for Particulate Matter"[5] and afterward strengthened the National Ambient Air Quality Standards (NAAQS) for daily $PM_{2.5}$ levels starting in 2006 (down from 65 to 35 $\mu g/m^3$).[6] The most recent scientific review coordinated by the EPA, the final report of the Integrated Science Assessment for Particulate Matter (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546), has also been made available publicly. These numerous changes and advances provide the rationale for the present updated AHA scientific statement on PM air pollution and CVD. This updated statement is similar in scope, content, and overall structure to the first document; however, it provides many additional conclusions and recommendations that can now be made because of the expanded number and quality of studies.

Objectives and Methods

The primary objective of this scientific statement is to provide a comprehensive updated evaluation of the evidence linking PM exposure with CVDs. The focus of this review is explicitly on PM because the majority of air pollution studies have centered on its cardiovascular effects, and the strength of the evidence makes it possible to provide consensus opinions and recommendations. Except for in a few circumstances, such as when copollutants have been shown to (or not to) modify the responses to PM exposure or to have independent cardiovascular effects in epidemiological studies of major importance, a detailed discussion of other air pollutants (eg, ozone and NO_2) is beyond the scope of this document. Additional objectives are to provide expert consensus opinions on aspects related to the current state of science, to specifically highlight the health and clinical implications of the reviewed findings, and to provide prudent and practical recommendations for measures to reduce PM exposure that might thereby lower the associated cardiovascular risk. This updated scientific statement is structured to first provide a clinical perspective on the cardiovascular risks posed by PM exposure and then briefly review the components of air pollution. The following sections highlight the major findings from epidemiological studies, including mortality, morbidity, and surrogate outcome results. Next, the animal and human mechanistic studies are reviewed, and an overall framework whereby PM exposure could cause CVDs is outlined. Finally, updated consensus opinions and conclusions are provided, followed by suggestions for areas of future research and policy considerations.

Members of the current writing group were selected from across a broad range of disciplines, including cardiovascular and environmental epidemiology and statistics, atmospheric sciences, cardiovascular and pulmonary medicine, basic science research, and public policy. The writing group identified studies published in the English language between January 1, 2004, and March 31, 2009, by a World Wide Web–based literature search using Medline, PubMed, and Google search engines. Key terms included *air pollution* or *particulate matter* plus any of the following: *cardiovascular, myocardial, heart, cardiac, stroke, heart failure, arrhythmia, heart rate variability, autonomic, sympathetic, atherosclerosis, vascular, blood pressure, hypertension, diabetes, metabolic, thrombosis,* and *coagulation*. Additional studies were identified within the references of these publications and by the personal knowledge of the writing group members. A few studies published after March 31, 2009, were added during the review process. All of the identified epidemiological studies that provided mortality data or hard cardiovascular outcomes (eg, MIs) and controlled human exposure protocols were included. In a few circumstances, studies before 2004 were included briefly in the discussion or tables when it was believed that they provided contextual background and/or relevant findings from earlier analyses of ongoing studies (eg, Harvard Six Cities and American Cancer Society [ACS] cohorts) from which new results after 2004 have been published. It is a limitation of the present review that it was not possible to cite all surrogate outcome human studies because of the enormous number of publications. Some were not included, without intentional bias with regard to results, when multiple referenced studies demonstrated similar findings. In such a situation (eg, heart rate variability [HRV]), this limitation was noted within the specific section. A main theme of the present statement is to provide clinical context and recommendations for healthcare providers, and thus, it was beyond the scope and not the intent of this document to include all animal, ex vivo, or toxicological studies. A number of these publications were also not included, without intentional bias with regard to results. The writing group included publications that were believed to have relevant implications for human cardiovascular health, those that formed the foundation of the mechanistic hypotheses, and studies that were deemed of major importance. Finally, the "evidence summary" statements and all points in the conclusions and recommendations represent consensus expert opinions agreed on by all members of the writing group during formal discussions. It is explicitly stated when no such agreement was reached. These statements and the points within Tables 6 and 7 do not represent the result of applying the standard AHA criteria (ie, level and class) to the sum findings of the present review, because those do not apply, but rather the qualitative consensus opinions agreed on by the writing group. The purpose is to provide expert opinions on the comparative relative ranking and the strength of the overall evidence regarding different areas within this field of science.

Perspective on the Air Pollution–Cardiovascular Risk Association

Traditional cardiovascular risk factors account for the major portion of the risk for ischemic cardiac events within a population.[7] Individuals with optimal levels of all risk factors have been shown to have a low lifetime cardiovascular event rate.[8] Thus, control of the traditional risk factors is recognized to be of paramount importance to prevent CVDs. In this context, there has been some debate about the overall clinical relevance and utility of adding novel risk factors to risk-prediction models to incrementally improve their overall predictive value, even when assessed by multiple methodologies.[9] On the other hand, the ability to predict future events by existing models remains imperfect. In addition to several mathematical and statistical explanations for this shortcoming,[10,11] it is important to recognize that the development of vascular or atherosclerotic disease (the factor predicted by most statistical models) is usually a necessary but insufficient cause of future ischemic events in and of itself. Cardiovascular events must also be triggered by an additional factor at some unknowable future time, and therefore, they transpire as a stochastic process within a population.[12] This is one of several reasons why PM air pollution is a uniquely important public health issue among the list of novel risk factors; PM inhalation is an established trigger of cardiovascular events that occur within hours to days after exposure.[12] Because of the ubiquitous and involuntary nature of PM exposure, it may continuously enhance acute cardiovascular risk among millions of susceptible people worldwide in an often inconspicuous manner. Moreover, beyond serving as a simple trigger, PM elicits numerous adverse biological responses (eg, systemic inflammation) that, in premise, may further augment future cardiovascular risk over the long term after months to years of exposure.

Effects of Short-Term Exposure

Time-series studies estimate that a 10-μg/m^3 increase in mean 24-hour $PM_{2.5}$ concentration increases the relative risk (RR) for daily cardiovascular mortality by approximately 0.4% to 1.0%.[3] Despite theoretical statistical risks ascribed to all individuals, this elevated risk from exposure is not equally distributed within a population. At present-day levels, $PM_{2.5}$ likely poses an acute threat principally to susceptible people, even if seemingly healthy, such as the elderly and those with (unrecognized) existing coronary artery or structural heart disease.[13] Therefore, the absolute risk rather than the RR of exposure may more effectively convey the tangible health burden within a population. A 10-μg/m^3 increase during the preceding day contributes on average to the premature death of approximately 1 susceptible person per day in a region of 5 million people (based on annual US death rates in 2005).[3,14] Although the dangers to 1 individual at any single time point may be small, the public health burden derived from this ubiquitous risk is enormous. Short-term increases in $PM_{2.5}$ levels lead to the early mortality of tens of thousands of individuals per year in the United States alone.[1,3,5]

Effects of Long-Term Exposure

Cohort studies estimate that the RR associated with living in areas with higher PM levels over the long term is of greater magnitude than that observed from short-term exposure increases (RR between 1.06 and 1.76 per 10 μg/m^3 $PM_{2.5}$).[3] In this context, the World Health Organization estimated that $PM_{2.5}$ contributes to approximately 800 000 premature deaths per year, ranking it as the 13th leading cause of worldwide mortality.[15] Hence, PM air pollution appears to be an important modifiable factor that affects the public health on a global scale.

Air Pollution

The first AHA statement on air pollution reviewed the size fractions, sources, and chemical constituents of PM and the main gaseous air pollutants: Nitrogen oxides (NO_x; ie, $NO+NO_2$), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3).[1] Therefore, this section within the updated statement focuses on several other contemporary aspects of air pollution characterization and exposure assessment, particularly in relation to their potential influences on cardiovascular health. In brief, PM is broadly categorized by aerodynamic diameter: All particles $<$10 μm (thoracic particles [PM_{10}]), all particles $<$2.5 μm (fine particles [$PM_{2.5}$]), all particles $<$0.1 μm (UFP), and particles between 2.5 and 10 μm (coarse particles [$PM_{10-2.5}$]). Hence, PM_{10} contains within it the coarse and $PM_{2.5}$ fractions, and $PM_{2.5}$ includes UFP particles. The concentrations of PM_{10} and $PM_{2.5}$ are typically measured in their mass per volume of air (μg/m^3), whereas UFPs are often measured by their number per cubic centimeter (Table 1). The major source of $PM_{2.5}$ throughout

Table 1. Ambient Air Pollutants

Pollutant	US Average Range	US Typical Peak*	Most Recent NAAQS for Criteria Pollutants (Averaging Time)
O_3†	0–125 ppb	200 ppb	75 ppb (8 h)‡
NO_2†	0.5–50 ppb	200 ppb	100 ppb (1 h)§ 53 ppb (Annual mean)
NO†	0–100 ppb	200 ppb	
SO_2†	0.1–50 ppb	150 ppb	140 ppb (24 h)‖ 30 ppb (Annual mean)
CO†	0.1–5 ppm	20 ppm	35 ppm (1 h)‖ 9 ppm (8 h)‖
PM_{10}¶	10–100 $\mu g/m^3$	300 $\mu g/m^3$	150 $\mu g/m^3$ (24 h)#
$PM_{2.5}$¶	5–50 $\mu g/m^3$ (Mean=13.4±5.6)	100 $\mu g/m^3$	15 $\mu g/m^3$ (Annual mean) 35 $\mu g/m^3$ (24 h)**
$PM_{2.5}$ lead¶	0.5–5 ng/m^3	150 ng/m^3	0.15 $\mu g/m^3$ (Rolling 3-month average)††
NH_3†	0.1–20 ppb	100 ppb	
HNO_3†	0–5 ppb	10 ppb	
Methane†	1–2 ppm	5 ppm	
Formaldehyde†	0.1–10 ppb	40 ppb	
Acetaldehyde†	0.1–5 ppb	20 ppb	
NMHC (VOC)¶	20–100 $\mu g/m^3$	250 $\mu g/m^3$	
Propane¶	2–20 $\mu g/m^3$	500 $\mu g/m^3$	
Benzene¶	0.5–10 $\mu g/m^3$	100 $\mu g/m^3$	
1,3-Butadiene¶	0.1–2 $\mu g/m^3$	10 $\mu g/m^3$	
Total suspended particles¶	20–300 $\mu g/m^3$	1000 $\mu g/m^3$	
$PM_{10-2.5}$¶	5–50 $\mu g/m^3$	200 $\mu g/m^3$	
Sulfate¶	0.5–10 $\mu g/m^3$	30 $\mu g/m^3$	
Nitrate¶	0.1–5 $\mu g/m^3$	20 $\mu g/m^3$	
Organic carbon¶	1–20 $\mu g/m^3$	30 $\mu g/m^3$	
Elemental carbon¶	0.1–3 $\mu g/m^3$	10 $\mu g/m^3$	
PAH¶	2–50 ng/m^3	200 ng/m^3	
UFP†	1000–20 000/cm^3	100 000/cm^3	

ppb Indicates parts per billion; ppm, parts per million; and PAH, polycyclic aromatic hydrocarbon.

*Generally not in concentrated plumes or locations of direct source emission impact.

†Typical hourly average concentrations reached in US cities.

‡The 8-hour standard is met when the 3-year average of the 4th highest daily maximum 8-hour average is less than or equal to the indicated number. In January 2010, the EPA proposed a more stringent 8-hour standard within the range of 60 to 70 ppb (http://www.epa.gov/air/ozonepollution/actions.html).

§To attain this standard, the 3-year average of the 98th percentile of the daily maximum 1-hour average at each monitor within an area must not exceed this value.

‖The level is not to be exceeded more than once per year.

¶Typical 24-hour average concentrations.

#The level is not to be exceeded more than once per year on average over 3 years.

**The daily standard is met when the 3-year average of the 98th percentile of 24-hour PM level is less than or equal to the indicated number.

††Although the typical concentrations shown in the table are for $PM_{2.5}$, the lead standard continues to be based on measurements in total suspended particulate.

the world today is the human combustion of fossil fuels from a variety of activities (eg, industry, traffic, and power generation). Biomass burning, heating, cooking, indoor activities, and nonhuman sources (eg, fires) may also be relevant sources, particularly in certain regions.

Common air pollutants and those designated as EPA criteria pollutants (ie, specifically targeted in regulations through limits on emissions or government standards such as the NAAQS) are listed in Table 1. The World Health Organization also provides ambient guidelines (http://www.euro.who.int/Document/E90038.pdf). As a result, many pollutant concentrations are tracked in the United States by nationwide monitoring networks, with up to approximately 1200 sites for O_3 and $PM_{2.5}$. Data are archived by the EPA and are available to the public (http://www.epa.gov/ttn/airs/airsaqs/). O_3 levels exceed the national standard in many areas, and thus, daily information is provided to assist the public in reducing their exposure. A lower standard for ozone concentrations was proposed recently, which will lead to more frequent occurrences of outdoor exposures deemed to be excessive (Table 1). The reporting of $PM_{2.5}$ is also becoming common because of its impact on public health and frequent violations of standards. Current and forecast air quality indices and information on both $PM_{2.5}$ and ozone are available (http://airnow.gov/). At the end of 2008, 211 US counties (or portions of counties) were in nonattainment of the 2006 daily $PM_{2.5}$ NAAQS (http://www.epa.gov/pmdesignations/2006standards/state.htm). On a positive note, the various regulations that have been established have led to substantial reductions in PM and other pollutant levels over the past 40 years in the United States and contributed toward similar improvements in other countries. However, reducing the levels of some pollutants, such as O_3, remains a challenge because of the complex chemical processes that lead to their formation in the atmosphere.[16] The population of many developing nations (China, India, Middle Eastern countries) continues to be exposed to high levels, particularly of PM, which can routinely exceed 100 $\mu g/m^3$ for prolonged periods (http://siteresources.worldbank.org/DATASTATISTICS/Resources/table 3_13.pdf).

Air Pollution Mixtures, Chemistry, and Sources

Detailed information regarding PM sizes, composition, chemistry, sources, and atmospheric interactions is beyond the scope of this document but can be found in the 2004 US EPA Air Quality Criteria for Particulate Matter final report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=87903). The source for much of the information provided in this brief summary is this document, unless otherwise specifically referenced. The typical range of ambient concentrations for several air pollutants in the United States, including the latest US NAAQS for the criteria pollutants, is given in Table 1. Classification of air quality according to 1 single pollutant and by size or mass provides an incomplete picture, because ambient air pollution is a complex mixture of gases, particles, and liquids that are continually changing and interacting with each other and natural atmospheric gases. Although $PM_{2.5}$ mass has rightfully attracted considerable attention as a target for regulation and epidemiological study, more than 98% of the air pollutant mass in the mixture we breathe in urban settings is from gases or vapor-phase compounds such as CO, nonmethane hydrocarbons or volatile organic carbons (VOCs), NO_2, NO, O_3, and SO_2. Each of these can have independent and potentially synergistic or antagonistic effects with each other and with PM; however, at present, the cardiovascular health impact of exposure to combinations of air pollutants is not well understood.

Most of the studies linking CVDs with PM exposures have focused on particle mass; thus, this association is evaluated and reported in the majority of epidemiological and toxicological studies reviewed. Although PM is regulated by mass concentration, the aspect of PM most harmful to cardiovascular health may not be best quantified by mass measurement alone. The sum effect of many features related to chemical composition and size/morphology (eg, oxidative stress potential, solubility, charge, surface area, particle count, lung deposition, and stability within the atmosphere and biological tissues) is important to consider. With regard to specific "toxic" compounds within PM, several lines of existing evidence support the idea that transition metals, organic compounds, semiquinones, and endotoxin are likely relevant in relation to promoting CVDs. In addition, certain characteristics of UFPs (eg, high surface area, particle number, metal and organic carbon content) suggest that they may pose a particularly high cardiovascular risk after short-term exposure.[17] Both the additional characterization of "criteria" pollutants and the measurement of several other pollutants (discussed below) are important to inform air quality management practices that involve air quality modeling, as well as epidemiological studies and risk assessment, which ultimately aim to improve risk-reduction strategies.

In addition to their mass concentration, pollutants can be characterized on the basis of their origin or chemical and physical properties. In terms of origin, nitrogen oxides ($NO+NO_2$), CO, SO_2, and $PM_{2.5,}$ as well as carbon dioxide (CO_2), are mainly associated with combustion of fuel or other high-temperature industrial processes. Combustion PM is composed of many chemical compounds, including organic carbon species, elemental or black carbon, and trace metals (eg, lead and arsenic). They range in size from molecular clusters a few nanometers in diameter to light-scattering particles that peak on a mass contribution basis in the diameter range of 200 to 1000 nm (0.2 to 1 μm). UFP numbers are also strongly linked to fresh combustion and traffic-related pollution. Ammonia, methane, pesticides (persistent organic pollutants), reduced sulfur compounds, resuspended dust, and natural coarse particles ($PM_{10-2.5}$) are associated with noncombustion surface or fugitive releases that arise from a variety of human (eg, agriculture) and natural (eg, erosion) activities. Agricultural emissions and releases from a range of industrial processes and waste management are also important sources. Road and windblown dust from agricultural practices and from certain industrial facilities (eg, mineral industry) also contribute to these particles, which are typically in the coarse ($PM_{10-2.5}$) or even larger ($>PM_{10}$) range.

In addition to pollutants formed directly by combustion, many others are produced primarily through chemical reactions in the atmosphere among directly emitted pollutants. These are known as secondary pollutants. Sunlight, water vapor, and clouds are often involved in this atmospheric chemistry, which leads to greater oxidation of the pollutants. Examples include PM-associated sulfate, nitrate, and ammonium and many of the organic compounds within $PM_{2.5}$. Besides O_3, which is the most prevalent secondary gaseous oxidant, a number of inorganic and organic acids and VOCs form in the atmosphere. Examples are the hydroxyl radical, peroxyacetyl nitrate, nitric acid, formic and acetic acid, formaldehyde, and acrolein.

VOCs and semivolatile organic compounds (SVOCs), the latter of which are found in both the gas and particle phase, are an additional large class of pollutants. They are associated with both combustion and fugitive emissions, as well as with secondary formation. Key examples are benzene, toluene, xylene, 1,3-butadiene, and polycyclic aromatic hydrocarbons. VOCs are among the 188 hazardous air pollutants listed by the EPA, and their main emission sources have been identified and are regulated (http://www.epa.gov/ttn/atw/mactfnlalph.html). VOCs can undergo reactions that convert toxic substances to less toxic products or vice versa. Many VOCs contribute to the formation of O_3 and are oxidized in the atmosphere, becoming SVOCs, and subsequently partition within particles and contribute to the composition of $PM_{2.5}$, as well as to its mass. A great deal of research has focused on $PM_{2.5}$ in the past decade, which has led to advances in measurement technologies[18] and greater understanding of its chemistry and atmospheric behavior.[19] Nonetheless, understanding is incomplete, particularly with regard to formation of the secondary organic fraction, the relative role of anthropogenic and biogenic emissions to organics, surface chemistry, oxidative potential,[20] and gas-to-particle partitioning.

An alternative to attempting to identify one by one which pollutant(s) or chemical compounds are most harmful is to focus on identifying the sources, which typically emit mixtures of pollutants, of greatest concern. It may be the mixture of pollutants (along with the source from which it is derived, which determines its characteristics) that is most pertinent to human health outcomes. Such information may actually be more relevant for aiding the development of effective air quality policies. One important example reviewed in the epidemiology section is that the evidence continues to grow regarding the harmful cardiovascular effects of traffic-related pollution. Traffic is ubiquitous in modern society, with a sizeable proportion of the population, particularly persons disadvantaged by low socioeconomic status, living close enough (within 500 m) to a major road or a freeway to be chronically exposed to elevated concentrations. Additionally, daily behavior brings most people close to this source, with the average US citizen over 15 years of age spending 55 minutes each day traveling in motor vehicles.[21] However, despite the consistent epidemiological findings, these studies have yet to elucidate which of the many pollutants or other associated risks (ie, noise) produced by traffic are responsible for the increase in risk for CVD. Until the most harmful agents are identified, the only practical manner to potentially reduce health consequences would be to reduce overall traffic and related emissions and to configure cities and lifestyles such that there is greater separation between the people and the source, so that we could spend less time in traffic (a major source of personal exposures in our society). There are also a myriad of other important pollutant sources of known toxic pollutants that have been implicated in health-effect studies (eg, power generation, industrial sources, steel mills, and wood smoke). A better understanding of the factors that influence population exposure to these sources, of how their emissions and mixtures of different sources affect health, and about the factors that make individuals more susceptible will aid in the development of more effective environmental health policies.

Determinants of Air Pollution Exposure

Many aspects of air pollution play a role in the characteristics of population- and individual-level exposures. Pollutants vary on multiple time scales, with emission rates, weather patterns, and diurnal/seasonal cycles in solar radiation and temperature having the greatest impact on concentrations. The temporal behavior of a pollutant is also governed by its formation rate and the length of time it remains in the atmosphere. As such, the concentrations of many air pollutants tend to co-vary. For example, NO_x and CO are emitted during combustion, as are some particle constituents (eg, elemental carbon) and VOCs, and thus, their concentrations peak during rush hour. On the other hand, O_3 and other photochemical oxidants, including secondary $PM_{2.5}$ and secondary VOCs, peak in the afternoon, particularly given certain meteorologic conditions (eg, more sunshine). Among the common air pollutants, O_3 and $PM_{2.5}$ have the longest atmospheric lifetime and thus can build up over multiple days and spread, by the prevailing winds, over large geographic regions. This can lead to similarities in their temporal and spatial patterns over broad regions and to greater numbers of people being exposed to similar levels, thus lessening interindividual variability in exposure.

Periods of suppressed horizontal and vertical mixing in the lower atmosphere lead to the buildup of multiple pollutants. These situations are most common under slow-moving or stationary high-pressure systems, which bring light winds, a stable atmosphere, and more sunshine. The frequency and seasonality of these meteorologic conditions and how they affect concentrations vary geographically, which leads to differences in the characteristics of pollution episodes from the western to the eastern United States, as well as within these regions.

The commonality of meteorology and emission sources leads to covariation in pollutant concentrations on multiple temporal and spatial scales, which makes it more challenging for epidemiological studies to identify the health effects of individual pollutants and the effects of copollutants or mixtures. Studies that depend on daily counts of mortality or morbidity events have difficulties separating the effects of the different pollutants in the urban mix. Even prospective panel studies measuring specific end points on a subdaily time scale are hindered by pollutant covariation. Some of these challenges could potentially be addressed by undertaking studies covering multiple geographic locations with differences in the structure of pollutant covariation due to different meteorology and source mixes. Indeed, this has been done, at least in part, by several existing multicity studies. Consistency in the findings in individual studies conducted in different cities also helps isolate the pollutants that may be more responsible for the health effects. The consistent positive findings with certain pollutants (eg, PM mass concentration) have helped strengthen the evidence regarding PM_{10} and $PM_{2.5}$ effects, but regardless of location, there remains the strong underlying commonality of fossil fuel combustion for many pollutants.

A final issue to consider is the cardiovascular health effects of exposures that occur at the personal level because of the different microenvironments or activities an individual experiences (eg, time in traffic, indoor sources, secondhand tobacco smoke, occupational exposure, and degree of indoor penetration of ambient PM into homes) versus the effects of exposures from less variable urban- to regional-scale ambient concentrations (ie, background pollution that most individuals encounter more uniformly). Personal monitoring demonstrates substantial variations among individual pollution exposures or characteristics among those living within the same metropolitan area and even the same neighborhood.[22,23] However, the differing additive, synergistic, and/or confounding effects on cardiovascular health of these 2 contrasting components of a person's overall exposure have not been well described. For the most part, the magnitude of the findings reported by the major epidemiological studies (see next section) are indicative of the effects of the urban- to regional-scale ambient concentrations. Actual exposures to all pollutants also vary at the personal level. The cardiovascular health importance of these individual-level variations (above and beyond the effect of urban/regional levels) remains largely unknown, in part because it has been difficult to quantify. The degree to which measurement of personal exposures or more precise exposure assessment (eg, use of geographic information systems, land-use regression models, spatial-temporal models, and adjustments for indoor penetration) can reduce the effects of exposure misclassification in epidemiological studies also remains to be fully elucidated.[24–26]

Epidemiological Studies of Air Pollution

Epidemiological studies of air pollution have examined the health effects of exposures observed in real-world settings at ambient levels. Associations between relevant health end points and measures of air pollution are evaluated while attempting to control for effects of other pertinent factors (eg, patient and environmental characteristics). Despite substantial study and statistical improvements and the relative consistency of results, some potential for residual confounding of variables and publication bias[27] of positive studies are limitations to acknowledge. Probably the most relevant, well-defined, and extensively studied health end points include mortality (all-cause and cause-specific), hospitalizations, and clinical cardiovascular events. This section reviews the results of the epidemiological research with a focus on new studies since the first AHA statement was published,[1] as well as on the cardiovascular health implications. In sum, numerous studies of varied design have been published in the interim that significantly add to the overall weight of evi-

Table 2. Comparison of Pooled Estimated of Percent Increase (and 95% CI or Posterior Interval or *t* Value) in RR of Mortality Estimated Across Meta-Analyses and Multicity Studies of Daily Changes in Exposure

	Primary Source	Exposure Increment	Percent Increases in Mortality (95% CI)		
			All-Cause	Cardiovascular	Respiratory
Meta-estimate with and without adjustment for publication bias	Anderson et al[27] 2005	20 μg/m^3 PM_{10}	1.0 (0.8–1.2) 1.2 (1.0–1.4)	…	…
Meta-estimates from COMEAP report to the UK Department of Health on CVD and air pollution	COMEAP[31] 2006	20 μg/m^3 PM_{10} 10 μg/m^3 $PM_{2.5}$	… …	1.8 (1.4–2.4) 1.4 (0.7–2.2)	… …
NMMAPS, 20 to 100 US cities	Dominici et al[34] 2003	20 μg/m^3 PM_{10}	0.4 (0.2–0.8)	0.6 (0.3–1.0)*	…
APHEA-2, 15 to 29 European cities	Katsouyanni et al[35] 2003 Analitis et al[36] 2006	20 μg/m^3 PM_{10}	1.2 (0.8–1.4)	1.5 (0.9–2.1)	1.2 (0.4–1.9)
US, 6 cities	Klemm and Mason[37] 2003	10 μg/m^3 $PM_{2.5}$	1.2 (0.8–1.6)	1.3 (0.3–2.4)†	0.6 (−2.9, 4.2)‡
US, 27 cities, case-crossover	Franklin et al[38] 2007	10 μg/m^3 $PM_{2.5}$	1.2 (0.3–2.1)	0.9 (−.1, 2.0)	1.8 (0.2, 3.4)
California, 9 cities	Ostro et al[39] 2006	10 μg/m^3 $PM_{2.5}$	0.6 (0.2–1.0)	0.6 (0.0, 1.1)	2.2 (0.6, 3.9)
France, 9 cities	Le Tertre et al[40] 2002	20 μg/m^3 BS	1.2 (0.5–1.8)§	1.2 (0.2–2.2)§	1.1 (−1.4, 3.2)§
Japan, 13 cities, age >65 y	Omori et al[41] 2003	20 μg/m^3 SPM	1.0 (0.8–1.3)	1.1 (0.7–1.5)	1.4 (0.9–2.1)
Asia, 4 cities	Wong et al[42] 2008	10 μg/m^3 PM_{10}	0.55 (0.26–0.85)	0.59 (0.22–0.93)	0.62 (0.16–1.04)
US, 112 cities	Zanobetti et al[43] 2009	10 μg/m^3 $PM_{2.5}$	0.98 (0.75–1.22)	0.85 (0.46–1.24)	1.68 (1.04–2.33)
		10 μg/m^3 $PM_{10-2.5}$‖	0.46 (0.21–0.71)	0.32 (0.00–0.64)	1.16 (0.43–1.89)
		10 μg/m^3 $PM_{2.5}$¶	0.77 (0.43–1.12)	0.61 (0.05–1.17)	1.63 (0.69–2.59)
		10 μg/m^3 $PM_{10-2.5}$¶	0.47 (0.21–0.73)	0.29 (−0.04, 0.61)	1.14 (0.043–1.85)

CI indicates confidence interval or posterior interval.
*Cardiovascular and respiratory deaths combined.
†Ischemic heart disease deaths.
‡Chronic obstructive pulmonary disease deaths.
§Includes general additive model–based analyses with potentially inadequate convergence.
‖Results for $PM_{10-2.5}$ are from 47 cities.
¶Results of 2 pollutant models controlling for alternate PM size in 47 cities.

dence that exposure to air pollutants at present-day levels contributes to cardiovascular morbidity and mortality.

Mortality and Air Pollution

Time-Series and Related Studies

Time-series and case-crossover studies explore associations between short-term changes in air pollution and daily changes in death counts. The sum of current evidence supports the findings of an earlier review[28] that demonstrated that short-term elevations in daily PM levels lead to a greater absolute risk for CVD-related mortality than for all other causes. Even if similar acute RR elevations ($\approx$1.01) are estimated between cardiovascular and pulmonary mortality, CVDs account for 69% of the increase in absolute mortality rates compared with 28% for pulmonary diseases attributable to short-term PM exposure. Recently, more rigorous modeling techniques have been used in attempts to better estimate pollution-mortality associations while controlling for other time-dependent confounding covariables.[29,30] There have been well over 100 published daily time-series studies reporting small but statistically significant PM-mortality associations that have been the subject of quantitative reviews or meta-analyses.[3,27,31–33] Table 2 summarizes recent multicity analyses and studies published since 2004.

To address concerns about city selection bias, publication bias, and influences of copollutants, several large, multicity, daily time-series studies have been conducted worldwide. One of the largest was the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). Published reports from this study included as few as 20 US cities,[44,45] as many as 100 cities,[46,47] and more recently, data for hundreds of counties (Table 2).[48] The observed relationship between PM exposure and excess mortality remained independent of several gaseous copollutants (NO_2, CO, or SO_2). Recent analyses suggest that O_3 may also independently contribute to cardiopulmonary mortality risk[49,50]; however, coexposures to secondary particle pollutants may be responsible in part for this latter association.[51]

Several studies have also been conducted outside the United States, including the Air Pollution and Health: A European Approach (APHEA and APHEA-2) projects, which examined daily PM-related mortality effects in multiple cities.[36,52] PM air pollution was significantly associated with daily mortality counts for all-cause, cardiovascular, and respiratory mortality (Table 2). Further analyses of the European data suggest that CVD deaths are also associated with exposure to NO_2[53] and CO.[54] A few new time-series studies have also confirmed similar increases in cardiovascular mortality related to short-term PM exposure in China[55–57] and Bangkok, Thailand.[42] Additional multicity studies have been conducted worldwide with analyses of CVD deaths (Table 2).[38–42,58–60] Finally, in a recent analysis that included several Asian cities, SO_2, NO_2, O_3, and PM_{10} were all associated with excess cardiovascular mortality.[42]

In an attempt to evaluate the coherence of multicity studies across continents, the Air Pollution and Health: A Combined European and North American Approach (APHENA) study analyzed data from the APHEA, NMMAPS, and Canadian studies.[61] The combined effect on all-cause mortality ranged from 0.2% to 0.6% for a 10-μg/m^3 elevation in daily ambient PM_{10}, with the largest effects observed in Canada. Among individuals older than 75 years, the effects were greater for cardiovascular mortality than for overall and pulmonary mortality (0.47% to 1.30%). Older age (>75 years) and higher rates of unemployment were related to greater PM mortality risks in both continents. Higher NO_2 levels were associated with larger PM_{10} effects on mortality, particularly in Europe. Finally, there appeared to be no lower-limit threshold below which PM_{10} was not associated with excess mortality across all regions.

Evidence Summary

The overall evidence from time-series analyses conducted worldwide since publication of the first AHA statement[1] confirms the existence of a small, yet consistent association between increased mortality and short-term elevations in PM_{10} and $PM_{2.5}$ approximately equal to a 0.4% to 1.0% increase in daily mortality (and cardiovascular death specifically) due to a 10-μg/m^3 elevation in $PM_{2.5}$ during the preceding 1 to 5 days (Table 2).

Cohort and Related Studies

Although short-term changes in PM concentrations have deleterious health effects, longer-term exposures may have a more pertinent clinical health effect on cardiovascular morbidity and mortality given that individuals are typically exposed to higher air pollution levels over extended periods of time. An additional source of exposure variability that has been exploited in epidemiological studies is spatial variability, which includes differences in average ambient concentrations over extended periods of time across metropolitan areas or across smaller communities within local areas. Recent emphasis has been on prospective cohort studies that control for individual differences in multiple confounding variables and cardiovascular risk factors. A summary of these studies is presented in Table 3 and Figure 1. These cohort studies generally demonstrate larger overall mortality effects than the results of time-series analyses.

Harvard Six Cities and ACS Studies

Two landmark cohort-based mortality studies, the Harvard Six Cities[62] and the ACS studies,[66] were reported in the mid 1990s and were discussed previously.[1] In both, $PM_{2.5}$ and sulfate particulate pollution were associated with increases in all-cause and cardiopulmonary disease (Table 3). In addition, intensive independent reanalyses[63] corroborated the original findings of both studies and resulted in innovative methodological contributions that demonstrated the robustness of the results to alternative modeling approaches. In both the Harvard Six Cities[62,64] and the ACS[67] studies, PM air pollution–related mortality was substantially higher for cardiovascular- than for pulmonary-related causes.

Since 2004, there have been further analyses of both studies. Laden et al[64] extended the mortality follow-up of the Harvard Six Cities cohort for an additional 8 years. $PM_{2.5}$ associations, similar to those found in the original analysis, were observed for all-cause and CVD mortality (Table 3). Furthermore, reductions in $PM_{2.5}$ concentrations for the extended follow-up period were associated with reduced mortality risk. Further analysis suggested that the health effects of changes in exposure were seen primarily within 2 years.[84] In addition to confirming the earlier mortality relationship, the recent observations suggest that the adverse health effects mediated by longer-term PM air pollution exposure can be estimated reasonably accurately by the previous few years of particle levels.

Extended analyses of the ACS cohort that emphasize efforts to control for the effects of other covariates and risk factors have corroborated the previously reported mortality associations with particulate and sulfur oxide pollution.[68] Elevated mortality risks were most strongly associated with $PM_{2.5}$. Coarse particles ($PM_{10-2.5}$) and gaseous pollutants, except for SO_2, were generally not significantly related to mortality. In another extended analysis,[67] the death certificate classifications of underlying causes of death due to $PM_{2.5}$ exposures were observed to be principally ischemic heart disease, arrhythmias, heart failure, and cardiac arrest. Finally, recent additional analyses attempted to control for the fact that variations in exposure to air pollution across cities or within cities may correlate with socioeconomic or demographic gradients that influence health and susceptibility to environmental exposures.[85,86] When controlled for individual risk factor data, the mortality associations for intrametropolitan $PM_{2.5}$ concentration differences within the Los Angeles, Calif, area were generally larger than those observed in the full cohort across metropolitan areas.[69] However, the results were somewhat sensitive to the inclusion of zip code–level ecological variables, which suggests potential contextual neighborhood confounding. Krewski et al[70] subsequently observed that full adjustments for multiple ecological covariates did not reduce the estimated $PM_{2.5}$-related mortality effect. The association for ischemic heart disease mortality in particular was highly robust across various study areas and modeling strategies and after controlling for both individual and ecological covariates.

An additional recent analysis of the ACS cohort evaluated the health effects of ozone compared with $PM_{2.5}$.[87] The findings reconfirmed the independent cardiovascular mortality increase related to fine-particle exposure. However, after adjustment for $PM_{2.5}$, ozone was associated solely with an elevated risk of death due to respiratory causes; there was no independent risk of ozone exposure on CVD-related mortality. This suggests that the positive findings reported in NMMAPS[50] regarding cardiopulmonary mortality and short-term ozone exposure could be explained at least in part by the enhanced risk of mortality due to lung disease categories.

Table 3. Summary of Cohort Study Results

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 $\mu g/m^3$ $PM_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Harvard Six Cities, original (Dockery et al[62] 1993)	≈8	1974–1991	Individual (smoking+others)	13 (4.2–23)	18 (6.0–32)	…	…
Harvard Six-Cities, HEI reanalysis, Krewski et al[63] 2004	≈8	1974–1991	Individual (smoking+others)	14 (5.4–23)	19 (6.5–33)	…	…
Harvard Six-Cities, extended, Laden et al[64] 2006	≈8	1974–1998	Individual (smoking+others)	16 (7–26)	…	28 (13–44)	…
Six-Cities Medicare cohort, Eftim et al[65] 2008	≈340	2000–2002	Individual (age, sex)	21 (15–27)	…	…	…
ACS, Original, Pope et al[66] 1995	≈500	1982–1989	Individual (smoking+others)	6.6 (3.5–9.8)	12 (6.7–17)	…	…
ACS, HEI reanalysis, Krewski et al[63] 2004	≈500	1982–1989	Individual (smoking+others) +ecological	7.0 (3.9 10)	12 (7.4–17)	13 (8.1–18)	…
ACS, extended I, Pope et al[67,68] 2002, 2004	≈500	1982–1998	Individual (smoking+others)	6.2 (1.6–11)	9.3 (3.3–16)	12 (8–15)	18 (14–23)
ACS, intrametro Los Angeles, Jerrett et al[69] 2005	≈23	1982–2000	Individual (smoking+others) +ecological	17 (5–30)	12 (−3–30)	…	39 (12–73)
ACS, extended II, Krewski et al[70] 2009	≈500	1982–2000	Individual (smoking+others) +ecological	5.6 (3.5–7.8)	13 (9.5–16)	…	24 (20–29)
ACS, Medicare cohort, Eftim et al[65] 2008	7333	2000–2002	Individual (age, sex)+ecological +COPD	11 (9–13)	…	…	…
US Medicare cohort, east/central/west, Zeger et al[71] 2008	13 200	2000–2005	Individual (age, sex)+ecological +COPD	6.8 (4.9–8.7),* 13 (9.5–17) −1.1 (−3 to 0.8)	…	…	…
Women's Health Initiative, Miller et al[72] 2007	≈66	1994–2002	Individual (smoking+others)	…	…	76 (25–147), 24 (9–41)†	…
Nurses' Health Study, Puett et al[73] 2008	≈66	1992–2002	Individual (smoking+others) ecological	7.0 (−3.0 to 18)‡	…	30 (0–71)‡	…
AHSMOG, males only, McDonnell et al[74] 2000	≈4	1977–1992	Individual (smoking+others)	8.5 (−2.3 to 21)	23 (−3 to 55)	…	…
AHSMOG, females only, Chen et al[75] 2005	≈4	1977–2000	Individual (smoking+others)	…	…	42 (6–90)	…
VA hypertensive male I study, Lipfert et al[76] 2006	≈42	1989–1996	Individual (smoking+others) +ecological	15 (5–26)§	…	…	…
VA hypertensive male II study, Lipfert et al[77] 2006	≈30	1997–2001	Individual (smoking+others) +ecological	6 (−6 to 22)	…	…	…
11 CA county, elderly, Enstrom[78] 2005	≈36	1973–2002	Individual (smoking+others) +ecological	4 (1–7)‖, 1 (−0.6 to 2.6)	…	…	…
French PAARC, Filleul et al[79] 2005	≈14	1974–2000	Individual (smoking+others)	7 (3–10)‡	5 (−2 to 12)‡	…	…
German women, Gehring et al[80] 2006	≈5	1980s, 1990s–2003	Individual smoking and socioeconomic status	12 (−8 to 38)	52 (9–115)	…	…

(*Continued*)

Table 3. Continued

Study	Size of Cohort (000s)	Follow-Up Period	Covariates Controlled for	Percent Increases in Mortality (95% CI) Associated With 10 μg/m^3 PM$_{2.5}$ (or Other When Indicated)			
				All-Cause	Cardiopulmonary	Cardiovascular	Ischemic Heart Disease
Oslo, Norway, intrametro, Naess et al[81] 2007	≈144	1992–1998	Individual age, occupational class, education	…	…	10 (5–16),¶ 14 (6–21), 5 (1–8), 3 (0–5)	…
Dutch cohort, Beelen et al[82] 2008	≈121	1987–1996	Individual (smoking+others) +ecological	6 (−3 to 16)	…	4 (−10 to 21)	…
Great Britain, Elliott et al[83] 2007	≈660	1966–1998	Socioeconomic status	1.3 (1.0–1.6)‡#	1.7 (1.3–2.2)‡#	1.2 (0.7–1.7)‡#	

HEI indicates Health Effects Institute; VA, Veterans Affairs; COPD, chronic obstructive pulmonary disease; and CA, California.

*Three estimates are for the East, Central, and West regions of the United States, respectively.

†Any cardiovascular event.

‡Associated with 10 μg/m^3 British Smoke (BS) or PM$_{10}$.

§Estimates from the single-pollutant model. Effect estimates were smaller and statistically insignificant in analyses restricted to counties with nitrogen dioxide data. County-level traffic density was a strong predictor of survival, and stronger than PM$_{2.5}$ when included with PM$_{2.5}$ in joint regressions.

||Two estimates are for the follow-up period 1973–1982 and the follow-up period 1983–2002, respectively.

¶Four estimates are for men 51–70 y old, women 51–70 y old, men 71–90 y old, and women 71–90 y old, respectively.

#Using last 0- to 4-year exposure window.

Additional Cohort Studies

Several additional cohort studies have been published in the past few years (Table 3). Eftim and colleagues[65] studied 2 very large "cohorts" of US Medicare participants who lived in locations included in the Harvard Six Cities and ACS studies. Effects of PM$_{2.5}$ exposure on mortality for the period 2000 to 2002 were estimated after controlling for multiple factors, although not at the individual patient level. For all-cause mortality, the PM$_{2.5}$-mortality associations were larger than those observed in the Harvard Six Cities or ACS cohorts. In an additional analysis of 13.2 million US Medicare participants for the time period 2000 to 2005,[71] PM$_{2.5}$-mortality associations were shown to be similar to those observed in the Harvard Six Cities and ACS studies in the East and Central regions of the United States (and when the data were pooled for the entire United States). However, PM$_{2.5}$ was not associated with mortality in the Western United States or for the oldest age group (>85 years old). These findings generally corroborate the earlier cohort studies and add evidence that aspects of exposure (PM sources or composition) and patient susceptibility might play important roles in determining the health risks.

In a cohort of postmenopausal women without prior CVD from the Women's Health Initiative Observational Study,[72] an association between longer-term PM$_{2.5}$ exposure (median follow-up of 6 years) and cardiovascular events (primary end point) was observed. After adjustment for age and other risk factors, an incremental difference of 10 μg/m^3 PM$_{2.5}$ was associated with a 24% (95% confidence interval [CI]9% to 41%) increase in all first cardiovascular events (fatal and nonfatal, with a total of 1816 cases). Notably, an incremental difference of 10 μg/m^3 PM$_{2.5}$ was also associated with a large 76% (95% CI 25% to 147%) increase in fatal cardiovascular events, based on 261 deaths. The risks for both coronary heart disease and strokes were found to be similarly elevated. Interestingly, within-city PM$_{2.5}$ gradients appeared to have larger cardiovascular effects than those between cities, although this difference was not statistically significant. Finally, overweight women (body mass index >24.8 kg/m^2) were at relatively greater cardiovascular risk due to particulate air pollution than leaner women. Noteworthy aspects of this study were improved assessment of the end points by medical record review (rather than by death certificate) and long-term particle exposure estimation. The control for individual-level confounding variables was also superior to that of previous cohort studies.

In another cohort of women, a subset of the Nurses' Health Study from the northeastern United States,[73] an increase of 10 μg/m^3 modeled estimates of PM$_{10}$ exposures was associated with an approximately 7% to 16% increased risk of all-cause mortality and a 30% to 40% increase in fatal coronary heart disease, depending on the level of adjustment for covariates. This study found that the strongest health risks for all-cause and cardiovascular mortality were seen in association with the average PM$_{10}$ exposure during the previous 24 months before death. Similar to the findings of the Women's Health Initiative, the cardiovascular mortality risk estimates were larger than those of previous cohort studies. In addition, obese women (body mass index >30 kg/m^2) were at greater relative risk, and the increases in mortality (all-cause and cardiovascular) were larger than the effects on nonfatal events. The results were also in accordance with the latest Harvard Six Cities analyses[64] that show that exposure over the most recent preceding 1 to 2 years can accurately estimate the majority of the health risks due to longer-term PM air pollution exposures.

The pollution-mortality association has also been assessed in several other cohort studies in the United States and Europe (Table 3).[76–83] In a recent analysis of the Adventist Health Study of Smog (AHSMOG) cohort with a much

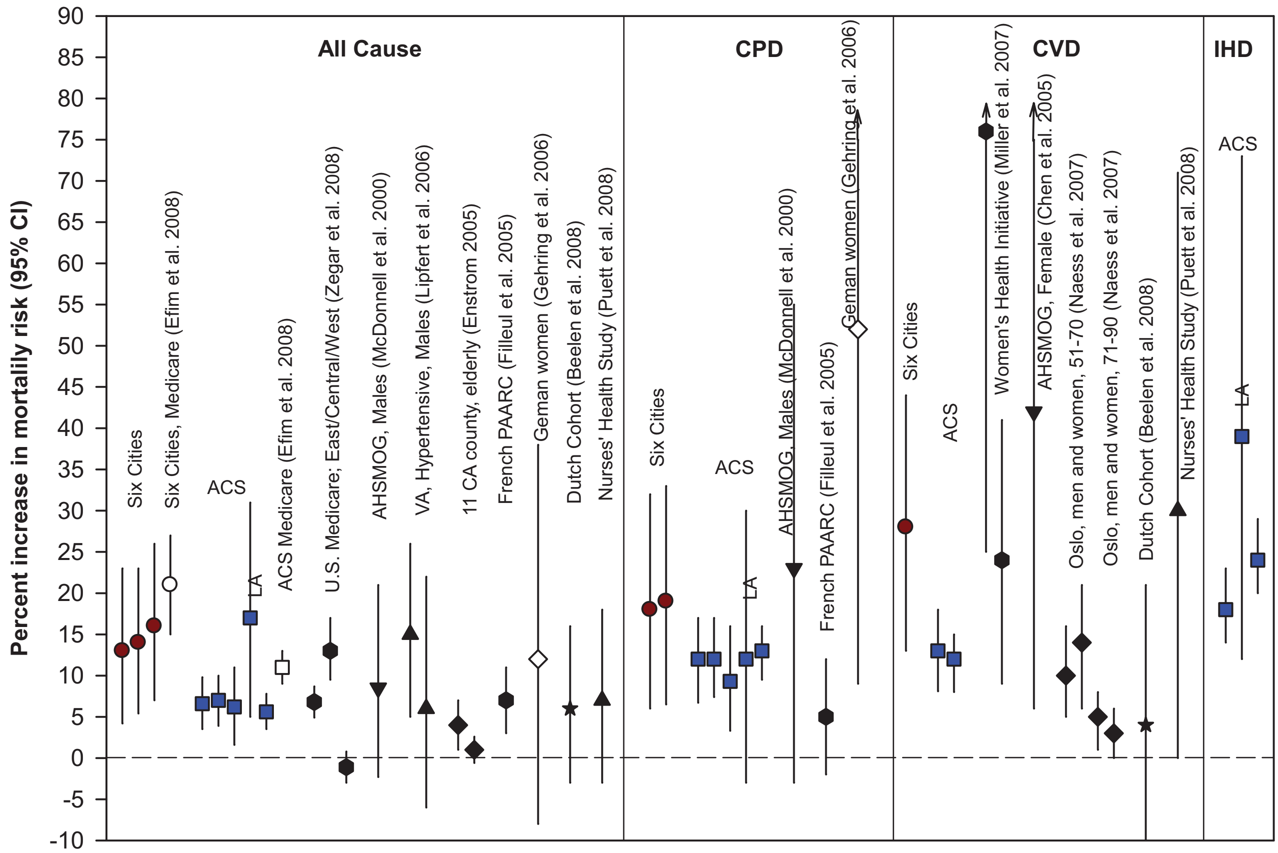

Figure 1. Risk estimates provided by several cohort studies per increment of 10 μg/m^3 in PM$_{2.5}$ or PM$_{10}$. CPD indicates cardiopulmonary disease; IHD, ischemic heart disease.

longer follow-up than the original studies,[74,88] fatal coronary heart disease was significantly associated with PM$_{2.5}$ among females but not males.[75] These observations along with the remarkably robust health effects in the Women's Health Initiative Observational Study and Nurses' Health Study suggest that women may be at special risk from PM exposure. The overall cohort study evidence demonstrates that a 10-μg/m^3 increase in PM$_{2.5}$ exposure is in general positively associated with excess mortality, largely driven by increases in cardiopulmonary or cardiovascular deaths (Figure 1). Independent results from the Women's Health Initiative Study,[72] the US Medicare cohorts,[71] the German women cohort,[80] and the intracity Oslo (Norway) study[81] contribute substantially to this evidence. Although the Dutch cohort,[82] AHSMOG,[74,75] French PAARC (Pollution Atmosphérique et Affections Respiratoires Chroniques [air pollution and chronic respiratory diseases]),[79] Veterans Affairs hypertensive male study,[77] and 11 CA county[78] studies observed increased mortality risks associated with higher PM$_{2.5}$ exposure that were statistically significant in some analyses, the observed health risks were less robust. A finding that is somewhat consistent across the Veterans Affairs hypertensive male study,[77] 11 CA county,[78] Oslo,[81] and US Medicare cohorts[71] is that the PM$_{2.5}$-mortality effect estimates tend to decline with longer periods of follow up or in a substantially older cohort. These studies also often observed elevated mortality risks according to alternative indicators of air pollution exposure, especially metrics of traffic-related exposure.

Evidence Summary

The overall evidence from the cohort studies demonstrates on average an approximate 10% increase in all-cause mortality per 10-μg/m^3 elevation in long-term average PM$_{2.5}$ exposure. The mortality risk specifically related to CVD appears to be elevated to a similar (or perhaps even greater) extent, ranging from 3% to 76% (Table 3). This broader estimated range in risk compared with the short-term effects observed in time series is due to several recent cohort studies[72,73] that demonstrated larger cardiovascular mortality risks (eg, >30%) than in earlier cohort observations. This may reflect superior aspects of these studies that allowed for a better characterization of the cardiovascular risk of long-term exposure, the fact that these cohorts consisted of only women, or other unclear reasons. Compared with cardiovascular mortality, there is less existing evidence to support an increase in the risk for nonfatal cardiovascular events related to PM$_{2.5}$ exposure among the existing cohort studies, because many of them did not specifically investigate nonfatal outcomes, and several of the more recent studies reported nonsignificant relationships.[72,73]

Natural Experiment and Intervention Studies

Several studies have shown improvements in health outcomes in association with exposures using well-defined natural experiments or interventions, such as abrupt reductions in air pollution[89–91] or changes over a longer period of time.[64,92]

Table 4. Comparison of Pooled Estimated of Percent Increase in Risk of Hospital Admission for CVD Estimated Across Meta-Analyses and Multicity Studies of Daily Changes in Exposure

	Primary Source	Exposure Increment	% Increase (95% CI)
Cardiac admissions, meta-analysis of 51 estimates	COMEAP[31] 2006	20 $\mu g/m^3$ PM_{10}	1.8 (1.4–1.2)
Cardiac admissions, 8 US cities	Schwartz[96] 1999	20 $\mu g/m^3$ PM_{10}	2.0 (1.5–2.5)
Cardiac admissions, 10 US cities	Zanobetti et al[97] 2000	20 $\mu g/m^3$ PM_{10}	2.6 (2.0–3.0)
Cardiac admissions, 14 US cities	Samet et al[98] 2000	20 $\mu g/m^3$ PM_{10}	2.0 (1.5–2.5)
	Schwartz et al[99] 2003		
Cardiac admissions, 8 European cities	Le Tertre et al[40] 2002	20 $\mu g/m^3$ PM_{10}	1.4 (0.8–2.0)
Cardiovascular admissions, 14 Spanish cities	Ballester et al[100] 2006	20 $\mu g/m^3$ PM_{10}	1.8 (7–3.0)
Cardiovascular admission, 8 French cities	Larrieu et al[101] 2007	20 $\mu g/m^3$ PM_{10}	1.6 (0.4–3.0)
Cardiovascular admissions, 202 US counties	Bell et al[102] 2008	20 $\mu g/m^3$ PM_{10}	0.8 (0.6–1.0)
Medicare national claims history files	Dominici et al[103] 2006	10 $\mu g/m^3$ $PM_{2.5}$	
Ischemic heart disease,			0.44 (0.02–0.86)
Cerebrovascular disease			0.81 (0.30–1.32)
Heart failure			1.28 (0.78–1.78)
Heart rhythm			0.57 (−0.01 to 1.15)

Small but statistically significant drops in mortality were associated with an 8½-month copper smelter strike that resulted in sharp reductions in sulfate PM and related air pollutants across 4 Southwest states, even after controlling for other factors.[93] Data from US Medicare enrollment files were used to estimate the association between changes in monthly mortality rates for US counties and average $PM_{2.5}$ concentrations for the previous 12 months.[94] $PM_{2.5}$-mortality associations were observed at the national scale but not the local scale, which raises concerns about possible statistical confounding due to unmeasured individual and ecological variables as a cause for any positive findings in this study. However, a recent large study found that reductions in PM air pollution exposure on a local scale (across US counties) over a 2-decade period (1980s and 1990s) were associated with increased life expectancy even after controlling for changes in socioeconomic, demographic, and proxy smoking variables.[95] Indeed, a decrease of 10 $\mu g/m^3$ in the long-term $PM_{2.5}$ concentration was related to an increase in mean life expectancy of 0.61 ± 0.20 years.

Hospitalization Rates

There are many daily time-series or case-crossover studies that have evaluated associations between cardiovascular hospitalizations and short-term changes in air pollution. Because of the great number of publications, all studies (particularly those focusing on nonparticulate air pollutants) cannot be discussed individually. Nevertheless, Table 4 presents a comparison of pooled estimates of percent increase in RR of hospital admission for general cardiac conditions across a previous meta-analysis of 51 published estimates (COMEAP [Committee on the Medical Effects of Air Pollutants]) and results from many selected multicity studies published after 2004. Several studies before 2004 are included in Table 4 only to demonstrate the consistency of effect.

Because of its comparatively large size and importance, the results of a recent analysis of Medicare files in 204 US urban counties with 11.5 million individuals older than 65 years merit discussion. Daily changes in $PM_{2.5}$ levels were associated with a variety of cardiovascular hospital admission subtypes.[103] A 10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure was related to increases in hospitalizations for cerebrovascular disease by 0.81% (95% CI 0.3% to 1.32%), peripheral vascular disease by 0.86% (95% CI −0.06% to 1.79%), ischemic heart disease by 0.44% (95% CI 0.02% to 0.86%), arrhythmias by 0.57% (95% CI −0.01% to 1.15%), and heart failure by 1.28 (95% CI 0.78% to 1.78%). The most rapid effects, which occurred largely on the same day of $PM_{2.5}$ elevation, were seen for cerebrovascular, arrhythmia, and heart failure admissions. Ischemic heart disease events tended to increase to a greater extent 2 days after exposures. A consistent finding was that the cardiovascular effects of pollution were much stronger in the Northeast than in other regions. In fact, there were few significant associations in Western US regions. It was speculated that these differences reflected variations in particle composition (eg, greater sulfate in the East and nitrate components in the West) and pollution sources (eg, power generation in the East and transportation sources in the West). In a follow-up analysis by Peng et al,[104] $PM_{10-2.5}$ levels were not statistically associated with cardiovascular hospitalizations after adjustment for $PM_{2.5}$. This suggests that the smaller particles (ie, $PM_{2.5}$) are principally responsible for the cardiovascular hospitalizations attributed in prior studies to the combination of both fine and coarse particles (ie, PM_{10}). Given the differences between the size fractions, the results imply that particles and their components derived from combustion sources (ie, $PM_{2.5}$) are more harmful to the cardiovascular system than larger coarse particles. Finally, there is some evidence that gaseous pollutants may also instigate hospitalizations. Hospital admissions for cardiovascular causes, particularly ischemic heart disease, were found to rise in relation to the previous-day and same-day level of SO_2, even after adjustment for PM_{10} levels.[105]

Table 5. Comparisons of Estimated Percent Increase in Risk of Ischemic Heart Disease Events due to Concurrent or Recent Daily PM Exposure

Event/Study Area	Primary Source	Exposure Increment	% Increase (95% CI)
MI events–Boston, Mass	Peters et al[110] 2001	10 $\mu g/m^3$ $PM_{2.5}$	20 (5.4–37)
MI, 1st hospitalization–Rome, Italy	D'Ippoliti et al[112] 2003	30 $\mu g/m^3$ TSP	7.1 (1.2–13.1)
MI, emergency hospitalizations–21 US cities	Zanobetti and Schwartz[113] 2005	20 $\mu g/m^3$ PM_{10}	1.3 (0.2–2.4)
Hospital readmissions for MI, angina, dysrhythmia, or heart failure of MI survivors–5 European cities	Von Klot et al[114] 2005	20 $\mu g/m^3$ PM_{10}	4.2 (0.8–8.0)
MI events–Seattle, Wash	Sullivan et al[115] 2005	10 $\mu g/m^3$ $PM_{2.5}$	4.0 (−4.0–14.5)
MI and unstable angina events–Wasatch Front, Utah	Pope et al[13] 2006	10 $\mu g/m^3$ $PM_{2.5}$	4.8 (1.0–6.6)
Tokyo metropolitan area	Murakami et al[109] 2006	TSP >300 $\mu g/m^3$ for 1 h vs reference periods <99 $\mu g/m^3$	40 (0–97)*
Nonfatal MI, Augsburg, Germany	Peters et al[111] 2004	Exposure to traffic 1 h before MI (note: not PM but self-reported traffic exposure)	292 (222–383)
Nonfatal MI, Augsburg, Germany	Peters et al[116] 2005	Ambient UFP, $PM_{2.5}$, and PM_{10} levels	No association with UFP or $PM_{2.5}$ on same day. Positive associations with $PM_{2.5}$ levels on 2 days prior

TSP indicates total suspended particulate matter.
*Adjusted rate ratio for MI deaths.

Evidence Summary

Excess cardiovascular mortality and increased rates of hospitalizations are similarly associated with day-to-day changes in PM air pollution (Tables 2 and 4). However, significant differences between geographic regions in the risk relationships have been observed, and more investigation is required to explain this heterogeneity.

Specific Cardiovascular Events/Conditions

Ischemic Heart Disease

Among the cohort studies that provided relevant results, the ACS study found a relationship between increased risk for ischemic heart disease death and long-term exposure to elevated $PM_{2.5}$ levels (Table 3).[67,69,106] Indeed, ischemic cardiac events accounted for the largest relative (RR 1.18, 95% CI 1.14 to 1.23) and absolute risk for mortality per 10-$\mu g/m^3$ elevation in $PM_{2.5}$.[67] A survival analysis of US Medicare data for 196 000 survivors of acute MI in 21 cities showed the risk of an adverse post-MI outcome (death, subsequent MI, or first admission for congestive heart failure) was increased with higher exposure to PM_{10}.[107] Data from the Worcester Heart Attack study also found that long-term exposure to traffic-related air pollution was associated with significantly increased risk of acute MI.[108] However, in the Women's Health Initiative[72] and the Nurses' Health Study,[73] only disease categories that included fatal coronary events, but not nonfatal MI alone, were statistically elevated in relation to $PM_{2.5}$. The effect size for cardiovascular mortality was much larger and much more statistically robust than for nonfatal events such as MI in both studies.

Various time-series and case-crossover studies have also reported increased ischemic heart disease hospital admissions associated with short-term elevated concentrations of inhalable and/or fine PM air pollution.[31,40,103] In the US Medicare study, a reduction of $PM_{2.5}$ by 10 $\mu g/m^3$ was estimated to reduce ischemic heart disease admissions in 204 counties by 1523 (95% posterior interval 69 to 2976) cases per year.[103] Several studies have also found positive associations between elevated PM or traffic exposures over a period as brief as a few hours[109–111] or a few days and an elevated risk for MI (Table 5).[13,110,112–115] In general, acute increases in risk for ischemic heart disease events have been observed consistently, even as rapidly as 1 to 2 hours after exposure to elevated PM, in case-crossover analyses.[109–111] Other studies have reported an increased risk for MI shortly after exposure to traffic. Peters et al[111] reported in 691 subjects in Augsburg, Germany, a strong association (odds ratio 2.92, 95% CI 2.22 to 3.83) between onset of MI and traffic exposure within the past hour, although whether this was a result of the air pollution or a combination of other factors (eg, noise and stress) is not certain. Additional analyses did not report an association between recent UFP exposures and MI onset; however, the levels of $PM_{2.5}$ and several gaseous pollutants 2 days earlier were related to MI risk.[116] The lack of relationship between MI and UFPs may be due to the fact that the levels were measured regionally and remote from the localized source and may therefore reflect exposure misclassification. Finally, in the only study in which participating subjects had coronary angiograms performed previously, ischemic cardiac events were found to occur in relation to PM air pollution exposure solely among individuals with obstructive coronary atherosclerosis in at least 1 vessel.[13] This finding suggests the importance of patient susceptibility (eg, the presence of preexisting coronary artery disease) for PM to trigger an acute ischemic event within hours to days after exposure.

Heart Failure

In the ACS cohort study, it appeared that deaths due to arrhythmias, heart failure, and cardiac arrest (RR 1.13, 95% CI 1.05 to 1.21 per 10 $\mu g/m^3$) were also associated with prolonged exposure to $PM_{2.5}$, although not as strongly as ischemic heart disease mortality,[67] although potential mortality misclassification on death certificates makes the actual cause of death not entirely certain in all circumstances. Heart failure rates or mortality associations were not reported in the other cohort studies.

Daily hospitalizations for heart failure have also been associated with short-term changes in PM exposure.[31] Heart failure associations with PM were observed in a large daily time-series analysis of $PM_{2.5}$ and cardiovascular and respiratory hospitalizations by use of a national database constructed from US Medicare files.[103] A 10-$\mu g/m^3$ increase in concurrent-day $PM_{2.5}$ was associated with a 1.28% (95% CI 0.78% to 1.78%) increase in heart failure admissions, the single largest cause for hospitalization in this cohort. A reduction of $PM_{2.5}$ by 10 $\mu g/m^3$ was estimated to reduce heart failure admissions in 204 counties by 3156 (95% posterior interval 1923 to 4389) cases per year.[103] Another analysis in Medicare recipients in 7 US cities found a 10-$\mu g/m^3$ increase in concurrent-day PM_{10} was associated with a 0.72% (95% CI 0.35% to 1.10%) increase in heart failure admissions.[117] Traffic-related air pollution has also been shown to be significantly associated with increased mortality risk after acute heart failure.[118] Finally, a study from Utah's Wasatch Front area explored longer lagged-exposure periods and found that a 14-day lagged cumulative moving average of 10 $\mu g/m^3$ $PM_{2.5}$ was associated with a 13.1% (95% CI 1.3% to 26.2%) increase in heart failure admissions.[119]

Cerebrovascular Disease

Among the cohort studies that provided pertinent results, the Women's Health Initiative reported significant increases in both nonfatal stroke (hazard ratio 1.28, 95% CI 1.02 to 1.61) and fatal cerebrovascular disease (hazard ratio 1.83, 95% CI 1.11 to 3.00) per 10-$\mu g/m^3$ elevation in prolonged exposure to $PM_{2.5}$.[72] However, no significant association between stroke mortality and PM air pollution was found in the ACS study.[67]

Several studies have also reported small but statistically significant associations between short-term PM exposure and cerebrovascular disease. Daily time-series studies of stroke mortality in Seoul, Korea,[120,121] observed that elevated air pollution (including measures of PM, NO_2, CO, and O_3) was associated with increases in stroke mortality. When analyzed separately by stroke type,[121] the pollution association was associated with ischemic but not hemorrhagic stroke. Risk of stroke mortality was also associated with daily increases in PM_{10} and NO_2 in Shanghai, China.[56] A daily time-series study in Helsinki, Finland,[122] found that $PM_{2.5}$ and CO were associated with stroke mortality in the warm but not the cold seasons. Several studies have also observed increased stroke or cerebrovascular hospital admissions associated with increased exposure to PM or related pollutants.[31,38,40,46,123–125] For example, a study of hospital admissions for Medicare recipients in 9 US cities[125] found that several measures of air pollution (PM_{10}, CO, NO_2, and SO_2) 0 to 2 days before admission were associated with ischemic but not hemorrhagic stroke. Studies of ischemic stroke and transient ischemic attacks based on population-based surveillance have also been conducted in Dijon, France,[126] where O_3 exposure (but not PM_{10}) was associated with ischemic stroke, and in Corpus Christi, Tex,[127] where both $PM_{2.5}$ and O_3 were associated with ischemic strokes and transient ischemic attacks.

Peripheral Arterial and Venous Diseases

There have been only a few studies that have explored a relationship between air pollution and peripheral vascular diseases. Studies using Medicare data for 204 US counties observed nearly statistically significant positive associations between daily changes in measures of PM pollution and hospitalizations for peripheral vascular diseases.[103,104] The ACS cohort found no association between other atherosclerotic and aortic aneurysm deaths and long-term $PM_{2.5}$ exposure.[67]

Recently, a case-control study from the Lombardy region of Italy found a 70% increase in risk of deep vein thrombosis per 10-$\mu g/m^3$ elevation in long-term PM_{10} level.[128] This is the first observation that particulate air pollution can enhance coagulation and thrombosis risk in a manner that adversely affects the venous circulation in addition to the arterial cardiovascular system.

Cardiac Arrhythmias and Arrest

Several studies have observed associations between fine PM and related pollutants and cardiac arrhythmias, often based on data from implanted cardioverter-defibrillators.[129–136] However, no clear pollution-related associations were observed in studies from a relatively clean metropolitan area, Vancouver, British Columbia, Canada,[137,138] or from a relatively large study in Atlanta, Ga.[139] Similarly, pollution-related associations have been observed with cardiac arrest in Rome, Italy,[140] and Indianapolis, Ind,[141] but not in Seattle, Wash.[142,143] The mixed results may reflect different PM compositions due to different sources or variations among the methods used.

Evidence Summary

On the basis of the available epidemiological studies that have reported the associations between PM exposures with specific subsets of cardiovascular outcomes (morbidity, mortality, or hospitalizations), the existing level of overall evidence is strong for an effect of PM on ischemic heart disease, moderate (yet growing) for heart failure and ischemic stroke, and modest or mixed for peripheral vascular and cardiac arrhythmia/arrest (Table 6).

Ambient Air Pollution and Subclinical Pathophysiological Responses in Human Populations

It is likely that many subclinical physiological changes occur in individuals in response to $PM_{2.5}$ exposures that do not become overtly manifest as a cardiovascular event (eg, death or MI). The illustration of these more subtle responses bolsters the plausibility of the observable outcome associations and provides insight into the pathways whereby air

Table 6. Overall Summary of Epidemiological Evidence of the Cardiovascular Effects of $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure at Ambient Levels

Health Outcomes	Short-Term Exposure (Days)	Longer-Term Exposure (Months to Years)
Clinical cardiovascular end points from epidemiological studies at ambient pollution concentrations		
Cardiovascular mortality	↑ ↑ ↑	↑ ↑ ↑
Cardiovascular hospitalizations	↑ ↑ ↑	↑
Ischemic heart disease*	↑ ↑ ↑	↑ ↑ ↑
Heart failure*	↑ ↑	↑
Ischemic stroke*	↑ ↑	↑
Vascular diseases	↑	↑†
Cardiac arrhythmia/cardiac arrest	↑	↑
Subclinical cardiovascular end points and/or surrogate measures in human studies		
Surrogate markers of atherosclerosis	N/A	↑
Systemic inflammation	↑ ↑	↑
Systemic oxidative stress	↑	
Endothelial cell activation/ blood coagulation	↑ ↑	↑
Vascular/endothelial dysfunction	↑ ↑	
BP	↑ ↑	
Altered HRV	↑ ↑ ↑	↑
Cardiac ischemia	↑	
Arrhythmias	↑	

The arrows are not indicators of the relative size of the association but represent a qualitative assessment based on the consensus of the writing group of the strength of the epidemiological evidence based on the number and/or quality, as well as the consistency, of the relevant epidemiological studies.

↑ ↑ ↑ Indicates strong overall epidemiological evidence.
↑ ↑ Indicates moderate overall epidemiological evidence.
↑ Indicates some but limited or weak available epidemiological evidence.
Blank indicates lack of evidence.
N/A indicates not applicable.
*Categories include fatal and nonfatal events.
†Deep venous thrombosis only.

pollutants mediate CVDs. The "Biological Mechanisms" section discusses the hypothesized global pathways and reviews the studies related to the fundamental cellular/ molecular mechanisms elucidated by controlled human and animal exposures and toxicological/basic science experiments. The following section reviews the recent evidence that ambient exposure to air pollution can mediate potentially harmful subclinical cardiovascular effects. In general, many positive associations are found (Table 6). Numerous complex interactions between variations in the characteristics, sources, and chemistry of the particles, coupled with diversity in time frames, mixtures of exposures, and degrees of individual susceptibility, likely explain some of the disparity among findings.

Systemic Inflammation

There is evidence that under some circumstances, exposure to ambient PM can be associated with elevated circulating proinflammatory biomarkers that are indicative of a systemic response after PM air pollution inhalation that is not limited to the confines of the lung. Early reports found associations with day-to-day variation in acute-phase proteins, such as C-reactive protein (CRP), fibrinogen, or white blood cell counts,[144–147] as reviewed previously.[1] Limited evidence on the association between cumulative PM exposures and fibrinogen levels and counts of platelets and white blood cells was also available.[148]

A number of more recent studies have reported positive associations with short-term ambient PM exposure and day-to-day elevations in inflammatory markers. These include increases in CRP in an elderly population[149] and individuals with coronary atherosclerosis[150]; CRP and fibrinogen in young adults[151] and elderly overweight individuals[152]; and CRP, tumor necrosis factor-α (TNF-α), and interleukin (IL)-1β in children.[153] Recent evidence has also been found for an upregulation of circulating soluble adhesion molecules (eg, intercellular adhesion molecule-1) in 92 Boston, Mass–area individuals with diabetes[154] and 57 male subjects with coronary artery disease in Germany.[150] In a larger analysis of 1003 MI survivors, also in Germany, CRP was not related to PM exposure; however, ambient particle number concentration and PM_{10} were associated with increased IL-6 and fibrinogen, respectively.[155] Short-term levels of in-vehicle $PM_{2.5}$ have also been linked to increases in CRP among healthy highway patrol troopers.[156] In a follow-up analysis, elevations in certain particulate components of traffic pollution (eg, chromium) were associated with increased white blood cell counts and increased IL-6 levels.[157] Short-term changes in ambient PM levels have also been linked to acute (1 to 3 days later) alterations in biomarkers of inflammation, oxidative stress, and platelet activation among elderly adults with coronary artery disease living in retirement communities in Los Angeles, Calif.[158,159] Pollutants associated with primary combustion (eg, elemental and black carbon, primary organic carbon) and UFPs rather than $PM_{2.5}$ appeared to be strongly associated with adverse responses in this population.

Regarding more long-term exposures,[160] a positive association between white blood cell count and estimated long-term 1-year exposure to PM_{10} was reported in the Third National Health and Nutrition Examination Survey. Among 4814 adults in Germany, small increases in annual mean $PM_{2.5}$ (3.9 $\mu g/m^3$) were associated with increases in high-sensitivity CRP by 23.9% and in fibrinogen by 3.9% among men only. Estimated long-term traffic exposure was not related to inflammatory changes in either sex.[161]

Several studies, including some with improved exposure assessment,[162] some that included analyses of large population cohorts,[163,164] and a recent evaluation of long-term annual PM_{10} levels in England,[165] have not found a relationship between particulate exposure and inflammation. It is conceivable that differences in the magnitude or character of the inflammatory response will occur because of variations in the particulate chemistry and duration/intensity of exposures. Certain individuals may also be more susceptible. The evidence suggests that subjects with underlying cardiovascular risk factors and the metabolic syndrome may exhibit stronger associations.[152,160,166] Conversely, antiinflammatory medications such as statins may mitigate the actions of ambient particles.[152,155] All together, there is some evidence for a positive association between recent and long-term PM exposure and a systemic proinflammatory response; nevertheless, there is variation in the strength and consistency of changes among the variety of biomarkers and patient populations evaluated (Table 6).

Systemic Oxidative Stress

A state of oxidative stress refers to a condition in which levels of free radicals or reactive oxygen/nitrogen species (eg, O_2^-, H_2O_2, $ONOO^-$) are higher than normal (eg, healthy individuals in whom they are countered by homeostatic processes such as antioxidants) and thus are capable of exerting many adverse biological effects (eg, lipid/protein/deoxyribonucleic acid [DNA] oxidation, initiation of proinflammatory cascades). Although many biomarkers of differing systemic responses are available (eg, lipid or protein oxidation products), oxidative stress may occur at the local cellular/tissue level and not be directly observable by circulating markers. In addition, oxidative stress is often induced by and elicits inflammatory processes. The 2 processes are biologically linked. Therefore, human studies investigating the effect of PM on oxidative stress per se are difficult to perform. Only a few studies have directly investigated the occurrence of systemic oxidative stress in humans in relation to ambient PM exposure. Three studies of young adults conducted in Denmark demonstrated elevations in biomarkers of protein, lipid, or DNA oxidation in relation to PM exposure from traffic sources.[167–169] In a study of 76 young adults from Taipei, Taiwan,[151] the investigators found evidence of increased levels of 8-hydroxy-2′-deoxyguanosine adducts in DNA in relation to short-term elevations in ambient PM. Two studies have also demonstrated increases in plasma homocysteine, evidence that exposure to ambient PM can elevate this circulating mediator of oxidative stress.[170,171] Finally, Romieu et al[172] found that dietary supplementation with omega-3 polyunsaturated fatty acids might be capable of altering the systemic oxidative stress response (reduction in copper/zinc superoxide dismutase and glutathione) induced by air pollutants among residents living in a nursing home in Mexico City, Mexico. Because of the relatively small number of studies, more investigation is required to make firm conclusions and to understand the nature of the systemic oxidative stress response potentially induced by ambient PM (Table 6).

Thrombosis and Coagulation

Early reports indicated that increased plasma viscosity[144] and elevated concentrations of fibrinogen[146] are associated with short-term changes in ambient PM concentrations. More recent evidence was found for an upregulation of circulating von Willebrand factor in 57 male subjects with coronary artery disease in Germany[150] and 92 Boston-area individuals with diabetes.[154] Riediker[157] found that components of in-vehicle $PM_{2.5}$ were also related to increased von Willebrand factor and decreased protein C among highway patrol troopers. In the Atherosclerosis Risk in Communities study, a 12.8-$\mu g/m^3$ elevation in ambient PM_{10} was associated with a 3.9% higher von Willebrand factor level,[173] but only among those with diabetes. There was no linkage between PM_{10} exposure and fibrinogen or white blood cell levels.

Alterations in other markers that indicate changes in thrombosis, fibrinolysis, and global coagulation have also been reported. An immediate elevation in soluble CD40-ligand concentration, possibly reflecting platelet activation, recently was found to be related to ambient UFP and accumulation-mode particle ($PM_{0.1-1.0}$) levels in patients with coronary artery disease.[155] Ambient PM_{10} levels have also been associated with augmented platelet aggregation 24 to 96 hours after exposure among healthy adults.[174] In this study, there were no concomitant observable changes in thrombin generation, CRP, or fibrinogen induced by PM_{10}. Increases in plasminogen activator inhibitor-1 and fibrinogen levels have been noted in healthy subjects,[151] as well as elevated plasminogen activator inhibitor-1 in patients with coronary artery disease only,[175] in association with ambient PM levels in Taipei. Chronic indoor pollution exposure to biomass cooking in rural India has also been associated with elevated circulating markers of platelet activation.[176] Recently, Baccarelli et al[128,177] demonstrated in healthy subjects and among individuals with deep venous thrombosis living in the Lombardy region of Italy that prothrombin time was shortened in relation to recent and long-term ambient PM_{10} concentrations. Nevertheless, some studies found no effects of ambient pollution,[178] nor have significant changes been reported among all the biomarkers or subgroups of individuals investigated.[150,154,170,173] Similar to the study on systemic inflammation, the results related to thrombosis/coagulation are quite variable given the differences in study designs, patients, biomarkers evaluated, and pollutants; however, these adverse effects appear somewhat more consistent among higher-risk individuals (Table 6).

Systemic and Pulmonary Arterial BP

Several studies have reported that higher daily PM levels are related to acute increases in systemic arterial BP (approximately a 1- to 4-mm Hg increase per 10-$\mu g/m^3$ elevation in PM).[179–184] In a small study of patients with severe heart failure,[185] pulmonary artery and right ventricular diastolic BP were found to increase slightly in relation to same-day levels of PM. Chronic exposure to elevated $PM_{2.5}$ was associated with increased levels of circulating endothelin (ET)-1 and elevated mean pulmonary arterial pressure in children living in Mexico City.[186] These results may explain in part the risk for heart failure exacerbations due to PM exposure; however, not all studies of systemic arterial BP have been positive.[187–189]

Recently, Dvonch et al[190] demonstrated significant associations between increases in systolic BP and daily elevations in $PM_{2.5}$ across 347 adults living in 3 distinct communities within metropolitan Detroit, Mich. Much larger effects were observed 2 to 5 days after higher $PM_{2.5}$ levels within a specific urban location of southwest Detroit (8.6 mm Hg systolic BP increase per 10-μg/m^3 $PM_{2.5}$) than throughout the entire region or cohort (3.2 mm Hg). This suggests that specific air pollution sources and components contribute significantly to the potential for PM exposure to raise BP. Interestingly, it was recently reported in a crossover study of 15 healthy individuals that systolic BP was significantly lower (114 versus 121 mm Hg) during a 2-hour walk in Beijing, China, while the subjects were wearing a high-efficiency particulate-filter facemask than when they were not protected.[191] Wearing the facemask was also associated with increased HRV, which suggests that the rapid BP-raising effects of particle inhalation may be mediated through the autonomic nervous system (ANS). In a similar fashion,[192] reducing exposure to particulate pollution from cooking stoves was shown to be associated with lower systolic (3.7 mm Hg, 95% CI −8.1 to 0.6 mm Hg) and diastolic (3.0 mm Hg, 95% CI −5.7 to −0.4 mm Hg) BP among Guatemalan women than among control subjects after an average of 293 days. These findings demonstrate that indoor sources of PM (eg, cooking, biomass) may have important cardiovascular health consequences and that reductions in particulate exposure are capable of lowering BP, and they suggest that chronic exposure to PM air pollution may alter long-term basal BP levels. Even given the rapid variability of BP on a short-term basis and the numerous factors involved in determining individual responses (eg, patient susceptibility, PM composition, and time frames of exposure), overall, it appears that ambient PM can adversely affect systemic hemodynamics, at least under certain circumstances (Table 6).

Vascular Function

In the first ambient PM study related to changes in vascular function, O'Neill et al[193] reported that both endothelium-dependent and -independent vasodilation were blunted in relation to air pollution levels in Boston. The largest changes occurred in association with sulfate and black carbon, suggestive of coal-burning and traffic sources, respectively. Significant adverse responses were observed within 1 day yet were still present and slightly more robust up to 6 days after exposure. Moreover, the adverse responses occurred solely among diabetic individuals and not in patients at risk for diabetes mellitus. Two other studies[184,194] also demonstrated impaired vascular function due to short-term changes in ambient PM among diabetic patients. In the study by Schneider et al,[194] endothelium-dependent vasodilation was blunted during the first day, whereas small-artery compliance was impaired 1 to 3 days after elevated ambient PM levels. Interestingly, higher concentrations of blood myeloperoxidase were related to a greater degree of endothelial dysfunction, which suggests that white blood cell sources of reactive oxygen species (ROS) may be involved.

In healthy adults, very short-term exposure to elevated levels of ambient PM from traffic sources while exercising for 30 minutes near roadways[195] and when resting by bus stops for 2 hours[196] has been related to impaired endothelium-dependent vasodilation. Daily changes in ambient gaseous pollutants (SO_2 and NO_x) in Paris, France, have also been associated with impaired endothelium-dependent vasodilation among nonsmoking men.[197] Finally, indoor particulate air pollution may also be harmful to vascular function. Bräuner and colleagues[198] recently reported that reductions in 48-hour $PM_{2.5}$ levels due to filtering of air in subjects' homes resulted in improved microvascular vascular function among elderly subjects. Nevertheless, changes in short-term ambient PM levels have not been linked with impaired conduit[197] or microvascular[178] endothelial function in all studies. Even when the few negative studies are considered, the overall evidence supports the concept that ambient PM is capable of impairing vascular function, particularly among higher-risk individuals (eg, those with diabetes) and after traffic-related exposure (Table 6).

Atherosclerosis

A few cross-sectional studies have reported an association between measures of atherosclerosis in humans and long-term exposures to ambient air pollution levels. The first study to demonstrate this relationship was an analysis of data from 798 participants in 2 clinical trials conducted in the Los Angeles area. A cross-sectional contrast in exposure of 10 μg/m^3 $PM_{2.5}$ was associated with an adjusted nonsignificant 4.2% (95% CI −0.2% to 8.9%) increase in common carotid intima-media thickness[199]; however, in certain subgroups of patients, such as women, the effect was much larger (13.8%, 95% CI 4.0% to 24.5%). In a population-based sample of 4494 subjects from Germany,[200] it was found that residential proximity to major roadways was associated with increased coronary artery calcification. A reduction in distance from a major road by half was associated with a 7% (95% CI 0.1% to 14.4%) higher coronary artery calcium score. Proximity to traffic was also related to an increased risk for peripheral artery disease in women but not men.[201] In an analysis of 3 measures of subclinical disease (carotid intima-media thickness, coronary calcium, and ankle-brachial index) among 5172 adults from the Multi-Ethnic Study of Atherosclerosis, only common carotid intima-media thickness was modestly (yet significantly) associated with 20-year exposure to $PM_{2.5}$.[202] In a related study from the same cohort, abdominal aortic calcium was associated with long-term $PM_{2.5}$ exposure, especially for residentially stable participants who resided near a $PM_{2.5}$ monitor.[203] Although it appears that long-term exposure to higher levels of ambient PM might accelerate the progression of atherosclerosis, more investigations are needed (Table 6).

Heart Rate Variability

Numerous studies have continued to explore associations between daily changes in PM air pollution exposure and alterations (typically reductions) in HRV metrics, putative markers of cardiac autonomic balance.[129,149,156,204–242] Recent observations in the Normative Aging Study cohort have shown strong effect modification of the PM-HRV relationship by obesity and genes that modulate endogenous oxidative stress or xenobiotic metabolism, such as glutathione S-transferase M1, methylenetetrahydrofolate reductase, and the hemochromatosis gene.[207,243,244] Additional findings suggest protective effects of statins, dietary antioxidants, and B vitamins, as well as omega-3 polyunsaturated fatty acids.[205,207,215,243,244] These results suggest that pathways that reduce endogenous oxidative stress have a protective effect that mitigates reductions in HRV due to ambient PM exposure.

However, the overall results are not entirely consistent. Some studies have reported increases in HRV mediated by PM, specifically among younger healthy people and patients with chronic obstructive lung disease.[156,208,216] Nevertheless, the general pattern suggests that PM exposure is associated with increased heart rate and reductions in most indices of HRV among older or susceptible individuals, such as those with obesity and the metabolic syndrome. Typically, time-domain measures (eg, standard deviation of normal RR intervals) and total power are reduced within hours after exposure. Most, but not all, pertinent studies have also found that the largest reduction in power is within the high-frequency domain. In sum, these observations provide some evidence that ambient PM air pollution exposure rapidly reduces HRV, a surrogate marker for a worse cardiovascular prognosis (Table 6). Although studies corroborating changes in autonomic activity by other methods (eg, microneurography or norepinephrine kinetics) have not been performed, the HRV findings are perhaps reflective of the instigation of a generalized cardiovascular autonomic imbalance due to relatively greater parasympathetic than sympathetic nervous system withdrawal.

Cardiac Ischemia and Repolarization Abnormalities

There has been limited direct evidence for the actual induction of cardiac ischemia or repolarization abnormalities in the electrocardiogram (ECG) by exposure to ambient levels of PM.[223,245] Recent follow-up analyses from the initial ULTRA study (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air)[245] suggested that traffic-related combustion pollutants were most strongly related to the promotion of ST-segment depression among elderly nonsmokers during exercise stress testing.[246] Moreover, even very acute $PM_{2.5}$ exposure within the past 1 or 4 hours has been associated with cardiac ischemia during exercise.[247] New findings support these associations in elderly subjects[248] and in patients with coronary artery disease in Boston.[249] In the latter study, traffic-related PM was most strongly related to the incidence of ST-segment depression during 24-hour Holter monitoring, and the risk for ischemia was greatest within the first month after a cardiac event among patients with diabetes. Overall, there is a modest level of evidence that PM exposure can promote cardiac ischemia in susceptible individuals (Table 6).

Epigenetic Changes

There have been relatively few studies examining gene–air pollution exposure interactions, and most have done so while investigating a small number of loci for genetic polymorphisms. Although some studies have suggested greater air pollution susceptibility with one or another genomic polymorphism,[207,243,244] few have evaluated the potential for epigenetic changes after exposures. Reduced levels of DNA methylation have been linked to aging, oxidative stress, and CVD. Recently, Baccarelli et al[250] have shown among 718 elderly participants in the Normative Aging Study that short-term exposures (over 1 to 7 days) to $PM_{2.5}$ and black carbon are associated with decreased "global" DNA methylation in long interspersed nucleotide elements. It was posited that oxidative stress from air pollution exposure could have interfered with the capacity for methyltransferases to interact with DNA or altered the expression of genes involved in the methylation process. This observed effect of pollution exposure was analogous to changes seen with 3.4 years of aging in the cohort. Additional findings among workers in a furnace steel plant support these observations.[251] Nevertheless, the mechanisms involved and the cardiovascular implications of these preliminary, although provocative, epigenetic changes require more investigation.

Traditional Cardiovascular Risk Factors

In addition to the fact that individuals with traditional risk factors are likely to be at higher risk for cardiovascular events due to PM exposure, air pollutants may also promote the development of these risk factors over a prolonged period of time. Few published studies have investigated this possibility. A report from the Multi-Ethnic Study of Atherosclerosis has demonstrated that residential proximity to major roadways was associated with a higher left ventricular mass index as measured by cardiac magnetic resonance imaging.[252] The degree of increase was analogous to a 5.6-mm Hg increase in systolic BP among the study participants. This suggests that traffic-related exposures may have increased left ventricular mass by chronically elevating systemic arterial BP, a common cause of left ventricular hypertrophy. However, other mechanisms cannot be excluded, such as systemic inflammation and oxidative stress, which could potentially activate neurohormonal pathways (eg, ANS imbalance, renin-angiotensin system) that could directly mediate such a finding. In addition, a recent study of adults older than 30 years of age (n=132 224) participating in the National Health Interview Survey reported a significant association between self-reported hypertension and estimated annual $PM_{2.5}$ exposure using US EPA monitoring data.[253] A 10-$\mu g/m^3$ elevation in $PM_{2.5}$ was associated with an adjusted odds ratio of 1.05 (CI 1.00 to 1.10) for the presence of hypertension. The increase in risk was found only among non-Hispanic whites. These studies provide some initial evidence that longer-term PM exposures may augment the risk for developing chronically elevated BP levels or even overt hypertension.

Brook et al[254] have also demonstrated a novel relationship between a metric of long-term traffic exposure (NO_2 level by residence) and the odds of having the diagnosis of diabetes mellitus among patients in 2 respiratory clinics in Ontario, Canada. In women only, the odds ratio of diabetes was 1.04 (95% CI 1.00 to 1.08) for each increase of 1 parts per billion (ppb) of NO_2. Across the interquartile range (4 ppb NO_2), exposures were associated with nearly a 17% increase in odds for diabetes mellitus. The first biological support for this finding comes from a study in Iran that demonstrated that the previous 7-day-long exposure to PM_{10} was independently associated with worse metabolic insulin sensitivity among 374 children 10 to 18 years of age.[255] These findings suggest that the systemic proinflammatory and oxidative responses due to long-term PM air pollution exposure could potentially increase the risk for developing clinically important aspects of the metabolic syndrome, such as hypertension and diabetes mellitus. Further studies in this regard are warranted.

Evidence Summary

Table 6 provides a consensus qualitative synopsis based on the expert opinions of the writing group members of the overall level of existing support, linking each surrogate or intermediate cardiovascular outcome with exposures to PM at ambient concentrations, based solely on the database of observational studies.

Additional Epidemiological Findings and Areas of Continued Research

Responsible Sources and Pollution Constituents

Although PM concentration (mass per cubic meter) has been associated with cardiovascular events in numerous studies, the specific particulate constituents and the sources responsible remain less clear. Despite the fact that it is a difficult undertaking, several epidemiological studies have attempted to identify the culprit components within the PM mixtures. With regard to PM-associated inorganic ions (nitrate and sulfate), it has been suggested that the overall toxicological data do not clearly implicate these compounds as responsible for mediating the cardiovascular health effects of $PM_{2.5}$.[256] Nevertheless, sulfate particles have been associated with cardiopulmonary mortality in the ACS and Harvard Six Cities studies.[62,68] A recent time-series analysis among 25 US cities found that cardiovascular risk was increased when PM mass contained a higher proportion of sulfate, as well as some metals (aluminum, arsenic, silicon, and nickel).[257] It is possible that these positive findings represent sulfate serving as a marker for an effect mediated by a toxic PM mixture derived from commonly associated sources (eg, coal combustion). Nevertheless, a direct role for particle sulfate in causing cardiovascular events cannot be excluded entirely.[256]

In California, short-term exposures to several different PM constituents that likely reflect combustion-derived particulates, including organic and elemental carbon and nitrates, were most strongly associated with higher cardiovascular mortality.[258] Certain metals (zinc, titanium, potassium, and iron) and sulfate levels in the winter months were also positively related. Similarly, ambient levels of organic and elemental carbon have been most strongly linked among PM constituents with hospitalizations for CVDs in multipollutant models in a study among 119 US cities.[259] Finally, $PM_{2.5}$ composed of higher levels of elemental carbon, along with the metals nickel and vanadium,[48] has also been linked with greater risks for cardiovascular hospitalizations.[260] These results support that the chemistry or composition of the $PM_{2.5}$ (eg, organic/elemental carbon and certain metals) along with the responsible source from which these mixtures are derived (eg, fresh combustion, traffic) may play important roles in determining the risk for cardiovascular events. However, the extent to which these constituents mediate specific responses, alone or together, and their importance beyond the concentration of $PM_{2.5}$ mass alone represent an area of active research that requires more investigation to reach firm conclusions.

Many experiments have demonstrated the especially toxic properties and strong oxidizing potential of the smallest particle sizes (eg, UFP) and of the specific chemical species typically rich within this size fraction (eg, transition metals, organic compounds, and semiquinones).[261] Although some epidemiological evidence suggests that exposure to ultrafine compounds[17] may be associated with higher cardiovascular risk (eg, an elevation of UFP count by 9748/cm^3 has been associated with an increase in cardiovascular mortality of approximately 3% within 4 days in Erfurt, Germany[262]) and adverse responses,[158,159] there have been few such studies because they are challenging to conduct, for numerous reasons. Moreover, there are few UFP monitors, and the levels measured at regional sites may not accurately reflect an individual person's exposure because of marked spatial heterogeneity, because the concentrations are dominated by local point sources of fresh combustion (eg, roadways). This could help explain some of the previously negative study findings.[116]

Similarly, coarse particulates between 0.25 and 1.0 μm in diameter may affect the cardiovascular system,[221,264,265] and although the available data related to hard events and cardiovascular mortality have suggested a relationship,[265,266] recent findings have been less consistent.[104] In the most recent time-series analysis of 112 US cities, coarse PM was independently associated with elevated all-cause, stroke, and pulmonary, but not cardiovascular, mortality after controlling for $PM_{2.5}$.[43] Coarse PM was also not associated with either fatal or nonfatal cardiovascular events after controlling for $PM_{2.5}$ levels in the Nurses' Health Study[267] or the Women's Health Initiative cohort analyses.[72] Additional research is required to establish whether there are independent health effects of the other particulate size fractions beyond those posed by fine particles. On the other hand, $PM_{2.5}$ mass concentration is the metric most consistently associated with cardiovascular morbidity and mortality. It remains to be determined whether this reflects limitations of available data, the long-lived and regionally homogenous atmospheric nature of $PM_{2.5}$, that few studies have investigated the independent effects of the other sizes, difficulties in performing epidemiology studies with adequate UFP exposure estimates, or that specific constituents within the fine PM fraction (or another unidentified agent correlated with that fraction) are actually responsible for causing cardiovascular events. Although particles <0.1 μm (ie, UFPs) do make up a small fraction of $PM_{2.5}$ mass, the correlation between UFP particle number and total $PM_{2.5}$ mass concentration is often weak. Because of their minute size, UFPs make up only a small portion of the total $PM_{2.5}$ mass, even though they represent the largest actual number of particles within fine PM. They also have the highest surface area and a differing surface chemistry. Therefore, changes in the underlying UFP concentration do not likely account for or explain the linkages between $PM_{2.5}$ mass concentration and cardiovascular events observed in large multicity studies. The overall epidemiological evidence thus indicates that fine PM poses an independent cardiovascular risk and that any putative effects of these other size fractions cannot fully explain the observed $PM_{2.5}$–cardiovascular morbidity/mortality relationship.

On the other hand, there is mounting evidence for a distinctive role played by motor vehicle traffic–related exposures in elevating cardiovascular risk.[108,111,268,269] Lipfert et al[76,77] interpreted the results of their analysis of the Veterans Affairs hypertensive male cohort as suggesting that traffic density was a more "significant and robust predictor of survival in this cohort" than $PM_{2.5}$. Analyses of the Oslo,[81] Dutch,[82] AHSMOG,[74,75,88] French PAARC,[79] and German women cohorts[80] and related studies from areas in the United Kingdom,[270] Canada,[271] Norway,[272] and Rome[273] found that measures that often indicate traffic-related exposure (NO_2, NO_x, traffic density, and living near major roads) were also associated with increased mortality. Long-term 5-year average traffic-generated air pollution exposure has been associated with an increased risk of fatal MI (odds ratio 1.23, 95% CI 1.15 to 1.32 per 31-$\mu g/m^3$ increase in NO_2) but not nonfatal MI in Stockholm County, Sweden.[274] The results mirror the results of several cohort studies[72,73] that found that air pollution exposures appeared to be more strongly linked with cardiovascular mortality than nonfatal events. Recently, an analysis from a cohort in the Netherlands demonstrated that several metrics of traffic-related air pollution exposure remained significantly associated with increased risk for cardiovascular events even after adjustment for higher levels of traffic noise.[275]

The effect of long-term traffic-related exposure on incidence of fatal and nonfatal coronary heart disease was recently assessed after adjustment for background air pollutants and cardiovascular risk factors in 13 309 adults in the Atherosclerosis Risk in Communities study.[276] Interestingly, background chronic ambient $PM_{2.5}$ concentrations were not related to the interpolated traffic exposure levels or to heart disease outcomes, which supports the highly localized nature of traffic sources of exposure. After 13 years of follow-up in 4 US communities, individuals residing within the highest quartile of traffic density had a relative risk of 1.32 (95% CI 1.06 to 1.65) for fatal and nonfatal heart disease events. Despite multiple statistical adjustments, the investigators also acknowledged the possibility for residual confounding as a potential source of bias. The specific traffic-related pollution components, such as UFP or gaseous-phase chemicals (eg, SVOCs), that are responsible for the positive findings among these studies remain unknown. The close proximity to roadways within these epidemiological studies (eg, 400 m) required to observe an association with elevated cardiovascular risk, however, matches the atmospheric fate of these shorter-lived pollutants. The findings may thus suggest the existence of cardiovascular health effects mediated by specific air pollutants rather than $PM_{2.5}$ per se. There is room for improvement in assessment of traffic exposures in epidemiological research, and better approaches are now being incorporated into research projects, such as accounting for associated factors (eg, noise or spatial autocorrelation with socioeconomic status).[275,277]

Geographic differences in cardiovascular risk due to PM have also been observed across US regions, with more consistent or stronger effects observed in Eastern versus Western states.[71,103,257] Differences between North American and European cities have also been reported.[61] PM exposures are typically, but not always,[258] associated with larger effects during warmer months (spring through fall) than in the winter.[45,103,257] Variations in pollution characteristics (eg, sulfate), time spent outdoors, air conditioning usage and particle penetration indoors, ambient temperature and meteorology, and mobile (eg, diesel) or stationary (eg, coal combustion) sources of exposure may help explain these differences. Finally, variations in the cardiovascular risk posed by PM may also occur because of heterogeneity in the metric of exposure, such as personal versus background regional,[25] indoor versus outdoor sources, and differences in intracity versus intercity gradients.[69] A better understanding of the responsible constituents and sources is important and could potentially lead to more targeted and effective regulations. On the other hand, finding continued evidence that the adverse cardiovascular health effects cannot be linked conclusively to a particular or specific chemical species or source of pollution but rather that they occur in response to a variety of exposure types or mixtures would support the present-day policy of reducing exposure to overall fine particulate mass to achieve public health benefits.

Time Course and Concentration-Response Relationships

Many studies have demonstrated that PM air pollution exposure does not simply advance the mortality by a few days of critically ill individuals who would have otherwise died (eg, mortality displacement or "harvesting").[278,279] There also appears to be a monotonic (eg, linear or log-linear) concentration-response relationship between $PM_{2.5}$ and mor-

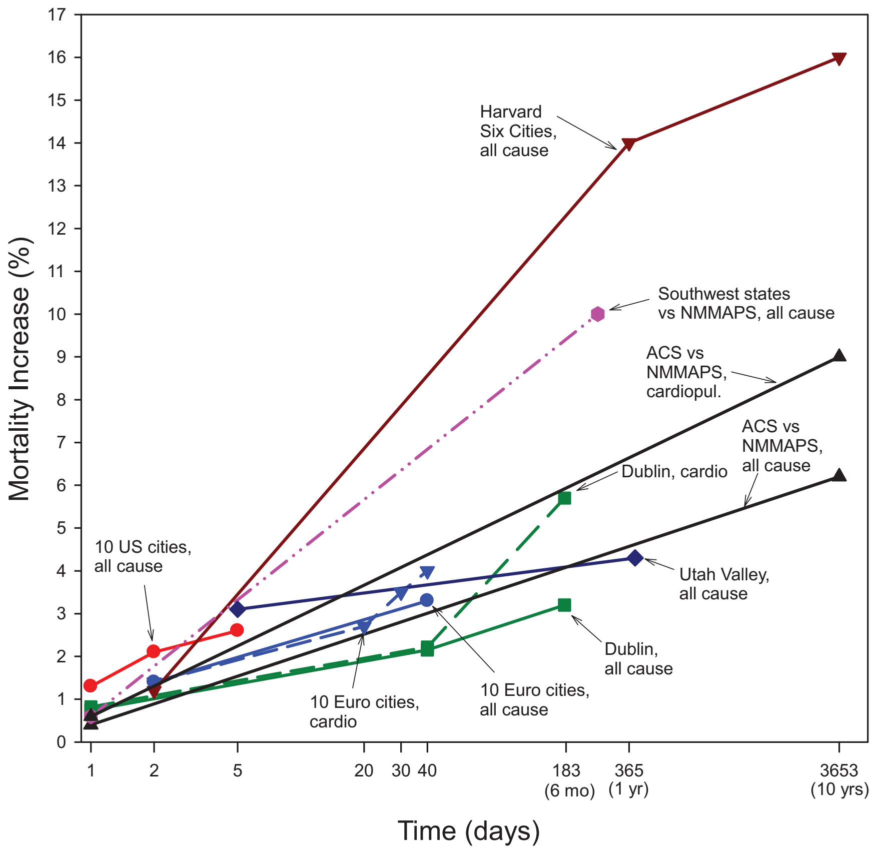

Figure 2. Comparison of estimates of percent change in mortality risk associated with an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ or 20 $\mu g/m^3$ of PM_{10} or British Smoke (BS) for different time scales of exposure (log scale of approximate number of days, updated and adapted from Pope[281a]). Euro indicates European; cardio, cardiovascular disease; and cardiopul, cardiopulmonary.

tality risk observed in cohort studies that extends below present-day regulations of 15 $\mu g/m^3$ for mean annual levels, without a discernable "safe" threshold.[67,70,84] Cardiovascular risk due to particle exposure was also shown to extend below 15 $\mu g/m^3$ in the recent analysis of the Women's Health Initiative Observational Study.[72] This monotonic association supports the idea that any reduction in particulate pollution will translate into health benefits within a population of people, each with their own individual level of susceptibility. It also suggests that a larger decrease in $PM_{2.5}$ exposures will produce a greater reduction in mortality. Finally, a recent analysis of the literature provided important new insights into the nature of the PM exposure-response relationship.[280] The risk for cardiovascular mortality was shown to increase in a linear fashion across a logarithmically increasing dosage of inhaled fine-particle levels that ranged from ambient PM air pollution (≈0.2 mg/d), through secondhand smoke (≈1 mg/d), to active smoking (200 mg/d). This means that the exposure response is extremely steep at very low PM levels (ie, ambient air pollution) and flattens out at higher concentrations (ie, active smoking). This may help explain the seemingly incongruent and comparatively very high degree of cardiovascular risk posed by the much lower levels of PM exposure from ambient pollution and secondhand smoke versus the much higher doses due to active smoking. Thus, the cardiovascular system may be extremely sensitive to very low levels of PM inhalation as encountered with ambient pollution.

At present, the underlying nature and full scope of the temporal-risk relationship posed by longer-term PM exposures remain uncertain.[2,281] The writing group members did concur that the available epidemiological studies demonstrate larger cardiovascular risks posed by more prolonged exposures to higher PM levels than observed over only a few days (Figure 2). Cohort studies using Cox regression survival analyses (over months to years) are capable of evaluating a more complete portion of the temporal-risk relationship than time-series analyses over only a few days that use Poisson regression. However, given the lack of complete information, no conclusions could be drawn on the full magnitude of the augmented risk posed by chronic exposures, the time window (a few months versus decades) required to exhibit this enhanced risk, the underlying biological causes, the extent to which statistical differences between study types explain the variations in risk, and whether clinically relevant chronic CVDs are precipitated by chronic exposures. Some writing group members believe it is important to differentiate as 2 distinct issues the potentially greater effect of long-term exposures on increasing the risk for acute events (eg, cardiovascular mortality) compared with the putative effect on initiating or accelerating the development of chronic CVD processes per se (eg, coronary atherosclerosis). As such, it is possible that the greater risks observed in cohort studies could be capturing the fact that repetitive exposures over months or years augment the risk for sudden cardiovascular events in susceptible people, without actually worsening an underlying "chronic" disease process.

On the one hand, the available studies demonstrate that the majority of the larger risk-effect sizes posed by longer-term versus short-term exposures appear to be manifested within only 1 to 2 years of follow-up. Extending the duration of follow-up increases cardiovascular risk, but to a progressively smaller degree over time (Figure 2). The discrepancy in the effect sizes among study types (eg, cohort versus time-series studies) could also reflect differences in statistical methodologies or population susceptibilities.[282–284] Recent attempts to investigate this matter[64,84] suggest that the risk for acute events associated with chronic exposures may be reasonably well estimated by only the most proximal 1 to 2 years of PM levels. The most recent time frames of exposure also explain a substantial portion of the excess cardiovascular risk observed in several cohort studies.[70,72,73,83] These findings bolster the argument that relatively rapid and pliable (and potentially reversible) biological responses, such as the instigation of plaque instability or the enhanced thrombotic potential caused by PM-mediated inflammation or endothelial dysfunction (which can occur and abate over only a few weeks to months), could explain the biology responsible for this greater relative risk.

On the other hand, cogent alternative arguments can be made to explain the differences in relative risk between the cohort and time-series studies. The likely high correlation of a recent year's exposure levels with exposures over many years, as well as the uniform rank ordering of exposure severity over time among cities, can explain why only a short period of PM exposure assessment is required to understand the risk of longer-term exposures. In addition, no studies have evaluated the potential risks of exposure over decades or a lifetime. PM augments the ability of traditional risk factors to accelerate the development of atherosclerosis in experimental settings. As such, it is also plausible that long-term exposures may enhance cardiovascular risk to an even greater extent by increasing an individual's susceptibility for future cardiovascular events or acute exposures. In addition, the full extent of this possibility may not be illustrated by the limited follow-up period (4 to 5 years) of the majority of cohort studies. The writing group thus agreed that this important issue requires more investigation.

It is also possible that these 2 explanations are not mutually exclusive. Furthermore, it cannot be concluded from available information that a long period of time is required for reductions in PM levels to translate into a decrease in cardiovascular risk. On the contrary, reductions in secondhand smoke[285] and PM air pollution levels[64,84,90,95] appear to produce fairly rapid decreases in cardiovascular event rates, within a few months to years.[284] At present, the available data do not allow for firm conclusions regarding the underlying biology and the full extent of the potentially nonuniform PM exposure–to–cardiovascular risk temporal relationship.

Susceptibility to Air Pollution Exposure

Susceptibility refers to a heightened risk for a particular cardiovascular end point or event to occur compared with the general population at the same concentration of PM exposure. Typically, this is indicative of an underlying medical condition (eg, diabetes) or personal characteristic (eg, old age) that causes this enhanced risk. This is in contrast to the term "vulnerability," which refers to a population of individuals at greater risk for more frequent or high levels of exposures.

Earlier studies reviewed in the first AHA scientific statement[1] suggested that susceptible populations include the elderly; individuals with diabetes; patients with preexisting coronary heart disease, chronic lung disease, or heart failure; and individuals with low education or socioeconomic status. In the ACS study, current and previous smokers appeared to be at the same or greater degree of risk.[67] Among more recent studies, the Women's Health Initiative also reported positive findings among active smokers and an elevated risk for cardiovascular mortality induced by $PM_{2.5}$.[72] Conversely, current smokers were found to be at no increased risk for cardiovascular mortality in response to $PM_{2.5}$ exposure in the Nurses' Health Study.[73] Thus, the effect modification of smoking status requires more investigation. The APHENA study of European and North American cities recently confirmed that elderly and unemployed individuals are at higher risk of short-term PM exposure.[61] In a multicity time-series study in Asia, women, the elderly, and individuals with lower education and socioeconomic status were also shown to be at elevated risk.[286] A few additional studies have reported some evidence of susceptibility to short-term PM exposures among older individuals, people with diabetes, and those with a lower level of education.[287–289] Finally, a recent study illustrated that present-day levels of $PM_{2.5}$ likely increase the risk for a cardiac event within a few days of exposure principally (or even solely) among individuals with preexisting significant coronary artery disease, even if they are seemingly healthy (eg, without anginal symptoms). Patients without obstructive lesions on heart catheterization were not at any risk for $PM_{2.5}$-induced myocardial events over the short term.[13] This is not surprising, because most acute cardiovascular events occur among individuals with underlying vulnerable substrate (eg, unstable plaques) and not in individuals with normal coronary arteries.

Obesity has been newly recognized as a possible susceptibility factor. Two cohort studies have shown that a greater body mass index enhances the susceptibility for PM-induced cardiovascular mortality, at least among women.[72,73] Although individuals with diabetes showed a trend toward greater risk in the Women's Health Initiative,[72] hypertension, high cholesterol, smoking, elderly age, education, and income did not alter the risk association. Overall, there appears to be little effect modification by race, hypercholesterolemia, or BP among the studies. Finally, sex may also be a risk-effect modifier. The particularly robust risk estimates of the 2 cohort studies that included only women,[72,73] the fact that PM increased cardiovascular risk in female but not male participants of the AHSMOG study,[75] and the multicity time-series findings in Asia[286] suggest that women may be at greater risk for cardiovascular mortality related to PM. Further studies are needed to clarify whether obese individuals and women are indeed susceptible populations.

Biological Mechanisms

There has been substantial improvement in our understanding of the biological mechanisms involved in PM-mediated

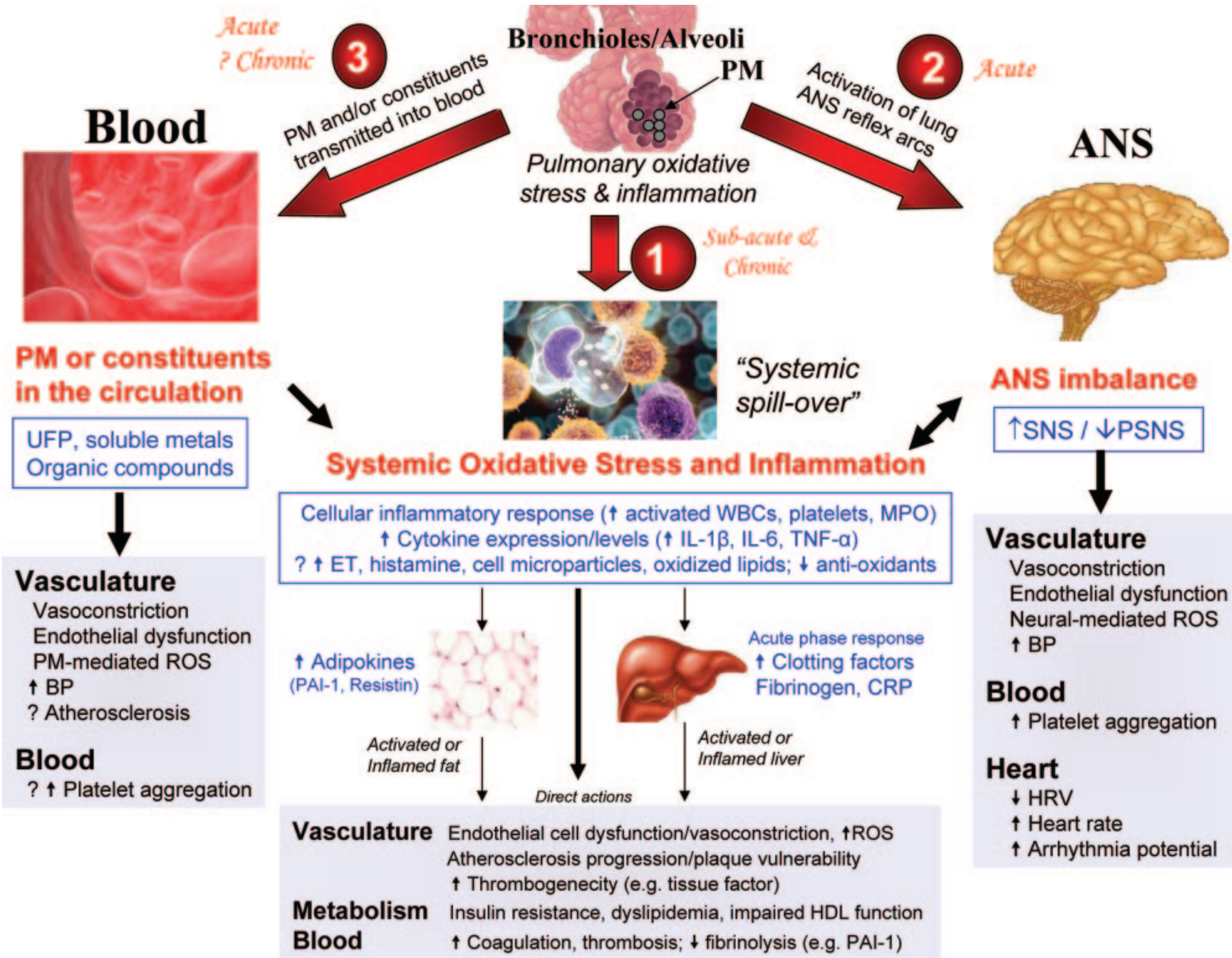

Figure 3. Biological pathways linking PM exposure with CVDs. The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating cardiovascular events are shown. MPO indicates myeloperoxidase; PAI, plasminogen activator inhibitor; PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; and WBCs, white blood cells. A question mark (?) indicates a pathway/mechanism with weak or mixed evidence or a mechanism of likely yet primarily theoretical existence based on the literature.

cardiovascular effects. Studies before 2004 were reviewed previously,[1] and only some are again discussed here for contextual background. A number of new experiments have demonstrated very rapid effects of air pollution, such as vascular dysfunction, which argues for the existence of pathways that convey signals systemically within hours of PM inhalation. On the other hand, there is also support for chronic biological effects, such as the promotion of atherosclerosis. At the molecular level, persuasive evidence supports an integral role for ROS-dependent pathways at multiple stages, such as in the instigation of pulmonary oxidative stress, systemic proinflammatory responses, vascular dysfunction, and atherosclerosis. In sum, new studies continue to support the idea that inhalation of PM can instigate extrapulmonary effects on the cardiovascular system by 3 general "intermediary" pathways. These include pathway 1, the release of proinflammatory mediators (eg, cytokines, activated immune cells, or platelets) or vasculoactive molecules (eg, ET, possibly histamine, or microparticles) from lung-based cells; pathway 2, perturbation of systemic ANS balance or heart rhythm by particle interactions with lung receptors or nerves; and pathway 3, potentially the translocation of PM (ie, UFPs) or particle constituents (organic compounds, metals) into the systemic circulation (Figure 3).

Exposure Considerations

Animal and human exposure studies are discussed separately and apart from the effect of ambient PM because their methodologies and clinical relevancies vary widely. Controlled exposure studies involve exposing a subject to various size fractions of PM within a chamber connected to ambient air (concentrated or nonconcentrated) or a source of aerosolized particles. Virtual impactor systems that deliver concentrated ambient particles (CAPs) from "real-world" ambient air are a commonly used approach for mimicking exposures to higher levels of ambient particles without requiring invasive methods or the generation of artificial particles.[3] Both a strength and limitation, however, is that CAPs can vary considerably from day to day in composition. Additionally, only certain particle size ranges are typically concentrated (eg, PM from 0.1 to 2.5 μm in the fine-CAP system), whereas ambient air contains a mixture of particle sizes, volatile organics, and gases that are not concentrated (and can be lowered). Potential interactions between PM and gaseous copollutants on health end points are therefore excluded, unless the latter are reintroduced in an artificial fashion. Other methods of controlled-inhalation exposures include diesel engine exhaust (diluted and aged mixtures of high numbers of fresh combustion UFPs with vapor-phase components), roadside aerosols, and wood-burning sources. Regarding animal exposures, intratracheal instillation methods may sometimes be required because of the limited availability of inhalation exposure systems. Unfortunately, particle size and surface characteristics—mostly retained in inhalation systems with fresh sources of pollution and which may be important in influencing biological effects—are likely significantly altered in instillation systems or by methods that use previously collected particulate. However, the use of carefully modeled exposures (eg, deposition calculation) and the recognition that areas of "hot spots" containing markedly higher PM levels within the lung may occur even during normal inhalation make the results of these experiments potentially relevant.[2] Further detailed discussions of exposure considerations are reviewed elsewhere.[290]

The protocol details vary considerably among the studies. Many aspects of exposure, including the duration, concentration, PM size ranges and composition, and gaseous copollutants, are important to consider. A wide variety of outcomes may be anticipated depending on the biological pathways evoked by differing exposures. Moreover, there are multiple determinants of the subsequent physiological responses, including the time frames of investigation, preexisting susceptibility, animal models, and the details of the outcomes investigated. All of these factors may explain some of the heterogeneity in the reported study results and must be taken into consideration when interpreting the findings.

Animal Exposure and Toxicological Studies

Studies that investigate the effects of exposure on susceptible animals (eg, those with preexisting cardiovascular or metabolic abnormalities) may be preferable in many circumstances because of the increasing recognition that the pathways underlying the biological effects of PM overlap (ie, modify and/or enhance) those of conventional cardiovascular risk factors. Such factors (eg, hypertension or atherosclerosis) may also be necessary or at least responsible for the evocation of a more readily observable or robust response. For example, in the context of systemic oxidative stress or inflammation, the cellular machinery for the generation of excess ROS and proinflammatory responses (eg, adhesion molecule and cytokine expression) is already primed or operational in susceptible animals.

Pulmonary Oxidative Stress and Inflammation

The molecular events responsible for triggering pulmonary oxidative stress and inflammation, along with the interactions between lung and immune cells, the inhaled PM, and the protective secretions (eg, surfactant, proteins, and antioxidants), are highly complex,[4–6] as reviewed in detail elsewhere.[290a,290b,414] In brief, size, charge, solubility, aggregation, ROS-producing potential, and chemistry play roles in determining the responses. These include the particle fate (eg, lung clearance versus retention rates), the nature of the PM-cell interactions (eg, immune versus lung cell uptake, host cell responses, and intracellular sequestration/location), and the dose (likely typically a small percentage of inhaled PM) and pathways of potential systemic transmission of PM or its constituents, such as in the circulation [free, intracellular within circulating cells, (lipo)protein-bound] or via lymphatic spread.[4,5,290a,290b] Because of their nano-scale size, UFPs may directly enter multiple lung cell types via nonphagocytic pathways and adversely affect organelles, such as mitochondria.[6,290a,290b] Larger unopsonized fine particles are more typically taken up by phagocytes through interactions with innate immunity receptors such as MARCO (macrophage receptor with collagenous structure) or other scavenger receptors.[5,290a,290b] This may in fact be a protective mechanism that sometimes prevents harmful lung inflammation. Certain particle compounds may directly generate ROS in vivo because of their surface chemistry (eg, metals, organic compounds, and semiquinones) or after bioactivation by cytochrome P450 systems (eg, polycyclic aromatic hydrocarbon conversion to quinones).[6,290a,290b] A particle surface or anions present on otherwise more inert particles may disrupt iron homeostasis in the lung and thereby also generate ROS via Fenton reactions.[291] Other PM constituents may do so indirectly by the upregulation of endogenous cellular sources (eg, nicotinamide adenine dinucleotide phosphate [NADPH]) oxidase)[292,293] or by perturbing organelle function (eg, mitochondria) by taken-up PM components.[261] Particle stimulation of irritant and afferent ANS fibers may also play a role in local and systemic oxidative stress formation.[294] Given the rich antioxidant defenses in the lung fluid, secondarily generated oxidization products of endogenous molecules (eg, oxidized phospholipids, proteins) or a reduction in endogenous antioxidants per se may be responsible at least in part for the state of oxidative stress in the lungs (along with instigating the subsequent cellular responses) rather than ROS derived directly from PM and its constituents.

Subsequent to oxidative stress, antioxidant and phase II defenses may be activated (eg, inducible nitric oxide synthase, glutathione) via transcription factor Nrf2-dependent pathways.[261] When inadequate, pathological oxidative stress can initiate a variety of pulmonary inflammatory responses. For example, ROS in the lungs has been shown to augment the signal transduction of membrane ligand (eg, epidermal growth factor by disrupting phosphatases) or pattern-recognition receptors (eg, toll-like receptors [TLR])[295–299] and/or stimulate intracellular pathways (eg, mitogen-activated protein kinases) that lead to the activation of proinflammatory transcription factors (eg, nuclear factor-$\kappa\beta$) that upregulate expression of a variety of cytokines and chemokines.[261] Alteration in lung cell redox status may itself stimulate nuclear factor-$\kappa\beta$. Biological components within coarse PM could also directly trigger inflammation (eg, nuclear factor-$\kappa\beta$ pathways) by binding to TLR2 or TLR4 receptors or other innate immune pattern-recognition receptors.[297] It is also possible that other components of metal-rich

PM could instigate inflammatory pathways via TLR activation directly or via the oxidation of endogenous biological compounds that then serve as TLR ligands.[300] Finally, there is some evidence that PM can activate inflammatory mitogen-activated protein kinase signaling by angiotensin II receptor–dependent pathways.[295] These inflammatory responses can also exacerbate the initial oxidative stress [eg, via upregulation of cellular NAD(P)H oxidase] and thus initiate a positive-feedback cycle.

Available studies support important contributions to pulmonary inflammation from innate immune cells such as neutrophils and macrophages (TNF-α, IL-6), as well as from the adaptive immune system, such as T cells (IL-1, IL-4, IL-6, and IL-10). Although the dominant source of cytokines likely represents the alveolar macrophages and lung epithelial cells, the role of other innate and adaptive immune cells cannot be ruled out.[299,301,302] Recently, myeloperoxidase activity was shown to increase after PM exposure in the same time course of appearance of cellular inflammation (primarily neutrophils) in the lung.[303] Gaseous components such as ozone may also amplify the toxicity of PM.[304]

Systemic Inflammation

In the context of examining the cardiovascular effects of air pollution, it is important to consider the inflammatory mediators that are released from lung cells after contact with PM, because some could conceivably spill over to the general circulation or increase liver production of acute-phase proteins (eg, CRP, fibrinogen). An increase in circulating proinflammatory mediators (eg, activated immune cells, cytokines) could thus serve as a pathway to instigate adverse effects on the heart and vasculature. Numerous experiments have demonstrated increased cellular and inflammatory cytokine content, such as IL-6, IL-1β, TNF-α, interferon-γ, and IL-8, of bronchial fluid and sometimes in circulating blood after acute exposure to a variety of pollutants.[292,305–311]

Critical roles for the elevations in systemic and pulmonary levels of IL-6 and TNF-α have been observed after PM exposure, typically coincident with pulmonary inflammation.[292,302,306,309,311–314] There is at least some evidence that the degree of pulmonary inflammation and systemic inflammation (IL-6) correlates with the elevation of systemic cytokines and systemic vascular dysfunction.[314] In a 4-week inhalation exposure to freshly generated diesel exhaust, IL-6 knockout mice did not demonstrate increased cellular inflammation or TNF-α in bronchial fluid, which implies a role for IL-6.[315] Consistent with these findings, acute intratracheal exposure to PM_{10} resulted in an increase in IL-6, TNF-α, and interferon-γ in the bronchial fluid.[316] However, in this study, IL-6$^{-/-}$ mice showed roughly the same levels of TNF-α in bronchial fluid as wild-type mice, although interferon-γ was decreased to control values.[316] The results also suggested that lung macrophages play an important role, because depletion of these cells abolished the increases in some of the cytokines and systemic cardiovascular responses. Although our understanding of the source of IL-6 and TNF-α and their involvement in the systemic inflammatory response after PM exposure remains incomplete, these and other experiments appear to suggest that at least with PM_{10} particles, alveolar macrophages play a dominant role.[309,314,316]

Among remaining uncertainties, the upstream signaling pathway responsible for the recognition of PM components that in turn produce the systemic inflammation has not been fully elucidated[317]; however, there is some evidence with other particulates and experimental models of lung injury that ROS generated by NADPH oxidase or pattern-recognition receptors may modulate some of these responses.[292,299,318] NADPH-oxidase knockout mice demonstrated significantly lower IL-6 and macrophage inflammatory protein-2 responses to collected PM than wild-type mice.[292] Extrapulmonary sources may also be involved in promulgating the systemic inflammation. $PM_{2.5}$ exposure in a model of diet-induced obesity in C57Bl/6 mice for a duration of 24 weeks resulted in elevations in TNF-α and IL-6. In addition, there were increases in circulating adipokines, such as resistin and plasminogen activator inhibitor-1.[319] The elevation in cytokines, thought to be derived from adipose sources, in addition to findings of adipose inflammation in that study, raises the possibility of additional systemic nonpulmonary sources of such cytokines.

Systemic Oxidative Stress

Numerous in vitro studies have demonstrated activation of ROS-generating pathways by PM incubation, such as NADPH oxidases, mitochondrial sources, cytochrome P450 enzymes, and endothelial nitric oxide synthase in cultured cells or in pulmonary and vascular tissue.[293,311,320–329] Similar to inflammation, the oxidative stress after PM inhalation may not always stay confined within the lungs.[330] The sources of excess ROS within cardiovascular tissue may include circulating immune cells or cytokines, depletion of defense mechanisms (eg, impaired high-density lipoprotein function), oxidation of lipoproteins or other plasma constituents,[331] activation of ANS pathways,[294] or circulating PM constituents (eg, soluble metals, organic compounds) reaching the vasculature.[261] Activation of ROS-dependent pathways modulates diverse responses with far-reaching consequences, including vascular inflammation/activation, atherosclerosis, impaired basal vasomotor balance, enhanced coagulation/thrombosis, and platelet activation.[290b]

Recent experiments have indeed confirmed the existence of footprints or markers of oxidative stress within the cardiovascular system in the in vivo context. Acute-exposure studies[332] have shown a relationship between the vascular dysfunction in spinotrapezius microvessels and the release of myeloperoxidase from leukocytes into the vasculature within only hours after the pulmonary instillation of PM.[332] Interestingly, an insoluble particle (TiO_2) induced very similar effects. More long-term studies[333] have demonstrated that 10 weeks of exposure to $PM_{2.5}$ increased superoxide production in response to angiotensin II and resulted in upregulation of NAD(P)H oxidase subunits and depletion of tetrahydrobiopterin in the vasculature. These effects had functional consequences in terms of increases in systemic vascular resistance and BP. In another investigation that involved apolipoprotein E–deficient (ApoE$^{-/-}$) fed a high-fat diet, chronic exposure to $PM_{2.5}$ exacerbated vascular oxidant stress and promoted atherosclerosis progression.[334] The proatherogenic effects of ambient UFPs[331] versus $PM_{2.5}$ in genetically susceptible $ApoE^{-/-}$ mice in a mobile facility close to a Los Angeles freeway have also been compared. Exposure to UFPs resulted in an inhibition of the antiinflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress, as evidenced by increased hepatic malondialdehyde and upregulation of Nrf2-regulated antioxidant genes.[331]

Other experiments[294] have suggested that ANS imbalance may play an important role in PM-induced cardiac oxidative stress. Pharmacological inhibition of the ANS could significantly reduce chemiluminescence in the heart after exposure.[303] More recently, an upstream modulator, the transient receptor potential vanilloid receptor-1, within the lung was identified as central to the inhaled CAP-mediated induction of cardiac chemiluminescence.[335] In these studies, capsazepine was able to abrogate ECG alterations in rats during the 5-hour exposure, which suggests that neural ANS pathways are crucial.

Thrombosis and Coagulation

Earlier studies using intratracheal instillation of high concentrations of diesel exhaust particles demonstrated the induction of lung inflammation, platelet activation, and increased peripheral vascular thrombosis in both arteries and veins after photochemical injury.[336,337] Thrombosis susceptibility was ascribed to direct passage of the instilled UFPs in the blood, because large polystyrene particles unlikely to cross the lung-blood barrier did not increase peripheral thrombosis. In a subsequent study, a persistent increase in thrombosis susceptibility to diesel exhaust particles was shown after 24 hours, an effect that was mitigated by pretreatment with sodium cromoglycate, which indicates that this response was secondary to histamine release from basophil degranulation.[338] These same effects, however, were mimicked by 400-nm polystyrene particles with a low likelihood of transgressing the pulmonary barrier, which implicates pulmonary release of histamine as a mediator of thrombosis at the later time point. Because histamine was increased in the plasma at 6 and 24 hours after exposure, and diphenhydramine mitigated diesel PM–induced thrombosis at later time points but not at 1 hour, it was hypothesized that additional direct effects of PM constituents reaching the circulation may be responsible for the earliest prothrombotic effects.[339] No increase in circulating von Willebrand factor was observed after instillation of both particles. Finally, pulmonary instillation of carbon nanotubes produced neutrophil lung influx 24 hours later. Circulating platelet-leukocyte conjugates were elevated 6 hours after exposure, whereas procoagulant microvesicular tissue factor activity and peripheral thrombotic potential were increased 24 hours later. Inhibition of P-selectin abrogated these responses, which demonstrates that rapid activation of circulating platelets by the pulmonary deposition of PM plays a vital role.[340] This series of studies suggests that release of lung cell–derived mediators (eg, histamine) after several hours along with the more rapid activation of circulating platelets by lung inflammation via P-selectin–dependent processes may mediate distant system prothrombotic effects without necessarily inducing systemic endothelial damage.

In a study using C57BL/6J mice, intratracheal PM_{10} particles rich in transition metals decreased bleeding, prothrombin, and activated partial thromboplastin times and enhanced the levels of several coagulation factors as well as thrombosis times in response to experimental $FeCl_3$ injury.[316] This prothrombotic effect was mitigated in $IL\text{-}6^{-/-}$ and macrophage-depleted mice, which suggests that IL-6, lung macrophages, and pulmonary inflammation are necessary initial steps. It is possible, however, that coarse-particle components (eg, endotoxin) could have been important mechanistically via TLR activation. The effect of fine PM or UFPs per se requires more investigation. Chronic ambient exposure to $PM_{2.5}$ has also been shown to increase tissue factor expression in macrophages and smooth muscle cells in atherosclerotic lesions. Complementary in vitro studies with cultured human smooth muscle cells and monocytes demonstrate dose-dependent increases in tissue factor in response to collected ambient particles.[341] Other findings also support potential procoagulant and thrombotic effects of PM.[342,343] These collective studies suggest that both short- and long-term PM inhalation can enhance thrombotic and coagulation tendencies, potentially via increases in circulating histamine and inflammatory cytokines and/or activated white cells and platelets. The plausibility of these pathways is supported by the well-recognized cross talk between inflammation and thrombosis.[344] Potential additional roles for UFPs or soluble constituents that reach the circulation and directly enhance platelet aggregation or systemic oxidative stress (thus activating the endothelium and blunting platelet-derived nitric oxide) require more investigation.

Systemic and Pulmonary Hypertension

Early animal studies suggested small or inconsistent effects of PM on BP,[345–347] sometimes dependent on the season[348] of exposures. A potential explanation may be variations in experimental protocols, including differences in the delivery, duration, and composition of exposure and the methods used to measure BP. Moreover, PM by itself may represent a relatively weak stimulus but may act more robustly in concert with other predisposing factors to affect BP. Sun et al[333] recently demonstrated a significant interactive effect of fine-CAP exposure with the vasoconstrictor angiotensin II in rats. Preexposure to $PM_{2.5}$ for a 10-week period resulted in enhancement of its prohypertensive response measured continuously by intra-arterial radiotelemetry. The exaggerated BP elevation was accompanied by endothelial dysfunction, including blunted endothelium-dependent vasodilation and enhanced vasoconstrictor reactivity, along with upregulation of NAPDH oxidase and Rho-kinase–signaling pathways. In vitro exposure to UFPs and $PM_{2.5}$ was also associated with an increase in Rho-kinase activity, phosphorylation of myosin light chain, and myosin phosphatase target subunit. Pretreatment with the nonspecific antioxidant *N*-acetylcysteine and Rho-kinase inhibitors prevented these responses, which suggests an ROS-mediated mechanism for particle-mediated effects on vascular smooth muscle constriction. Further studies corroborated the role of exaggerated Rho-kinase pathway activity in potentiating the hypertensive response to angiotensin II in mice exposed to $PM_{2.5}$.[349] Moreover, particle exposure augmented angiotensin-mediated cardiac hypertrophy and collagen deposition. Blockade of Rho-kinase abolished these effects. These responses suggest that chronic $PM_{2.5}$ exposure disrupts normal vascular homeostasis and vasoactive mediator balance through ROS-dependent mechanisms in a manner that sensitizes the vessel toward vasoconstrictors. Activation of RhoA/Rho-kinase signaling pathways appears to play an important mechanistic role.

In conscious canines with implanted BP catheters, systemic arterial BP increased and baroreceptor sensitivity was rapidly altered over a few hours during CAP exposure.[350] Interestingly, α-adrenergic antagonism abrogated the responses. The findings support a mechanistic role for acute activation of the sympathetic nervous system by inhaled particles. In a study with Wistar-Kyoto male rats, CAP exposure for 4 days upregulated ET-A receptor expression in the heart. This alteration was also weakly correlated with an increase in BP, which suggests a role for enhance ET activity.[351] PM has also been demonstrated to alter the release of ET-1 and ET-3 from the lungs.[352] Elevation in pulmonary vascular resistance and pulmonary arterial pressure, which suggests constriction of the pulmonary vessels, has also been demonstrated in response to respirable carbon black particles.[353] Recently, ultrafine carbon particles were shown to increase BP in spontaneously hypertensive rats 1 to 3 days after a 24-hour exposure.[354] This response occurred concomitant with increased ET-1 messenger ribonucleic acid levels in lung tissue and small elevations in plasma renin concentration and angiotensin I and II in the systemic circulation. These findings further support the idea that ET may play a role in cardiovascular responses to PM exposure and suggest that activation of the renin-angiotensin system may also be involved. It is not clear whether the elevated circulating ET levels reflect increased release from the lungs and whether this mediates a systemic vasoconstrictor response. Alternatively, the increase may be more indicative of enhanced vascular tissue activity of these systems. Longer-term exposures of carbon black for 4 weeks in Sprague-Dawley rats has also been shown to significantly increase systolic BP concomitant with increases in serum levels of IL-6 and CRP.[355]

Finally, in vitro exposure to soluble and insoluble components of UFPs induces constriction in isolated pulmonary arterial rings and activates intracellular signaling pathways such as phosphorylation of extracellular signal–regulated kinase-1/2 and p38 mitogen-activated protein kinase in pulmonary endothelial cells. These effects were antagonized by losartan, and several metal components (copper and zinc) could replicate the responses.[295] This suggests a possible role for activation of angiotensin II receptor pathways relevant for the maintenance of vasomotor tone and smooth muscle constriction after inhalation of metal constituents within PM.

In sum, the studies demonstrate that long-term PM exposures over a period of weeks are capable of enhancing vasoconstrictive responsiveness of the vasculature (eg, increased Rho-kinase activity and reduced nitric oxide bioavailability) by inflammatory and ROS-dependent cell-signaling pathways. Shorter-term exposures over several hours to days may lead to vasoconstriction and increased pulmonary and systemic BP by pathways dependent on enhanced ET or angiotensin II signaling. Lung cells may release ET into the systemic circulation and thus increase its systemic activity, or the vascular ET system may be relatively upregulated because of increased ROS or reduced nitric oxide. Activation of the renin-angiotensin system may also occur because of systemic oxidative stress or inflammation or as a consequence of ANS imbalance. The very acute increase in BP that occurs concomitant with the inhalation of particles or within only minutes to hours after exposure appears to be mediated by autonomic imbalance that favors a relative activation of the sympathetic nervous system. No study has evaluated the effect of air pollution on renal sodium handling or long-term pressure natriuresis mechanisms, which are fundamental to the generation of chronic hypertension.

Vascular Dysfunction and Atherosclerosis

Many early experiments demonstrated the capacity of PM constituents to blunt nitric oxide–dependent dilation and enhance vasoconstrictor tone in ex vivo vascular studies because of excess ROS formation.[1] The first in vivo experiment demonstrated the proatherosclerotic actions of intratracheal PM_{10} instillation.[356] More recently, the pulmonary instillation of several different PM types was shown to rapidly impair microvascular endothelium-dependent vasodilation within days, likely by proinflammatory or ROS-dependent mechanisms (eg, myeloperoxidase).[332] Several animal studies have now demonstrated that long-term exposure to ambient $PM_{2.5}$, by use of ambient-exposure facilities without direct pulmonary instillation, not only causes endothelial dysfunction but also accelerates the progression of atherosclerosis. Sun et al[334] demonstrated that exposure of atherosclerosis-prone $ApoE^{-/-}$ mice to environmentally relevant levels of CAP, derived from regional northeastern $PM_{2.5}$, for 6 months in conjunction with a high-fat chow diet potentiated plaque development and heightened vascular inflammation (CD68+ macrophage infiltration and inducible nitric oxide synthase expression) and oxidant stress. The atherosclerotic plaque progression was also accompanied by alterations in vasomotor tone, including decreased endothelium-dependent vasodilation and heightened vasoconstriction to adrenergic stimuli. Importantly, the normalized average $PM_{2.5}$ concentration over the entire period was 15.2 $\mu g/m^3$, which approximates the annual NAAQS. Similar findings were reported in other chronic CAP exposures that involved an $ApoE^{-/-}$ model.[357] However, exposures to a double-knockout model of ApoE-deficient and low-density lipoprotein receptor–deficient mice increased plaque cellularity, reflective of inflammation, but did not enhance plaque burden. It is possible that the atherosclerotic severity of this phenotype precluded the observation of more subtle effects of CAP exposures.

Intratracheal instillation of UFP can acutely impair aortic endothelium-dependent vasodilation.[358] Moreover, repeated 10-week-long endotracheal dispersion of UFP carbon black increased atherosclerosis in low-density lipoprotein receptor–

knockout mice.[359] This occurred without evidence of systemic translocation of particles into the cardiovascular tissues. UFP inhalation by use of exposure facilities has also recently been shown to augment atherosclerosis, perhaps to a greater degree than $PM_{2.5}$. When investigating the effects of different PM size fractions, Araujo et al[331] compared the proatherogenic potential of exposure over 40 days to ambient particles <0.18 μm versus $PM_{2.5}$ in ApoE$^{-/-}$ mice. UFPs caused more adverse cardiovascular responses (eg, systemic oxidative stress, impaired high-density lipoprotein function) and greater potency in accelerating atherosclerotic lesion formation, although $PM_{2.5}$ did demonstrate qualitatively similar effects. Recent studies have also demonstrated that PM exposure likely promulgates systemic atherosclerosis by mechanisms that overlap those of other conventional cardiovascular risk factors.[360] Intratracheal instillation of PM_{10} particles caused a rapid impairment in endothelium-dependent vasodilation, stimulation of bone marrow–derived cells, and increased migration of monocytes into atherosclerotic plaques.[361,362] Systemic inflammation (IL-6) was also related to the degree of endothelial dysfunction.[314] Finally, the most compelling evidence for rapid impairment in nitric oxide bioavailability being directly involved in the origin of PM-induced endothelial dysfunction was demonstrated recently. Both fine-PM and UFM inhalation for only a few hours in normal rats blunted agonist-stimulated nitric oxide production within the microvasculature, measured by direct electrochemical sensors, concomitant with an observed impairment in vasomotor relaxation. Inhibition of myeloperoxidase or NADP(H) oxidase partially restored normal nitric oxide bioavailability and endothelial function, which suggests a role of activation of these endogenous radical-generating enzymes in this biological response.[363]

Potentially relevant adverse vascular effects of nonparticulate PM components should not be discounted. There may also exist some synergy between vapor phase, gas, and particle constituents in relation to instigation of cardiovascular responses. Recently,[364] it was demonstrated in apoE$^{-/-}$ mice that whole gasoline engine exhaust over 1 or 7 days increased vascular messenger ribonucleic acid expression of matrix metalloproteinase (MMP)-2 and MMP-9. Levels of ET-1 and ROS were similarly increased. The vascular ROS and MMP-2 elevations were attenuated by tempol. Endothelial receptor antagonism ameliorated the vascular expression of MMP-2, MMP-9, and ROS. In separate experiments, diesel exhaust exposure to rats for 5 hours augmented ET-induced vasoconstriction, potentially via a blunting of ET-B–induced nitric oxide release.[365] The findings suggest that exposure to a fresh mixture of PM, gases, and vapors may play a role in rapidly triggering atherosclerotic plaque vulnerability via ROS and ET-dependent upregulation of MMP levels.

Some studies suggest that predisposed animals may be more susceptible to air pollution–mediated vascular dysfunction. Diesel exhaust particles delivered by intraperitoneal injection impaired nitric oxide–dependent vasodilation only in apoE$^{-/-}$ mice with atherosclerosis and not in healthy control animals.[366] Aortas from prediabetic rats were found to be more susceptible to repeated exposures to oil combustion particles in causing noradrenergic-mediated constriction and impaired endothelium-dependent vasodilation.[367]

Taken together, the available studies suggest that short- and long-term particle exposures (including PM_{10}, $PM_{2.5}$, and UFP) can impair conduit and resistance arterial endothelium-dependent vasodilation. Chronic exposures have been shown to be capable of promoting atherosclerosis progression and enhancing plaque vulnerability. The underlying mechanisms likely involve vascular sequelae of systemic inflammation (due to interactions with innate immune cells and cytokines) or exaggerated oxidative stress pathways. Excess vascular ROS and inflammation will impair endogenous vasodilator bioavailability (eg, nitric oxide), enhance vasoconstrictor tone (eg, ET), and chronically activate multiple intracellular pathways that promote atherosclerosis.[368–370]

Heart Rate Variability

Some of the earliest indications of systemic effects of PM came from ECG studies in rats.[371] In general, reductions in several measures of HRV have been shown.[372–376] Most of the recent research has focused on exploring the roles of susceptibility and exposure characteristics. Decreases in heart rate and HRV indices have been reported to be pronounced in senescent mice, which indicates that aging may be a susceptibility factor.[353] Using an anesthetized model of postinfarction myocardium sensitivity, Wellenius and colleagues[377] did not demonstrate an effect of 1 hour of CAP exposure on heart rate or spontaneous ventricular arrhythmias. In contrast, in a post-MI heart failure model in Sprague-Dawley rats, diesel exhaust emissions reduced HRV in both healthy and heart failure groups and increased the incidence of premature ventricular contractions. Studies in mice have also indicated a potential role for transition metals and nickel in HRV alterations[376] and provide initial clues on the PM components that could influence autonomic tone.[48]

Some beginning insight into the neural pathways involved has been reported recently. PM-induced ECG changes in rats were shown to be prevented by inhibiting the transient receptor potential vanilloid receptor in the lungs. This suggests that the relevant neural mechanism that leads to alterations in HRV or heart rhythm may be induced by activation of receptor-mediated autonomic reflexes in the lung.[335] Circulating particle constituents or inflammatory mediators interacting with myocardial ion channels or electrophysiology did not appear to be a pertinent mechanism, at least in these studies.[335] However, it is unknown whether similar mechanisms can account for the HRV changes observed in humans, and a more detailed understanding of the anatomic pathways involved is required. Finally, it remains unclear whether the changes in cardiac HRV are actually caused by or merely illustrate an underlying alteration in ANS balance. Experiments that clearly define the direct contribution of sympathetic and parasympathetic nervous system activities (eg, microneurography, norepinephrine spillover rates, or autonomic receptor or ganglionic blockade) are needed.

MI and Arrhythmia

PM exposure can increase experimental infarct size and potentiate myocardial ischemia and arrhythmias in experimental MI models. Relatively high concentrations of intratracheal UFP instillation induced pulmonary inflammation and doubled MI size in mice.[358] Conscious dogs exposed to fine CAP for several days experienced greater ST-segment changes during transient coronary artery occlusion.[378] These studies suggested that particulate-related changes in myocardial blood flow may be responsible, a hypothesis recently supported by experiments in chronically instrumented dogs exposed to fine CAP before transient occlusion of the left anterior descending artery. PM exposure was associated with a small but significant decrease in total myocardial flow, especially in the ischemic zone, and increases in coronary vascular resistance without an alteration in rate-pressure product.[379] The abnormalities were inversely related to PM mass, particle number, and black carbon concentration.

Exposure to residual oil fly ash increases arrhythmia frequency in rats with preexisting premature ventricular complexes, which suggests that PM sensitizes ischemic myocardium to abnormal automaticity[372]; however, CAP had no effect in rats.[380] Nevertheless, the data suggest that PM exposure may potentially be capable increasing the sensitivity of the myocardium to ischemia, likely by impairing myocardial blood flow and perfusion. In theory, this could play a role in enhancing the propensity for ventricular arrhythmias.

Insulin Resistance

Recently, Sun et al[319] exposed C57BL/6 mice fed high-fat chow to fine CAP or filtered air for 24 weeks. Mice exposed to $PM_{2.5}$ exhibited marked worsening of whole-body insulin resistance, systemic inflammation (increased IL-6 and TNF-α), and higher levels of adipokines, such as resistin and plasminogen activator inhibitor-1. $PM_{2.5}$ increased visceral adiposity and inflammation (F4/80$^+$ cells), with stromal vascular cells expressing higher TNF-α and IL-6 and lower IL-10 levels. Exposure also induced insulin-signaling abnormalities and reduced phosphorylation of Akt and endothelial nitric oxide synthase in aortic tissue, accompanied by abnormalities in vascular relaxation to insulin. Additionally, there was evidence that $PM_{2.5}$ exaggerated adhesion of monocytes in mesenteric microvessels, culminating in accumulation in visceral adipose. These intriguing findings suggest that longer-term exposure to PM air pollution may promote the chronic development of insulin resistance, obesity, and the metabolic syndrome.

Controlled-Exposure Studies in Humans

Several new human exposure studies have been published, a few of which have even included patients with CVD or risk factors. Similar to the animal studies, large variations among the exposure protocols, measured outcomes, and subject susceptibilities likely explain much of the differences among findings and must be considered when interpreting the results.

Systemic Inflammation

Controlled human exposure studies have measured the effects on circulating inflammatory markers such as CRP, IL-6, and TNF-α. In many of these single-episode short-term exposures, no overt changes in plasma cytokine levels were observed after CAP[381–383] or diesel exhaust.[345,384–386] Similarly, CRP levels have not consistently been found to increase in the time frame and context of most of these studies.[313,384–386]

However, there have also been some positive findings. Increases in IL-6[313] and TNF-α 24 hours after exposure to diesel exhaust in healthy adults have been reported. High levels of ambient particles can stimulate the bone marrow to enhance the release of neutrophils, band cells, and monocytes into the circulation, which causes a cellular inflammatory response.[387,388] Some controlled-exposure studies corroborate the existence of a cellular proinflammatory response that manifests as increases in circulating white blood cell or immune cell counts. In 1 study, increased peripheral basophils in healthy older adults were noted 4 hours after a 2-hour exposure to fine CAP.[389] In a similar study, increased white blood cell counts were observed in healthy young adults 12 hours after exposure.[381] Recently, investigators observed an increased in total white blood cell and neutrophil levels immediately after a 2-hour exposure to CAP in downtown Toronto, Ontario, Canada.[390] Conversely, decreases in blood monocytes, basophils, eosinophils, and CD54 and CD18 adhesion molecule expression on monocytes after exposure to ultrafine carbon (10 to 50 $\mu g/m^3$) among exercising asthmatic individuals and healthy adults have also been reported.[391] The authors suggested in the latter study that these results may represent the sequestration of these cells in tissue compartments such as the lung or vasculature, where there may be selective expression of the corresponding receptors for these ligands.[362] However, other recent human clinical studies have found no association between peripheral blood cell counts and exposure to fine PM or UFPs such as zinc oxide,[392] ultrafine carbon,[393] or diesel exhaust.[313,384,385]

More subtle, yet physiologically relevant or functional proinflammatory changes may be overlooked by the measurement of circulating cytokines or cell counts alone in human studies. Peretz et al[394] recently evaluated gene expression using an expression array in monocytes after 2 hours of exposure to diesel exhaust. Although initially a small study, 10 genes involved in the inflammatory response were modulated in response to exposure (8 upregulated, 2 downregulated). These findings will need to be reproduced in larger studies and raise the possibility that functional changes in inflammatory cells may occur without discernible changes in their levels in the peripheral circulation.[394]

In sum, the findings from controlled human exposures do not demonstrate a robust inflammatory response; however, they have been limited by the fact that they are, by necessity, of short duration and relatively low concentration. Additionally, the results do not preclude an effect of higher exposures, the presence of more subtle responses, or alterations in other cellular inflammatory pathways not measurable by circulating markers.

Systemic Oxidative Stress

The demonstration of systemic oxidative stress is difficult in human studies. Nonetheless, a few studies have reported positive findings. These include an increase in urinary excretion of free 8-iso-prostaglandin-2α among healthy adults after a 4-hour exposure to concentrated wood smoke[395] and an increase in plasma antioxidant capacity 24 hours after a 1-hour exposure to diesel exhaust in a group of healthy volunteers.[313] The investigators speculated that systemic oxidative stress after exposure may have been responsible for this upregulation in antioxidant defense.[313] Other investigators[394] have observed significant differences in expression of genes involved in oxidative stress pathways due to diesel exhaust exposure. Bräuner et al[167] recently investigated the effect of ultrafine traffic particles on oxidative stress–induced damage to DNA in healthy young adults exposed to low concentrations of ambient urban particles ($PM_{2.5}$ and $PM_{10-2.5}$ mass of 9.7 and 12.6 $\mu g/m^3$, respectively) in an exposure chamber above a busy road with high traffic density. The authors observed increased levels of DNA strand breaks and formamidopyrimidine-DNA glycosylase sites in monocytes after exposure to PM but no changes in the DNA repair enzyme 7,8-dihydro-8-oxoguanine-DNA glycosylase. Similar to their previous findings with ambient levels,[168] the results suggest that short-term exposure to UFPs may result in damage to DNA. This may occur through oxidative stress pathways, although there was no increase in messenger ribonucleic acid levels in heme oxygenase-1, a gene known to be regulated by Nrf2, a transcription factor regulated by oxidative stress.[396] Moreover, more recent observations by the same investigators failed to demonstrate significant biomarker signals for lipid or protein oxidative damage after similar near-roadway exposures.[178] Although not entirely consistent, the available studies demonstrate that acute exposure to PM, perhaps even at ambient levels, may be capable of inducing acute systemic oxidative stress in human subjects under certain circumstances. The assays used to assess the footprint of systemic "oxidative stress" or damage may also play a significant role in the results.

Thrombosis and Coagulation

Several new studies of controlled human exposure have evaluated the effects of PM on hemostatic markers (eg, factor VII, fibrinogen, platelet count, D-dimer, and von Willebrand factor). Although some of these studies have not observed changes after acute exposures,[392] others have reported increases in fibrinogen levels at 8 to 24 hours after exposure to CAP.[381,397] Mills and colleagues[384,385] recently demonstrated a significant effect of diesel exhaust on fibrinolytic function in response to intermittent exercise both in healthy men and in men with coronary heart disease. In both groups of volunteers, bradykinin-induced release of tissue plasminogen activator was observed to decrease compared with filtered air at 6 hours after exposure to diesel exhaust. These perturbations in tissue plasminogen activator release did not persist 24 hours after exposure.[313] In a randomized, controlled crossover study involving "at-risk" metabolic syndrome patients, no changes in plasminogen activator inhibitor-1 were noted over a 24-hour duration; paradoxically, a decrease in von Willebrand factor was noted in this study.[398] In a similar experiment conducted in healthy adults, diesel exhaust had no effect on D-dimer, von Willebrand factor, CRP, or platelet counts compared with filtered air up to 22 hours after exposure.[386] Other investigators[395] recently evaluated the effect of wood smoke on markers of coagulation, inflammation, and lipid peroxidation in young healthy subjects. Serum amyloid A and the ratio of factor VIII to von Willebrand factor, an indicator of an increased risk of venous thromboembolism, were increased at 4 hours after exposure.[395] Samet et al[383] reported an association between various coagulation markers and exposure to ultrafine, fine, and thoracic coarse CAP among healthy young adults. Although exposure to coarse CAP did not result in significant changes in hemostatic variables, the overall trend suggested a prothrombotic effect. Exposure to UFPs increased D-dimer levels, whereas fine-CAP effects tended to increase fibrinogen, similar to previously reported findings.[381]

The measurement of blood levels of coagulation factors or biomarkers of thrombosis could potentially miss a relevant biological effect at the vascular wall. Recently, ex vivo thrombus formation was assessed by use of the Badimon chamber after controlled exposures to dilute diesel exhaust in healthy volunteers.[399] This protocol measures thrombus formation in native (nonanticoagulated) whole blood triggered by exposure to a physiologically relevant substrate, under flow conditions that mimic those found in diseased coronary arteries. It may therefore provide a superior estimate of actual in vivo conditions related to thrombosis potential. Interestingly, dilute diesel exhaust exposure increased thrombus formation within 2 hours, in association with increased platelet activation (ie, increased circulating platelet-monocyte aggregates and soluble CD40 ligand). Taken together, these new studies have provided additional evidence that short-term exposure to PM at near-ambient levels may have small yet potentially significant effects on hemostasis in humans. Whether direct interactions of circulating PM constituents with platelets, activation of platelets due to lung inflammation or secondary to elevated systemic cytokine levels, or an increase in procoagulant factors (eg, fibrinogen) as an acute-phase response to inflammation (or a combination of these pathways) is responsible warrants attention in future studies.

Arterial BP

Although several studies have evaluated the BP response to acute exposures, many inconsistencies in results have been reported.[400] This must be considered in the context that BP was not the primary outcome of interest in most studies, nor was it typically assessed with adequate sophistication. In one of the earliest studies, $PM_{2.5}$ increased systolic BP in healthy subjects but decreased it in asthmatic individuals.[401] Three other controlled studies did not report changes among healthy adults.[345,402,403] However, in a more detailed reanalysis of the changes in BP during the actual period of exposure to CAP plus ozone, Urch et al[404] found a significant increase in diastolic BP of 6 mm Hg. The magnitude of response was associated with the concentration of organic carbon within $PM_{2.5}$.[405] Recent follow-up studies redemonstrated an acute prohypertensive response during the inhalation of CAP in 2 separate cities.[390] The $PM_{2.5}$ mass during exposure and decreases in several HRV metrics were associated with the magnitude of the short-lived diastolic BP elevation. This suggested that the most plausible mechanism for this acute response was CAP-induced ANS imbalance that favored sympathetic over parasympathetic cardiovascular tone. Whether this reaction occurred because of a generalized stress response, as a consequence of specific soluble PM constituents directly altering central nervous system activity, or via altered ANS reflex arcs due to the interaction of inhaled particles with lung receptors/nerve endings remains to be elucidated.

The effect of inhaled particulates on BP has also been investigated in several other recent controlled human exposure studies. Two new studies assessed BP changes after a 1-hour exposure to diesel exhaust. Mills et al[384] found a 6-mm Hg increase in diastolic BP 2 hours after exposure, which was of marginal statistical significance ($P=0.08$); however, this trend did not persist for 24 hours,[384] nor was it found among patients with coronary artery disease.[385] The available data to date suggest that short-term exposure to $PM_{2.5}$ or diesel exhaust is capable in certain circumstances of rapidly raising BP. The most consistent and largest effects were seen concomitant with the inhalation of particles. Thus far, the most likely mechanism for such rapid hemodynamic responses appears to be ANS imbalance. However, it is possible that reductions in nitric oxide bioavailability that modulate basal arterial tone toward vasoconstriction or increases in ET among other hemodynamically active molecules (eg, angiotensin II) also play a role in some circumstances.

Vascular Dysfunction

The first controlled human exposure study related to vascular function reported that CAP plus ozone exposure caused acute conduit arterial vasoconstriction in healthy adults.[1] Endothelium-dependent and -independent vasodilation remained intact. Recent follow-up experiments determined that $PM_{2.5}$, not ozone, was responsible for the adverse vascular effects. However, in these subsequent and larger experiments, fine-CAP exposure did prove capable of diminishing conduit artery endothelium-dependent vasodilation 24 hours (but not immediately) after exposure.[390] Postexposure $PM_{2.5}$ mass and TNF-α level were both associated with the degree of endothelial dysfunction, which suggests that systemic inflammation induced by higher levels of particles was likely responsible. Finally, the CAP-induced endothelial dysfunction occurred during exposures in Toronto, Canada, but not Ann Arbor, Mich, which suggests that the composition of the particles is probably an important determinant of the vascular responses.

An acute alteration in vascular function/tone after short-term controlled PM air pollution exposure was corroborated recently.[406] In 27 adults (10 healthy adults and 17 with the metabolic syndrome), a 2-hour exposure to dilute diesel exhaust caused a dose-dependent constriction of the brachial artery and elevation in plasma ET level without impairing endothelium-dependent vasodilation. Contrary to the hypothesis that metabolic syndrome patients would show greater effects, vasoconstriction was greater in magnitude among the healthy participants. In an additional study, 2-hour exposure to UFPs composed of elemental carbon impaired peak forearm blood flow response to ischemia 3.5 hours later. There were no other vascular changes or alterations at other time points. BP was also not affected.[407]

Several recent studies have also shown that dilute diesel exhaust can impair peripheral resistance vessel responses to acetylcholine, bradykinin, and nitroprusside 6 hours after exposure.[384] The blunted responses to acetylcholine persisted for 24 hours in healthy adults.[313] In contrast, bradykinin and sodium nitroprusside–mediated vasodilation and bradykinin-induced acute plasma tissue plasminogen activator release were not altered 24 hours later. In subsequent studies, patients with stable coronary artery disease exposed to dilute diesel exhaust for 1 hour during intermittent exercise demonstrated reduced bradykinin-mediated tissue plasminogen activator release; however, microvascular endothelial function was not impaired.[385] This may be related to some degree of preexisting endothelial dysfunction in these patients. However, exercise-induced ST-segment depression and ischemic burden were significantly greater during diesel compared with filtered air exposure. These important findings experimentally highlight that PM air pollution exposure can trigger, or augment existing, myocardial ischemia extremely rapidly (in fact, concomitant with exposure). Reduced coronary flow reserve (that was not observed or resolved at the time of the postexposure brachial artery studies) due to rapid alterations in coronary microvascular function may have contributed to the acute myocardial ischemia. Alternatively, acute ANS imbalance induced by diesel exhaust inhalation may have acutely altered coronary tone and impaired myocardial perfusion.

In a study that exposed healthy young adults to 100 $\mu g/m^3$ of diesel exhaust for 2 hours,[364] it was recently demonstrated that this air pollution mixture acutely raised plasma ET-1 and MMP-9 expression and activity within 30 minutes. These results corroborate the animal data that even short-term exposures can rapidly alter factors, such as MMP activity, that are mechanistically linked with causing atherosclerotic plaque disruption (and thus acute MI). The increase in ET levels also corroborates previous studies[406] that showed that diesel exhaust can acutely affect important endogenous regulators of vasomotor tone.

Controlled air pollution exposures have not always been shown to impair endothelial function or vasomotor tone. Despite an increase in exhaled 8-isoprostane concentrations that suggested pulmonary oxidative stress, fine CAP did not affect brachial flow–mediated dilation or basal diameter in northern Scotland exposures.[382] However, the $PM_{2.5}$ consisted of relatively inert ambient sea-salt particles and was extremely low in combustion-derived sources. This is in contrast to the particle chemistry in the investigators' previous diesel exposure studies that showed positive findings.[408,409] Moreover, 24-hour exposure to ambient pollution shunted into a chamber next to a busy street did not impair microvascular endothelial function in 29 healthy subjects, as assessed by digital tonometry.[178] This exposure to near-roadway ambient air, which consisted of ambient UFP and $PM_{2.5}$, did not alter biomarkers of inflammation, hemostasis, or protein and lipid oxidation. The authors speculated that the relatively low concentrations of UFP numbers and PM mass or the young, healthy status of the subjects could explain the null findings. Taken together, these studies suggest that brief PM exposure can trigger conduit arterial vasoconstriction, possibly in relation to increased ET activity or augmented sympathetic ANS tone. Under certain circumstances, conduit and resistance arteriole endothelium-dependent vasodilation can also be impaired within a few hours. This abnormality is more likely due to reduced nitric oxide bioavailability as a consequence of systemic proinflammatory and oxidative responses; however, alternative mechanisms and endogenous vasoactive pathways have not been fully explored. It is also apparent that the composition, source, and concentration of pollution, along with the susceptibility of the human subjects, play important roles in determining the vascular effects of acute air pollution exposure.

Heart Rate Variability

The results of several new controlled human exposure studies provide limited evidence to suggest that acute exposure to near-ambient levels of PM may be associated with small changes in HRV. There are at least 4 studies to support this. In the first study, healthy elderly individuals experienced significant decreases in HRV immediately after exposure.[233] Some of these changes persisted for at least 24 hours. Gong et al[410] studied healthy and asthmatic adults exposed to coarse CAPs with intermittent exercise. HRV was not affected immediately after the exposure but decreased in both groups at 4 and 22 hours after the end of the exposure; greater responses were observed in nonasthmatic individuals.[410] In another study, healthy elderly subjects and patients with chronic obstructive pulmonary disease were exposed to approximately 200 $\mu g/m^3$ CAP and filtered air for 2 hours with intermittent mild exercise. HRV over multihour intervals was lower after CAP than after filtered air in healthy elderly subjects but not in subjects with lung disease. A significant negative effect of CAP on ectopic heartbeats during or after CAP exposure relative to filtered air was noted in the healthy subjects, whereas the group with pulmonary disease experienced an improvement during or after CAP relative to filtered air.[389] Other investigators recently compared the effects of 2-hour exposures with intermittent exercise to ultrafine (average concentration 47 $\mu g/m^3$), fine (average concentration 120 $\mu g/m^3$), and coarse (average concentration 89 $\mu g/m^3$) CAP among healthy subjects.[383] In both the ultrafine and coarse studies, a crossover design was used in which each subject was exposed to both PM and filtered air. In the case of the fine-PM study, subjects did not serve as their own control but were exposed to either PM or filtered air. Thoracic coarse fraction CAP produced a statistically significant decrease in the standard deviation of normal-to-normal heart rate 20 hours after exposure compared with filtered air. No statistically significant effects on HRV were observed after exposure to UFPs as measured during controlled 5-minute intervals. However, the authors did observe a significant decrease in the standard deviation of normal-to-normal heart rate after exposure to UFPs based on an analysis of the 24-hour measurements. No differences were reported in HRV with fine-PM exposures. Although some controlled-exposure studies have reported either no acute changes[390] or, on occasion, increases in HRV metrics in subsets of individuals,[208,393,401] these studies generally demonstrate that acute PM exposure is capable of reducing HRV. More consistent reductions have been found among older adults (compared with younger subjects or those with lung diseases, who show mixed responses) and perhaps with exposures to larger particles.[233,389] Whether pulmonary ANS reflex arcs are activated by the deposition of PM within the lung or whether other pathways are responsible for these physiological changes in human exposure studies requires more investigation.

Table 7. Summary of Level of Evidence Supporting Global Biological Pathways and Specific Mechanisms Whereby $PM_{2.5}$, Traffic-Related, or Combustion-Related Air Pollution Exposure Can Affect the Cardiovascular System

	Animal Studies	Human Studies
General "intermediary" pathways whereby PM inhalation can instigate extrapulmonary effects on the cardiovascular system		
Pathway 1: Instigation of systemic proinflammatory responses	↑↑↑	↑↑↑
Pathway 2: Alterations in systemic ANS balance/activity	↑	↑↑
Pathway 3: PM and/or associated constituents directly reaching the systemic circulation	↑	↑
Specific biological mechanisms directly responsible for triggering cardiovascular events		
Vascular dysfunction or vasoconstriction	↑↑↑	↑↑
Enhanced thrombosis or coagulation potential	↑↑	↑↑
Elevated arterial BP	↑↑	↑↑
Enhanced atherosclerosis or plaque vulnerability	↑↑	↑
Arrhythmias	↑	↑

The arrows are not indicators of the relative size of the association but represent a qualitative assessment based on the consensus of the writing group of the strength of the mechanistic evidence based on the number and/or quality, as well as the consistency, of the relevant studies.

↑↑↑ Indicates strong overall mechanistic evidence.

↑↑ Indicates moderate overall mechanistic evidence.

↑ Indicates some but limited or weak available mechanistic evidence.

Blank indicates lack of evidence.

Evidence Summary and Contextual Framework for Biological Mechanisms

Table 7 provides an outline of the level of evidence supporting the generalized intermediary pathways and specific mechanisms whereby PM exposures can be capable of eliciting cardiovascular events. At the molecular level, oxidative stress as a critically important cause and consequence of PM-mediated cardiovascular effects has a sound experimental basis.[261,290b,294,319,333,334,345–349,351,361–364,411] At the integrated physiological level, the collective body of evidence continues to support the existence of 3 general pathways (Figure 3). Some of these responses, such as systemic inflammation (via pathway 1), likely require antecedent pulmonary oxidative stress or inflammation in order to be initiated. Others, including ANS imbalance (via pathway 2) and PM or its constituents reaching the systemic circulation (via pathway 3), may not. Although PM-associated metals[412] and certain UFPs[261,413–415] might be capable of translocating into the blood stream, some studies have been negative in this regard.[355,416] Many issues related to this pathway are controversial and require resolution.[416] These include the relevance of the dosages delivered to cardiovascular organs, the consequences of particle constituent modifications after interactions with lung tissue/fluids and plasma components, the means of transport within the circulation (eg, protein bound or within cells),[417] and the time course and ultimate sites of PM sequestration. It is also possible that increases in some vasoactive mediators or molecules with adverse effects on cardiovascular tissue, such as ET-1,[351–354] may occur in the lung and systemic circulation without the need for antecedent lung inflammation. Moreover, the 3 general pathways represent a simplification of complicated biological processes. They may not be mutually exclusive, may overlap temporally, and likely exhibit synergies in causing manifest cardiovascular disease events. Many of the biological pathways are also known to exhibit mutual interactions (eg, inflammation with thrombosis/coagulation and with autonomic function). The pathways are also likely to be principally active at differing time points (eg, more rapid cardiovascular effects of autonomic imbalance than systemic inflammation) and likely vary in importance in relation to different durations of exposure and in causing different cardiovascular sequelae. The chemical characteristics and sizes of inhaled PM may also determine the pathways activated. As opposed to UFPs or some particulate components or chemicals, larger fine and coarse PM are not likely transported into the circulation to any large degree and therefore are more apt to require intermediary pathways to cause extrapulmonary effects. It may also be that surface-bound components may be delivered into the circulation, whereas larger particles themselves serve as a means to deliver the responsible constituent into the pulmonary tree.

The hyperacute physiological responses that occur minutes to hours after PM inhalation are likely mediated principally via pathways 2 and 3. These include ANS-mediated changes (eg, elevated BP, arrhythmias, and vasoconstriction), along with direct effects of circulating PM constituents on platelets (eg, procoagulant and thrombotic changes) and the endothelium (eg, oxidative stress and vasoconstriction). These responses are liable to be the dominant mechanisms responsible for the actual triggering of acute cardiovascular events. Clinically meaningful effects undoubtedly become manifest only in the context of a susceptible patient, typified by the individual with "vulnerable plaque" in the case of acute coronary syndromes or strokes, "vulnerable myocardium" in the context of arrhythmias, or the "vulnerable circulation" in the context of a heart failure patient at risk for circulatory overload. On the other hand, the biological consequences of systemic inflammation, such as activated white cells and elevated cytokines (via pathway 1), typically require longer periods. Their penultimate effect is the induction of a chronic underlying vulnerable milieu that leads to atherosclerotic plaque vulnerability, enhanced coagulation/thrombotic and arrhythmia potential, and impaired basal vasomotor balance. These actions thereby predispose individuals for future cardiovascular events, particularly when they occur in conjunction with traditional risk factors or prompt susceptibility to the acute biological actions (via pathways 2 and 3) of later air pollution exposures.

This hypothetical segregation of the biological effects of PM exposure as acute or chronic and into the broad pathways is artificial. It is useful in the broad context of understanding potential pathways; however, there is no doubt a large degree of overlap among the mechanisms and the timing of physiological responses. This is most aptly conveyed as the influence of "acute on chronic" actions of exposure. For example, the activation of circulating platelets by the pulmonary deposition of particles or lung inflammation (eg, by P-selectin–dependent pathways, histamine, or IL-6) could occur within hours and more rapidly than typical of the other consequences of inflammation (eg, progression of atherosclerosis). In the presence of a vulnerable or eroded coronary plaque due to long-term air pollution exposure, this sudden prothrombotic tendency could instigate an acute ischemic event (alone or in conjunction with other effects of short-term PM exposure via pathways 2 and 3). Furthermore, the epidemiological cohort studies demonstrate a larger relative risk for increased cardiovascular-related mortality than for morbidity.[72,73,227,274] If this is a true biological response and not simply a statistical phenomenon or a shortcoming of the available data, it not only suggests that exposures are capable of triggering acute cardiovascular events but that PM air pollution may also exaggerate their severity even if they would have otherwise occurred for reasons unrelated to air pollution. Therefore, exposure to PM could also be responsible for promoting fatal over nonfatal events.

Conclusions and Recommendations

A wide array of new studies that range from epidemiology to molecular and toxicological experiments have provided additional persuasive evidence that present-day levels of air pollutants contribute to cardiovascular morbidity and mortality. Although not unexpected given the numerous and heterogeneous nature of the published studies, all findings related to every single cardiovascular end point have not been consistent. However, the overall weight of scientific evidence now supports several new conclusions since the 2004 statement. These consensus points are given below by the AHA writing group after considering the strength, consistency, and coherence of the epidemiological findings, as well as in the context of evaluating the extent of the studies that provided related mechanistic support.

- The preponderance of findings indicate that short-term exposure to $PM_{2.5}$ over a period of a few hours to weeks can trigger CVD-related mortality and nonfatal events, including myocardial ischemia and MIs, heart failure, arrhythmias, and strokes.
- The increase in risk for acute $PM_{2.5}$-associated cardiovascular morbidity and mortality is principally among susceptible, but not necessarily critically ill, individuals. Several studies suggest that susceptible individuals at greater risk may include the elderly, patients with preexisting coronary artery disease, and perhaps those with diabetes. Recent data suggest that women and obese individuals might also be at higher risk.
- Most studies support the idea that longer-term $PM_{2.5}$ exposures increase the risk for cardiovascular mortality to an even greater extent than short-term exposures. Because most studies have focused on mortality data, the effect of long-term exposures on nonfatal cardiovascular events is less consistent and requires more investigation.
- The $PM_{2.5}$ concentration–cardiovascular risk relationships for both short- and long-term exposures appear to be monotonic, extending below 15 $\mu g/m^3$ (the 2006 annual NAAQS level) without a discernable "safe" threshold.
- Long-term exposure to elevated concentrations of ambient $PM_{2.5}$ at levels encountered in the present-day environment (ie, any increase by 10 $\mu g/m^3$) reduces life expectancy within a population probably by several months to a few years. Given that $PM_{2.5}$ is most strongly associated with cardiovascular deaths in the cohort studies, the reduced life expectancy is most likely predominantly due to excess cardiovascular mortality.
- The available studies are suggestive that reductions in PM levels decrease cardiovascular mortality within a time frame as short as a few years.
- Many potential biological mechanisms exist whereby PM exposure could exacerbate existing CVDs and trigger acute cardiovascular events (over the short term) and instigate or accelerate chronic CVDs (over the long run). Experimental support is increasingly strong for several mechanisms, which lends biological plausibility for the epidemiological findings.
- The existing evidence suggests that PM air pollution is capable of augmenting the development and progression of atherosclerosis. There is some support for a potential effect on several other chronic CVDs, including hypertension, heart failure, and diabetes.
- Most recent studies support the conclusion that the overall absolute risk for mortality due to PM exposure is greater for cardiovascular than pulmonary diseases after both short- and long-term exposures.

There are several additional areas worthy of highlighting in which the study results are reasonably consistent but in which the writing group believed further research was required to formulate firm conclusions.

- Although there is only limited epidemiological evidence directly linking UFPs with cardiovascular health problems,[262] the toxicological and experimental exposure evidence is suggestive that this size fraction may pose a particularly high risk to the cardiovascular system. The likelihood of health effects and the causal pathways mediated specifically by UFP exposure have been debated among experts recently.[418] Future research may help to more fully elucidate whether particles within the ultrafine size range (0.001 to 0.1 μm) and/or their constituents are more harmful to the cardiovascular system or pose a relatively greater cardiovascular risk than particles between 0.1 and 2.5 μm in diameter.
- Similarly, many studies have found a strong association between metrics of traffic-related air pollution exposure and elevated cardiovascular risk. Whether this represents the harmful effects of UFPs or diesel exhaust particulates, major components of the traffic mixture, or other pollution components is unclear. Diesel and UFPs possess toxic properties that instigate harmful biological responses in experimental models. However, the particle size fraction(s) and roles played by other copollutants (gases, VOCs, SVOCs) within the traffic-related mixture have not been fully elucidated. Nevertheless, traffic-related pollution as a whole appears to be a specific source associated with cardiovascular risk. It likely poses a major public health burden, regardless of a putative higher toxicity, because of the commonness of exposure in modern society (eg, accounting for $\approx$60% of daily UFP exposure; http://www.catf.us/projects/diesel/).
- The importance of other specific sources, regional differences in pollution composition, and other specific constituents remains less clear. However, toxicological studies have identified several transition metals (eg, iron, vanadium, nickel, copper, and zinc), organic carbon species, semiquinones, and endotoxin as specific PM-related components capable of prompting oxidative stress and inflammation and thus likely imparting biological harm. Some source-apportionment studies also demonstrate that attention should be given to these compounds as being among the most likely mediators of clinical CVD. More studies are required in this regard to clarify this issue and to better define these and other potentially responsible constituents and sources.
- Although the focus of the present statement is on PM, we recognize that other air pollutants may also pose cardiovascular risk alone or in conjunction with fine-particle exposure. In this context, we believe additional research is necessary to make firm conclusions regarding the independent cardiovascular risks posed by several gaseous pollutants (eg, ozone and NO_2). Although ozone has been linked to increased cardiopulmonary mortality,[50] strokes,[126] and MIs[419] in some short-term studies, long-term exposure was not associated with cardiovascular mortality after accounting for PM in a recent analysis.[87] The recent finding that small changes in low levels of ambient carbon monoxide concentrations are related to cardiovascular hospitalizations also merits further exploration.[420]
- Several secondary aerosols (eg, nitrate and sulfate) are often associated with cardiovascular mortality; however, whether these compounds are directly harmful or are surrogate markers of toxic sources of exposure requires

more investigation. Similarly, the current literature regarding the independent cardiovascular risks posed by coarse particles is mixed, with most recent findings not supporting an association after accounting for the effects of $PM_{2.5}$.[43,72,104]

- Several recent cohort studies and intermediate end-point experiments suggest that obese individuals (and/or those with the metabolic syndrome) may be a susceptible population at greater risk for cardiovascular events due to $PM_{2.5}$ exposure. This is a tremendously important public health issue to corroborate because of the enormous and growing prevalence of obesity worldwide.

This updated review by the AHA writing group corroborates and strengthens the conclusions of the initial scientific statement. In this context, we agree with the concept and continue to support measures based on scientific evidence, such as the US EPA NAAQS, that seek to control PM levels to protect the public health. Because the evidence reviewed supports that there is no safe threshold, it appears that public health benefits would accrue from lowering $PM_{2.5}$ concentrations even below present-day annual (15 $\mu g/m^3$) and 24-hour (35 $\mu g/m^3$) NAAQS, if feasible, to optimally protect the most susceptible populations. Evaluations of the effectiveness of such efforts would be warranted as well. Within the framework of attempting to establish causality between associated variables in epidemiological studies, there are several generally accepted "aspects" that have been evaluated (the following phrases in italics per the Bradford Hill criteria)[421]: With regard to cardiovascular mortality and $PM_{2.5}$ exposure, there is a *consistent association* that satisfies both a *temporal and exposure-response relationship*. There is *coherence of findings* among several fields of science, including toxicology, human and animal exposures, and different types of epidemiological studies and time frames of exposure. Rigorous experiments demonstrate multiple *plausible biological mechanisms*. Finally, natural experiments have confirmed that a change (ie, reduction) in exposure produces a change (ie, decrease) in cardiovascular mortality. In this case, *specificity of outcomes* and *strength of the observation* are less pertinent, because PM exposure could be capable of causing multiple different types of events (eg, MIs, arrhythmias, and heart failure exacerbations), and the overall cardiovascular mortality relative risk posed for any single individual is expected to be small. Nevertheless, given the ubiquity of exposure, the overall public health consequences can be substantial and observable in population- or large cohort–based studies.

It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality. This body of evidence has grown and has been strengthened substantially since publication of the first AHA scientific statement.[1] At present, no credible alternative explanation exists. These conclusions of our independent review are broadly similar to those found in the EPA's Integrated Science Assessment for Particulate Matter final report (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546). In summary, the AHA writing group deems that $PM_{2.5}$ exposure is a "modifiable factor contributing to cardiovascular morbidity and mortality."

Clinical Recommendations

Several precautionary recommendations can be made for healthcare providers who interact with individuals who are at risk for CVDs. Although they have not been clinically tested or proven to reduce mortality, they are practical and feasible measures that may help to reduce exposures to air pollution and therefore potentially lower the associated cardiovascular risk. Moreover, a recent observational study found that patient awareness of air quality indices and media alerts along with health professional advice can significantly affect reported changes in outdoor activity to avoid exposure to air pollution.[422]

- Evidence-based appropriate treatment of the traditional cardiovascular risk factors should be emphasized. This may also lessen the susceptibility of patients to air pollution exposures.
- All patients with CVD should be educated about the cardiovascular risks posed by air pollution.
- Consideration should also be given to educating patients without CVD but who are at high risk (eg, the elderly, individuals with the metabolic syndrome or multiple risk factors, and those with diabetes).
- Part of patient education should include the provision of information regarding the available sources (local and national newspapers [*USA Today*], EPA World Wide Web site [http://airnow.gov/], and The Weather Channel and its World Wide Web site [http://www.weather.com/]) that provide a daily EPA Air Quality Index.
- On the basis of the forecast Air Quality Index, prudent recommendations for reducing exposure and limiting activity should be provided based on the patient's level of risk. A list of such recommendations is provided on the EPA World Wide Web site (http://airnow.gov/). For example, when the Air Quality Index for PM is "unhealthy" (151 to 200), then the recommendations are as follows: "People with heart or lung disease, older adults, and children should avoid prolonged or heavy exertion. Everyone else should reduce prolonged or heavy exertion." The action recommendations are as follows: "You can reduce your exposure to particles by 1) planning strenuous activity when particle levels are forecast to be lower, 2) reducing the amount of time spent at vigorous activity, or 3) choosing a less strenuous activity (eg, going for a walk instead of a jog). When particle levels are high outdoors, they also can be high indoors. Certain filters and room air cleaners are available that can help reduce particles indoors."
- Practical recommendations to reduce air pollution exposure should be given to at-risk patients. Although unproven to reduce cardiovascular events, there are a number of prudent and feasible measures, including reducing optional or unnecessary exposures. Additional measures could include eliminating or reducing nonmandatory travel to highly polluted regions and avoiding exposures or outdoor activities (eg, exercising, commut-

ing) during highly polluted times (eg, rush hours) or in proximity to major sources of pollution (eg, roadways, industrial sources). Choosing to exercise indoors with windows closed and using efficient air conditioning and filtering systems may be prudent for certain high-risk patients, particularly during peak pollution periods. Indeed, not only can central air conditioners reduce the indoor exposure level to PM from outdoor sources, there is some evidence that they might reduce the risk for cardiovascular hospitalizations associated with higher ambient pollution levels.[423] If travel/commutes cannot be avoided, maintaining optimal car filter systems, driving with windows closed, and recycling inside vehicle air may help reduce PM exposures (http://www.catf.us/projects/diesel/).[424,425]

However, at present, no specific recommendations regarding the appropriateness of undertaking more aggressive measures, even those shown to provide some benefits in a few studies (eg, wearing facemasks, installing PM filters in households), can be made based on the limited evidence. Similarly, although measures that decrease long-term PM exposures may produce even greater cardiovascular health benefits than the provided recommendations that focus on reducing short-term exposures, no specific recommendations (eg, moving to less polluted regions) can be prudently made at this time given the limited evidence. We acknowledge that occupational and indoor sources along with secondhand tobacco smoke are additional significant sources of personal PM exposures that should be avoided or reduced as much as possible. Finally, in developing nations, reducing exposure to indoor cooking sources of PM and air pollution from biomass combustion is a major issue of concern.[426] Additional suggestions are available on the EPA World Wide Web site.

Finally, although the existing evidence supports a causal relationship between $PM_{2.5}$ and cardiovascular mortality, we acknowledge the importance of continued research in areas of controversy and uncertainty to further understand the full nature of this issue. Although numerous insights have greatly enhanced our understanding of the PM-cardiovascular relationship since the first AHA statement was published,[1] the following list represents broad strategic avenues for future investigation:

Mechanistic Studies

- Better describe the physiological relevance in humans and the fundamental details of the mechanisms underlying the intermediate general mediating pathways (ie, PM or constituent transport into the circulation versus effects of inflammatory cytokines or activated immune cells versus ANS imbalance or other pathways) through which PM inhalation might mediate cardiovascular effects remote from the site of pulmonary deposition.
- Understand the clinical significance and relative importance of the observed biological responses (eg, vascular dysfunction, thrombosis, arrhythmia, ANS imbalance) in relation to the various causes of PM-mediated cardiovascular morbidity and mortality.
- Examine the efficacy of preventive measures (eg, patient education) and treatment modalities (eg, statins, antioxidants, fish oil, treatment of traditional risk factors, and reducing exposures by engineering controls, including filtration, personal protection via facemasks, or behavior modification) on cardiovascular health outcomes.
- Investigate the interaction between preexisting traditional cardiovascular risk factors (eg, diabetes, hypertension) and PM exposure, as well as the potential of air pollutants to exacerbate or worsen these risk factors. Determine the extent to which treatment of such factors (eg, with statins, aspirin, or angiotensin-converting enzyme inhibitors), especially among patients with known CVD, may modify the risk associated with PM exposure.
- Describe the biological effects of acute on top of chronic exposures (eg, synergistic effects versus reduced susceptibility to acute exposures due to augmented protective mechanisms).
- Determine the ability of long-term exposure to precipitate the development of chronic diseases, including clinically relevant atherosclerosis, hypertension, diabetes, and other vascular, metabolic, renal, or neurological diseases.

Epidemiological and Exposure Studies

- Expand our knowledge related to the "responsible" PM pollution constituents (eg, metals, organic compounds, semiquinones, endotoxin, and VOC and SVOC compounds), size fractions (eg, UFPs), sources (eg, traffic, power generation, and biomass combustion), and mixtures of pollutants.
- Investigate the cardiovascular health implications and importance of regional and intracity differences in composition and combinations of pollutants.
- Better understand the effects of mixtures of ambient pollutants (ie, potential synergism between PM and gaseous or vapor-phase pollutants such as ozone).
- Investigate the feasibility and utility of quantifying risk coefficients (concentration-response functions) according to PM source or relevant indices of pollutant mixtures, as a function of susceptibility (eg, age, preexisting disease), for reliable application in integrated, multipollutant risk assessments.
- Investigate the relative importance of various time frames of exposure in relation to PM causing cardiovascular events, including the relevance of epochs not well described, such as ultra-acute peak PM excursions (eg, 1 to 2 hours) and exposures of intermediate duration (eg, 1 to 12 months).
- Better document the time course and specific cardiovascular health benefits induced by reductions in PM.
- Better define susceptible individuals or vulnerable populations.
- Determine whether any "safe" PM threshold concentration exists that eliminates both acute and chronic cardiovascular effects in healthy and susceptible individuals and at a population level.

Acknowledgments

We would like to thank Robert Bard Consulting for reviewing and editing the manuscript and Tom Dann from Environment Canada and Joseph Pinto from the US EPA for assistance in the preparation of Table 1.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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Yuling Hong	American Heart Association‡	None	None	None	None	None	None	None
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David Siscovick	University of Washington	MESA AIR (ancillary study to MESA) funded by EPA†; NIEHS Discovery Center Study focused on air pollution and CVD†; NIH†	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina	None	None	None	None	None	None	None
Laurie Whitsel	American Heart Association	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

‡Dr Hong is currently with the Centers for Disease Control and Prevention, Atlanta, Ga.

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Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Doug Dockery	Harvard University	National Institute of Environmental Health Sciences†; Health Effects Institute†	None	None	None	None	Science Advisory Board to MESA Air Study, University of Washington*	None
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Eur Respir J 2008; 31: 179–196
DOI: 10.1183/09031936.00128106

REVIEW

Air pollution, oxidative stress and dietary supplementation: a review

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ABSTRACT: **The aim of the present review was to provide an up-to-date overview of the biological and epidemiological evidence of the role of oxidative stress as a major underlying feature of the toxic effect of air pollutants, and the potential role of dietary supplementation in enhancing antioxidant defences.**

A bibliographic search was conducted through PubMed. The keywords used in the search were ''air pollutant'', ''oxidative stress'', ''inflammation'', ''antioxidant polyunsaturated fatty acids'' and ''genetics''. In addition, the authors also searched for biomarkers of oxidative stress and nutrients.

The review presents the most recent data on: the biological and epidemiological evidence of the oxidative stress response to air pollutants; the role of dietary supplementation as a modulator of these effects; and factors of inter-individual variation in human response. The methodology for further epidemiological studies will be discussed in order to improve the current understanding on how nutritional factors may act.

There is substantial evidence that air pollution exposure results in increased oxidative stress and that dietary supplementation may play a modulating role on the acute effect of air pollutants. Further epidemiological studies should address the impact of supplementation strategies in the prevention of air-pollution-related long-term effects in areas where people are destined to be exposed for the distant future.

KEYWORDS: **Air pollution, antioxidants, nutrition, oxidative stress**

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Received:
October 02 2006
Accepted after revision:
August 20 2007

SUPPORT STATEMENT
The work was supported by the National Center for Environmental Health, Centers for Disease Control and Prevention (Atlanta, GA, USA), the GA^{2}LEN project (EU contract FOODCT-2004-506378) and the Spanish Ministry of Education and Science (SAB2004-0192).

STATEMENT OF INTEREST
None declared.

Epidemiological studies have clearly shown that air pollution exposure is associated with a range of respiratory and cardiovascular health effects and increased mortality [1]. Recent research has identified oxidative stress as one potential feature underlying the toxic effect of air pollutants, which trigger a number of redox sensitive signalling pathways, such as those of inflammatory response and cytokine production [2–5]. Toxicity may arise from an imbalance of biological pro-oxidant and antioxidant processes [6] linked to increased exposure to oxidants or the presence of impaired antioxidant defences [7, 8]. This imbalance has long been recognised in investigations of ozone (O_3) [9], one of the most potent oxidants, and more recent studies have focused on this particular mechanistic hypothesis [10]. Since diet is a major source of antioxidants, it is important to examine whether antioxidant defence mechanisms could be increased by dietary means to protect against air pollutants as this could have major public health consequences [11]. To provide an up-to-date overview on the biological and epidemiological evidence of the role of oxidative stress as a major underlying feature of the toxic effect of air pollutants and the potential role of dietary supplementation as an enhancer [11] of antioxidant defences, a bibliogaphic search was conducted through PubMed. The keywords used in the search were ''air pollutant'', ''oxidative stress'', ''inflammation'', ''antioxidant'' (vitamin C, vitamin E, carotenoids), ''polyunsaturated fatty acids'' (PUFA) and ''genetics''. In addition, the current authors searched for biomarkers of oxidative stress, biomarkers of antioxidant intake (selenium, flavonoids, carotenoids, vitamin C, vitamin E), and n-3 PUFA. Various recent reviews have been published on these issues [1–5, 7–10, 12–34], therefore, the present authors refer to these and mostly focus on the latest findings. Thus, the purpose of this up-to-date overview is five-fold. First, the relevance of oxidative stress as a common mechanism for

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

effects of ambient air pollutants will be summarised. Secondly, the role of antioxidants in oxidative stress will be briefly discussed. Thirdly, the evidence for dietary supplements as modulating the adverse effects due to air pollution will be reviewed. Fourthly, the relevance of factors that may interact with a subjects' response to exogenous oxidative stress will be discussed. Finally, the need to further investigate the relevance of dietary supplementation as an approach to protect from adverse effects of air pollution will be discussed.

BIOLOGICAL AND EPIDEMIOLOGICAL EVIDENCE

Oxidative stress and air pollutants

Several air pollution components have been related to particulate toxicity. An important determinant of the acute inflammatory response appears to be the dose of bio-available transition metals (such as copper, vanadium, chromium, nickel, cobalt and iron), organic compounds (such as polycyclic aromatic hydrocarbons) and biological fractions (such as endotoxins) [35, 36]. The oxidative stress mediated by particulate matter (PM) may arise from: direct generation of reactive oxygen species (ROS) from the surface of soluble compounds; altered function of mitochondria or reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase; and activation of inflammatory cells capable of generating ROS and reactive nitrogen species (RNS), as well as oxidative DNA damage [37, 38]. The particle provides a template for electron transfer to molecular oxygen in these reduction and oxidation (redox) cycling events [39]. In addition, target cells, such as airway epithelial cells and macrophages, generate ROS in response to particle uptake by biologically catalysed oxidation reactions that occur in the cell membrane and mitochondria [4, 40–42]. *In vitro* studies have shown that inhaled PM causes expression of nuclear factor (NF)-κB-related genes and oxidant-dependent NF-κB activation [43, 44]. The dose of bio-available transition metal, rather than particulate mass, may be the primary determinant of acute inflammatory response [35, 37, 44]. However, other studies suggest that the hydrosoluble fraction is responsible for the oxidative damage to DNA [45]. The biological component of particles also seems to be related to oxidative stress [46], as well as bacterial endotoxin that induce the liberation of tumour necrosis factor (TNF)-α and interleukin (IL)-6 by macrophages [36].

Strong oxidative activity and the effective depletion of lung lining fluid antioxidants have been reported in large studies of ambient PM <2.5 μm ($PM_{2.5}$) [17]. To defend against the oxidative damage, cells use up their stores of a key antioxidant, glutathione. The glutathione depletion can induce a state of cellular stress, which triggers an increase in the production of antioxidant enzymes through activation of a transcription factor nuclear factor-erythroid 2-related factor 2 [17]. Failure to overcome oxidative stress leads to the activation of additional intracellular signalling cascades that regulate the expression of cytokine and chemokine genes [15]. These products are produced locally in target tissues as well as systemically, and lead to widespread pro-inflammatory effects remote from the site of damage. In addition, PM appears to inhibit protective enzymes involved in oxidative stress responses depending on their toxicity (copper/zinc superoxide dismutase, manganese superoxide dismutase, glutathione peroxidase and glutathione reductase) [47].

Diesel exhaust particles (DEPs) have a high content of elemental and organic carbon and are thought to be particularly toxic [15]. These particles consist of a carbon core with adsorbed organic compounds, such as polyaromatic hydrocarbons, quinones and redox-active metals, and the capacity of DEPs to induce oxidative stress is largely related to these adsorbed components. Animal experimental models, cell culture experiments and cell free systems involving DEPs have shown oxidative stress response and oxidative DNA damage. Human studies have shown increased neutrophils, B cells and alveolar macrophages in bronchoalveolar lavage fluid and an increased amount of pro-inflammatory cytokines, chemokines and adhesion molecules [48]. Exposure to DEPs has been shown to increase airway resistance, increase IL-6 and IL-8 in lavage fluid, increase IL-8 mRNA expression in bronchial mucosa and upregulate endothelial adhesion molecules P-selectin and vascular cell adhesion molecule-1 [49]. ROS formed at the epithelial level after DEP exposure upregulate IL-10, promoting antigen-presenting cells and allergy to pollen [15]. However, controlled exposure to DEP in human subjects has been shown to respond with an increase in low molecular antioxidants in the alveolar compartment [50]. The role of oxidative stress in response to DEPs and other particles is further supported by *in vitro* studies in which ROS are generated by macrophages, neutrophils, eosiniphils and epithelial cells after stimulation by DEPs or particles [15]. Interestingly, low sulphur diesel combined with engine filters blocked a range of responses to DEPs including the oxidative stress responses in mice [51].

Alteration of autonomic functions also appears to be partly associated with oxidative stress [14]. Long-term exposure to low concentrations of $PM_{2.5}$ has been shown to alter vasomotor tone, lead to vascular inflammation and potentiate atherosclerosis induced by high-fat chow in susceptible mice [52]. Although epidemiological evidence suggests that it is the fine ($PM_{2.5}$) or ultrafine (PM <0.1 μm) fraction that contains the toxic components; the large spectrum of disease end-points (from cardiovascular to asthma attack) suggest that more than one component may be driving the health effects [2].

O_3 is a very reactive gas whose uptake depends on the availability of antioxidants in the lining fluids, and its toxicity appears to be transmitted to the respiratory epithelium by secondary ROS formed by direct ozonisation of respiratory tract lining fluid lipids [16]. Alteration of the cell membrane translating an induction of lipid peroxidation and a significant modification of the redox status has been observed [53], as well as the activation of transcription factors such as NF-κB and increased expression of a range of pro-inflammatory cytokines and adhesion genes [2, 6]. O_3 has been shown to react readily with ascorbic acid, uric acid and thiols, and exposure of these molecular species to O_3 results in their rapid depletion [6]. When these defence mechanisms are overwhelmed, O_3 may injure the underlying cells by inducing lipid peroxidation and activating inflammatory gene expression [6, 53]. Like O_3, nitrogen dioxide (NO_2) reacts with substrates present in the lung lining fluid compartment. The oxidised species arising from the reaction between NO_2 and lining fluid are responsible for the signalling cascade of inflammatory cells into the lung [54–56].

A hierarchical oxidative stress model has been proposed to explain the dose–dependent response to air pollutant exposure [57]. Low exposure would lead to the formation of ROS activating an antioxidant response, followed by the transcription of enzymes important in detoxification, cytoprotective and antioxidant responses. These include phase II enzymes, whose induction serves as a detoxification mechanism (*e.g.* NAD(P)H:quinone oxidoreductase 1 (Nqo1) and glutathione *S*-transferase). At higher exposure, the transcription NF-κB and activator protein-1 responses would be activated. This would lead to NF-κB and mitogen-activated protein kinase signalling, altering the function of mitochondria or NADPH, and to increased expression of pro-inflammatory cytokines (such as TNF-α and IL-8 and IL-6) and genes coding adhesion molecules [2, 6, 15, 43, 44]. Any enhanced inflammatory response would lead to additional generation of ROS and RNS, together with oxidative DNA damage (fig. 1) [15, 37, 38].

Antioxidants and oxidative stress

Antioxidants in the lung are the first line of defence against oxygen free radicals. The respiratory tract lining fluids (RTLF) contain a range of low molecular weight antioxidants similar to those found in blood plasma, including reduced glutathione, ascorbic acid (vitamin C), uric acid and α-tocopherol (vitamin E). They also contain antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, thioredoxin reductase, catalase and the metal binding proteins ceruloplasmin and transferrin [2, 7]. All these antioxidants are free radical scavengers but also function as sacrificial targets for O_3 (ascorbate and urate) and react rapidly with this oxidant to limit its interaction with RTLF lipids and proteins [58]. The composition and quantity of antioxidants in the RTLF may represent an important determinant of individual responsiveness to air pollutants but should be thought of as a dynamic equilibrium with the antioxidant defences within the epithelium and the more remote plasma pool [59]. Controlled studies suggest that exposure to O_3 results in a depletion of RTLF antioxidants followed by an enhancement of the movement of antioxidants to the RTLF [60] or increased synthesis [3, 59]. Similarly, low-dose diesel exposure challenge in healthy volunteers was followed by an increase of inflammatory markers in bronchial lavage. No inflammatory response was seen in the alveolar compartment, but both reduced glutathione and urate concentrations were increased following diesel exposure suggesting differential antioxidant responses in the conducting airway and alveolar regions [50].

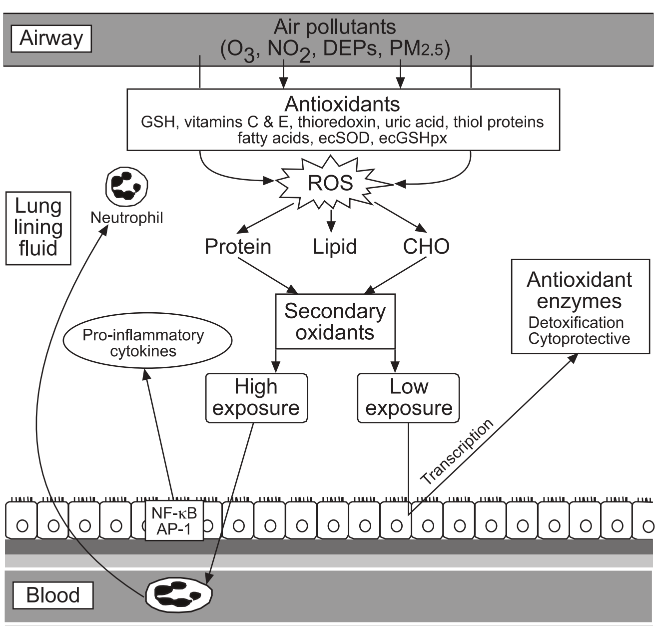

FIGURE 1. A model of the reaction of oxidants in the airway. Inhaled pollutants, such as ozone (O_3), nitrogen dioxide (NO_2), particulate matter <2.5 μm ($PM_{2.5}$) or diesel exhaust particulates (DEPs), react with nonenzymatic antioxidant constituents of the respiratory tract lining fluid including: reduced glutathione (GSH); vitamin C; uric acid; and enzymatic antioxidants, such as extracellular superoxide dismutase (ecSOD), extracellular glutathione peroxidise (ecGSHpx) and thioredoxin. These molecules provide a protective screen against these pollutants. If defences are exceeded, the production of reactive oxygen species (ROS) is increased and oxidants may react with organic molecules, such as proteins or lipids, and alter the epithelium resulting in: cell activation and initiation of the inflammatory process; activation of neutrophils; and liberation of cytokines, chemokines and adhesion molecules. CHO: carbohydrate; NF-κB: nuclear factor-κB; AP-1: activator protein-1. Modified from [3].

Although the inter-relation among antioxidant levels in RTLF, cellular and plasma levels is not well understood, it appears that the susceptibility of the lung to oxidative injury depends largely on its ability to upregulate protective ROS- and RNS-scavenging systems and that the speed at which lost antioxidant defences can be replaced is a major determinant [58].

As many antioxidants are derived from the diet, several dietary factors have been implicated; mainly because of their potential role in inflammatory reactions. The following section will focus mostly on nutrients that have been used in supplementation studies to modulate the impact of air pollutants or might interact with the immune response. These factors include antioxidant vitamins, omega-3 fatty acids and other micronutrients that might affect the immune response.

Antioxidant nutrients

Vitamin C

Vitamin C, a water-soluble vitamin, is an abundant antioxidant substance and is widely distributed throughout the body including the extracellular lining fluid of the lung [17]. Ascorbate is an excellent reducing agent and scavenges free radical and oxidants. *In vitro* evidence suggests that vitamin C has a role as a chemical reducing agent both intracellularly and extracellularly. Intracellular vitamin C might prevent protein oxidation and regulate gene expression and mRNA translation. This is particularly relevant for the lung which is exposed to oxidative substances. Extracellular vitamin C protects against oxidants and oxidant-mediated damage [61]. It contributes to antioxidant activity through scavenging a variety of free radicals and oxidants, *in vitro*, including superoxide radical (O^{2-}), peroxyl radicals, hydrogen peroxide, hypochlorous acid, singlet oxygen, oxidant air pollutants and oxidants that leak from activated neutrophils and macrophages [59, 61]. While the terminating product dehydroascorbate can be regenerated to ascorbate by intracellular enzymes, in particular thioredoxin reductase, which catalyses its regeneration [62], this regeneration is unlikely in the RTLF because of the lack of enzymes. Therefore, the maintenance of ascorbate level in the RTLF requires transportation from cellular sources or from the plasma pool [59]. Ascorbate also acts indirectly to prevent lipid peroxidation [59] and contributes to the regeneration of membrane-bound oxidised vitamin E [63]. Ascorbate plays a role in immune function and is transported into neutrophils and lymphocytes [18]. Whilst ascorbate has many antioxidant actions, it also has the capacity to act as a pro-oxidant in the presence of transition metals [64].

Vitamin E

Vitamin E, a lipid-soluble vitamin, represents the principal defence against oxidant-induced membrane injury in human tissue because of its role in breaking the lipid peroxidation chain reaction [64]. It is a potent peroxyl radical scavenger and especially protects PUFAs within the phosphsolipid biological membrane and in plasma liproteins [65]. It also decreases production of prostaglandin E_2, a metabolite of arachidonic acid produced by lipid peroxidation of lung cells after O_3 exposure [19]. Vitamin E appears to play a major role as an integral constituent of alveolar surfactant, whose quantity and composition conditions normal lung function [66].

β-Carotene

β-Carotene, a precursor to vitamin A and other carotenoids, accumulates in tissue membranes, scavenges O^{2-} and reacts directly with peroxyl free radicals generated by O_3 [67]. It could, therefore, play a role in the control of inflammation and immune response through its antioxidant properties. However, recent research has shown that high-dose carotenoid supplementation may lead to both antioxidant and pro-oxidant reactions [68], depending on the redox potential of the biological environment in which it acts [69].

Other antioxidants, such as flavonoids, are scavengers of superoxide anions and peroxyl radicals [70]. In addition to antioxidant activities, flavonoids can modulate cell signalling pathways [20]. Selenium, an essential trace element that plays a role in the detoxification of peroxides and free radicals [67], could also play an important role in the prevention of lung injury [21]. As an integral part of the glutathione peroxidases and thioredoxin reductase, selenium probably interacts with every nutrient that affects the pro-oxidant/antioxidant balance of the cell. It also appears to support the activity of vitamin E in limiting lipid oxidation [71].

Omega-3 PUFA

Increased intake of omega-3 PUFA (n-3 PUFA) can decrease the inflammatory reaction by changing the contents of lipid membranes and other substrates, which are in turn the substrates for eicosanoid production [72]. The substitution of n-3 PUFA (α-linoleic acid; 18:3n-3 and eicosapentaenoic acid (EPA); 20:5n-3) for n-6 fatty acids (linoleic acid; 18:2n-6) in the membrane leads to the production of less potent inflammatory mediators (prostaglandin E_3 instead of prostaglandin E_2, and leukotriene 5 instead of leukotriene 4) [72]. Prostaglandin E_2 has been shown to act on T-lymphocytes to reduce the formation of interferon (IFN)-γ without affecting the formation of IL-4. This may lead to the development of allergic sensitisation, since IL-4 promotes the synthesis of immunoglobulin E whereas IFN-γ has the opposite effect [73]. Leukotriene 4, a potent stimulator of airway smooth muscle cells, increases post-capillary vascular permeability and mediates asthma by vasoconstriction and mucus secretion. The competitive interactions between n-6 PUFA and n-3 PUFA determine the cellular contents of arachidonic acid and EPA.

Increased intake of n-3 PUFA appears to decrease the risk of sudden and nonsudden death from myocardial infarction and nonfatal myocardial infarction [74–76]. The protective effect of n-3 PUFA may be linked, in part, to its cardiac and arrhythmic effects, including increasing heart rate variability (HRV) [22, 74, 77]. There is a positive correlation between the baseline cell membrane concentrations of n-3 PUFA and the degree of HRV, both in healthy subjects and in patients with coronary artery disease [23, 78]. Along with increasing HRV, other anti-arrhythmic mechanisms of n-3 PUFA have also been described, including the capacity to stabilise the electrical activity of cardiac myocytes by modulating sarcolemmal ion channels and voltage-dependent sodium channels [24], and the capacity to reduce myocardial infarct size in animal models of ischaemia and reperfusion [24]. N-3 PUFA also appear to: decrease the risk of thrombosis; decrease serum triglyceride levels, slowing the growth of atherosclerotic plaque; improve vascular endothelial function; lower blood pressure; and decrease inflammation [79].

Other micronutrients and immune functions

Micronutrients such as zinc, vitamin A and folic acid can also influence several components of immunity, altering the function of macrophages and thus their role in innate immunity and inflammation. Studies have shown that deficiencies in these micronutrients can significantly alter macrophage phagocytosis and their production of cytokines (IL-1 and IL-6, TNF-α and IFN-γ). These deficiencies also alter natural killer cell function, neutrophil motility and antimicrobial activity [25].

Nutrient supplementation and effects of air pollution

The effects on air pollutant toxicity of nutrient supplementation at levels higher than is physiologically required have been studied in both animals and humans and summarised previously [2, 11, 17, 80].

Experimental animal studies

Results of animal studies suggest that supplementation with vitamin C and vitamin E modulates the pulmonary response to exposure to photo-oxidants, such as O_3 or NO_2 [17, 81], and that vitamin C, uric acid and glutathione located in the respiratory tract lining fluid are consumed on exposure to O_3 and NO_2 [16, 82, 83]. Dietary deficiency of vitamin C appears to quickly translate to decreased levels of vitamin C in blood and RTLF [84]. Temporary vitamin E deficiency may induce reversible changes in the expression of pro-inflammatory markers, reduce surfactant lipid synthesis in alveolar type II cells and favour the development of injury in response to air pollution insults [66]. Further experimental studies using antioxidants, iron chelators or other substances support the role of ROS as mediators of the effects of particulates [37, 54]. Oxidative stress appears to play a critical role in the activation of NF-κB, and cytokine-induced NF-κB activation is prevented after treatment with antioxidants or metal chelators [54]. *N*-acetylcysteine, a powerful antioxidant, had a protective effect on inflammatory response and oxidative stress damage in rats exposed to coal dust [85] and on changes in heart rate and decrease in HRV in rats exposed to urban air particles [86].

Human studies

There is little information on the impact of antioxidant supplementation on the acute effects of air pollution exposure in humans. Most existing studies have focused on the changes of acute lung function. Other outcomes included bronchial airway reactivity, inflammatory response and changes in HRV but are less numerous and consistent. All these studies were experimental studies using supplements.

Antioxidant supplementation

Lung function and airway reactivity

Early studies used experimental protocols with single pollutants and a small number of healthy adults. Levels of O_3 and NO_2 were very high (usually close to 1,000 $\mu g \cdot m^{-3}$ and >3,000 $\mu g \cdot m^{-3}$, respectively) and subjects were supplemented for a relatively short period of time with high doses of vitamin C or vitamin E (eight to 16 times the USA recommended daily allowance of vitamin C (60 $mg \cdot day^{-1}$) and vitamin E (8 $mg \cdot day^{-1}$)) [2, 87–89]. A modulating effect of antioxidant supplementation was observed in some studies of acute lung function changes [89] and airway reactivity [87] but not in others.

More recent experimental studies have addressed conditions in which the O_3 level and supplement doses were lower. In a study of asthmatic adults, a cocktail of vitamin C (500 mg) and vitamin E (400 UI) protected against a decrease in peak expiratory flow from SO_2 challenge after O_3 exposure [90]. In another study [91], subjects were first deprived of vitamin C and then supplemented with a relatively low dose of vitamin C (250 mg), vitamin E (100 mg) and vegetable cocktail. Supplementation protected against acute change in lung function (forced expiratory volume in one second and forced vital capacity) after O_3 challenge. However, in well nourished individuals sensible to O_3, supplementation with vitamin C (500 mg) and vitamin E (100 mg) provide no protective effect on inflammatory response or lung function decrease after O_3 challenge. This lack of protection was observed despite elevated plasma vitamin C (+60.1%) and vitamin E (+51.4%) concentrations following supplementation, and increased vitamin C concentrations in the airways after supplementation following O_3 exposure [92].

Supplementation studies conducted in free-living populations of healthy exercising adults (the Netherlands) or adults exposed to high levels of air pollutants (Mexico) support the hypothesis that antioxidant supplementation protects against the acute effects of O_3 on lung function. In these studies, healthy adults were randomised to receive vitamin C (650 mg), vitamin E (75 mg) and β-carotene (15 mg) for several weeks [80, 93–95]. More recently, a study of asthmatic children exposed to high levels of air pollutants in Mexico City also suggested that supplementation with vitamin C (250 $mg \cdot day^{-1}$) and vitamin E (50 $mg \cdot day^{-1}$) had a modulating effect on acute lung function changes [96]. The positive effect of antioxidant supplementation was mostly found in children genetically susceptible to the effects of oxidants (glutathione *S*-transferases (GST)M1 null genotypes) [97].

Inflammatory response

Only three studies have evaluated the impact of antioxidant supplementation on airway inflammatory response to air pollutant exposure. SAMET *et al.* [91] observed no difference in the bronchoalveolar lavage content of polynuclear cells and other inflammatory markers between supplement and placebo groups after O_3 challenge. Similarly, Mudway *et al.* [92] reported no effect of supplementation with vitamin C and vitamin E on O_3-induced neutrophilia in healthy individuals responsive to O_3. In contrast, asthmatic children heavily exposed to air pollutants and supplemented with vitamin C and vitamin E had significantly lower levels of IL-6 and IL-8 in nasal lavage than children receiving placebo [98].

n-3 PUFA supplementation

Lung function and inflammatory response

The impact of n-3 PUFA supplementation on asthmatic symptoms and exercise-induced bronchoconstriction has been examined among asthmatic subjects in various recently reviewed studies [12, 34, 99]. Most of these studies enrolled a small number of asthmatic patients randomly assigned to receive a high dose of n-3 PUFA (3–4 g of EPA) for a short time-period (6–10 weeks); results were inconsistent. Studies with longer intervention periods, from 6 months to 1 yr, also led to inconsistent results with some studies showing improvement in lung function [100, 101] or inflammatory markers [101–103], or no effect [104]. The dosage and duration of n-3 PUFA supplementation, and the type of asthmatic patients differed between studies and may explain the discrepancy between these studies [12, 34]. The Cochrane database of systematic reviews identified 22 studies but included only nine that fulfilled the inclusion criteria and concluded that data were insufficient to determine the effect of n-3 PUFA in asthma. None of these studies include information on air pollution.

Cardiovascular effect

Increased intake of n-3 PUFA either from dietary sources or as a pharmacological supplementation has been shown to decrease the risk of mortality from coronary heart disease [105]. In a randomised trial conducted in nursing home residents, supplementation with 2 $g \cdot day^{-1}$ of fish oil (each 1 g capsule contained 83.2 % of omega-3 fatty acids) significantly decreased the effect of $PM_{2.5}$ on time and frequency domain parameters of HRV [106] This is one of two studies providing evidence that oxidant stress is one of the mechanisms explaining the effect of particle air pollution on the cardiovascular system [107]. The other study reported that statins had a mitigating effect on the HRV effects of particulate air pollution in subjects genetically susceptible to oxidative stress (lacking the GSTM1 allele) [108].

Modifiers of an individual's response to oxidative stress

Under the biological model of oxidative stress one would expect factors that modify the response to oxidative stress to also alter the effects of air pollution. Thus, nutritional status, chronic diseases and genetic factors are candidates to determine susceptibility to oxidative stress-related effects of air pollution [26] as all these conditions are related to poor antioxidant defence.

Nutritional status

Antioxidant vitamin supplementation provides some protection against the adverse effect of O_3 on lung function in asthmatic children with slight deficiencies in these nutrients [96], and to adults depleted in vitamin C [91]. In contrast, vitamin supplementation did not protect against O_3-induced lung function decrement in well nourished subjects [109].

Chronic diseases

Most chronic diseases are associated with chronic inflammation [13, 27, 28, 110–112], which might increase susceptibility to the additional oxidative stress caused by air pollution exposure. In particular, subjects with asthma [29], chronic obstructive lung diseases [113], diabetes [114] and cardiovascular diseases [115] have all been shown to have antioxidant deficiency [13] and be more susceptible to the effects of air pollution [108, 115]. As observed in the case of cigarette smoke, a significant source of oxidative stress, air pollutants would lower antioxidant defences, with deleterious health consequences [116, 117]. Evidence of the potential beneficial effect of antioxidants can be found in studies of elderly subjects in which treatment with statins [108] and n-3 PUFA supplementation [106] had a beneficial effect on response to particulate exposure.

Genetic susceptibility

As oxidative stress is an important pathway activated/involved in the adverse effects of air pollution, the genes involved are of primary interest. Most studies have focused on single gene polymorphisms; however, it is likely that there will be a hierarchy of genes determining susceptibility, rather than one individual gene driving this process [15].

GST enzymes: GSTM1, GSTP1

GST are phase II xenobiotic metabolising enzymes that participate in the detoxification of ROS by catalysing their conjugation with glutathione [118, 119]. The common null allele of *GSTM1* results in a complete lack of the enzyme and reduced or no conjugation activity [120]. It has been associated with an increase in asthma and wheezing among children exposed to environmental tobacco smoke *in utero*, with a decrease in lung function growth [121, 122], and also with a rapid decline in lung function in smokers [123]. In addition, polymorphic *GSTM1* has been shown to act as a modifier of the lung response to fire smoke [124] and O_3 [125]. Antioxidant supplementation with vitamin C and E appears to modulate the effect of O_3 in asthmatic children homozygous for the *GSTM1* null allele [97]. Allergen sensitive subjects with low responsive genotypes show enhanced susceptibility to the adjuvant effects of DEP [126]. A *GSTM1* polymorphism has also been shown to increase sensitivity to PM, as evidenced by greater changes in HRV [108]. Moreover, glutaryl coenzyme A inhibitors, *i.e.* statins, with known antioxidant and anti-inflammatory properties mitigate against the effects of ambient particles on HRV in subjects lacking the *GSTM1* allele [107, 108].

Other genes

The Toll-like receptor 4 (*TLR4*; xr 4) gene has been implicated in innate immunity and endotoxin susceptibility [127] and has been hypothesised to play a role in O_3-induced hyperpermeability [26]. TNF-α (Xr17) has been related to lung function changes after O_3 exposure [128] and to an increased risk of asthma and wheezing that can be modified by O_3 exposure [129]. TNF has been identified as a candidate gene for O_3-induced airway inflammation and hyperresponsiveness [130]. Polymorphisms in TNF and lipoteichoic acid have been associated with respiratory effects of O_3 in humans [128]. *Arginase II* has been associated with an increased risk of asthma in children, and the association appeared stronger among children with a smoking parent [131] suggesting that air pollutants could also play a role.

Gene–gene interactions

O_3-induced acute effects on respiratory function have been shown to be smaller in subjects with *GSTM1* null and *NOQ1* Pro/Pro genotypes [132]. Similarly, a study examining asthma risk in a population highly exposed to O_3 showed that the risk of asthma was significantly associated with the *NOQ1* genotype in subjects with the null genotype for *GSTM1* [133]. Both genes have a specific function in antioxidative activities.

FURTHER EPIDEMIOLOGICAL RESEARCH

There is now substantial evidence that air pollution exposure results in increased oxidative stress, alterations in immune regulation and repeated inflammatory responses that overcome lung defences to disrupt the normal regulatory and repair processes [10, 15]. As summarised previously, despite a plausible mechanistic model linking air pollution, oxidative stress and dietary supplementation, evidence is not sufficient. Further randomised controlled trials (RCTs) are needed in order to better understand the potential protective effect of nutrient supplementation on the effect of air pollution on respiratory and cardiovascular functions and inflammatory responses.

RCTs provide a good alternative to maximise contrast in nutrient intake for evaluating the interaction of dietary factors and air pollutants and should be conducted in both the controlled setting and in free-living populations. A controlled setting will allow assignment of air pollutant exposure and, therefore, provide an accurate representation of the health effects and potential modulating effects of supplementation, while RCT conducted in free-living populations will have the advantage of representing real-life conditions.

Susceptible subjects, such as those with pre-existing respiratory or cardiac disease, micronutrient deficiency or genetic susceptibility, are the most likely to benefit from nutritional intervention (see Modifier of response section); therefore, RCTs should focus on these population subgroups. Short- and long-term effects can be studied; however, the major challenge in long-term effect studies is to assess the appropriate time-frame of exposure for the induction of the disease and, therefore, the relevant period and duration of the supplementation. There is accumulating evidence that exposure during lung development in foetal life and early childhood plays a major role, as in the case of maternal smoking [134–136]. Therefore, RCTs of pregnant females with specific risks (such as asthmatic or

TABLE 1 Biomarkers of oxidative stress most commonly used in clinical and epidemiological studies

Type of measurement	Biomarker	Biological sample	Laboratory technique	Sensitivity and specificity	Comments	[Ref.]
TAC	TRAP TRAP + R-PE	Plasma Serum	Fluorescence	Good Possible artefactual confounding	Measures the cumulative action of all antioxidants present in plasma and body fluids TRAP: indirect measure TRAP+R-PE: direct measure of peroxyl radical attack on R-PE. Affected by protein concentration Plasma better than serum	[140–142]
Lipid peroxidation	TBARS	Tissue Plasma Serum	Spectrophotometry Colourimetry Fluorometry	Low specificity	Easy to use Indirect measure	[143, 144]
	MDA-TBA derivatisation	Plasma Serum EBC Urine	TBARS HPLC/MS HPLC-UV/Vis HPLC with fluorescence detection	Low specificity Good	Measures MDA, end product of lipoperoxidation. MDA is generated mainly by arachidonic acid and docosahexaenoic acid With HPLC detection, MDA is not a specific product of lipid peroxidation	[143–145]
	Free MDA	Plasma Serum	HPLC HPCE	Good Good	Low amount of plasma needed Fast and practical for clinical measurements Low detection limit	[145, 146]
	4-hydroxynonenal 4-hydroxy	Tissue Blood Urine	ELISA GC/MS	Good	HNE is a toxic product of lipid peroxidation and second toxic messenger of free radicals	[147, 148]
	Hydrocarbons: ethane and pentane	EBC	GC	Penthane: low specificity Ethane: good	Hydrocarbons are produced through peroxidation of fatty acids in cellular biomembranes, by ROS Ethane: faster chromatographic measurement compared with other hydrocarbons; better marker for lipid peroxidation Background level of pentane and isoprene in human breath difficult to separate pentane from isoprene by chromatography Possible contamination with ambient air ethane and pentane	[149–152]
	Conjugated dienes	Plasma Serum	Spectrophotometry HPLC	Validity still questionable	Other biological substances, even polyunsaturated fatty acids, absorb in the same UV region CD generation continues *ex vivo* after sampling Plasma CD is >90% derived from 9, 11 diene-conjugated linoleic acid from dietary dairy products	[150, 153]
	LDL oxidation	Plasma	*Ex vivo* LDL by CD assay with spectrophotometric determination	Good	Measures the rate of CD formation Cannot be known for certain whether the *in vitro* situation accurately reflects *in vivo* events Should reflect the antioxidant defence system. Vitamin E has shown reasonably consistent effects in increasing the resistance of LDL to oxidation	[143, 153–155]
		Plasma Serum	*In vivo* LDL-BDC with spectrophotometric determination	Good	Faster and simpler to perform than the *ex vivo* procedure Measures amount baseline diene conjugation	[156]
	Oxidised LDL	Plasma	ELISA	Poor	These modifications may occur independently of lipid peroxidation Still unclear whether it can serve as a peripheral marker High variability	[144, 152, 157]
	Lipid hydroperoxides: CEOOH	Plasma	HPLC assay with chemiluminescence detection	Not confirmed	Not detectable in young healthy controls Direct indicator of lipid peroxidation	[144, 158]

TABLE 1 Continued.

Type of measurement	Biomarker	Biological sample	Laboratory technique	Sensitivity and specificity	Comments	[Ref.]
Eicosanoids	F2-isoprostane	Plasma Serum Urine EBC	HPLC GC/MS ELISA	Good	These markers reflect respiratory tract integrity between reactive nitrogen species and ROS Interaction with other prostanoids Potent biological activity 8-iso-$PGF_{2\alpha}$ is a major component of total F_2 isoprostanes In plasma, possibility of artefactual generation due to arachidonic acid autoxidation Better in urine - less interaction	[143, 144, 152, 159, 160]
	PGE_2	EBC Plasma Sputum	HPLC/MS/MS ELISA GC/MS	 Good	Not flow dependent in healthy subjects	[159–162]
	LTB_4	EBC Plasma Serum Urine Sputum BAL	GC/MS HPLC ELISA	Good	LTB_4 is a potent neutrophil chemoattractant and may contribute to airway narrowing by producing local oedema and increasing mucus secretion	[159–161]
Nitrogen reactive species	Nitrite: NO_2^- Nitrate: NO_3^-	EBC Plasma	Colourimetry Fluorometry Ionic chromatography GC/MS HPLC	Good	In healthy children, nitrite values are not related to levels of exhaled NO Both nitrite and nitrate quantification	[159, 163–166]
	S-nitrosothiols 3-nitrotyrosine	Plasma BAL	Fluorometry GC/MS	Good	Formed by glutathione peroxidise; a selenium-dependent enzyme	[159, 167–169]
DNA oxidation	8-OHdG	Urine DNA	ELISA CG/MS HPLC/ECD	Poor	May be influenced by the metabolic rate and also by excision repair GC/MS: level of 8-OHdG overestimated ELISA values higher than HPLC values	[143, 170–173]
	8-oxoGua	DNA	CG-MS HPLC-ECD HPLC-MS Comet assay ELISA	Good	HPLC-ECD generally yields lower values Enzymatic approach: FPG may detect lesions other than 8-oxo-7, 8-dihydroguanine; the method relies on indirect calibration Reported strong correlation between overnight and 24 h urinary 8-oxodGuo#	[174, 175]
	8-oxodGuo	24 h urine	CG-MS HPLC-ECD HPLC-MS Comet assay ELISA	Good	HPLC-ECD generally yields lower values Enzymatic approach: FPG may detect lesions other than 8-oxo-7, 8-dihydroguanine; the method relies on indirect calibration Reported strong correlation between overnight and 24 h urinary 8-oxodGuo#	[174, 175]
	Modified comet assay	DNA	SCGE	Good	Measures DNA strand breaks Proportion of DNA in the tail indicates the frequency of breaks Particularly sensitive to oxidative attack by H_2O_2	[143, 176]
	HmdU	Plasma Serum	ELISA	Good	Autoantibody to oxidised DNA Product of thymine oxidation	[143, 177, 178]
Protein oxidation	Protein carbonyl	Plasma Lung aspirate	Colourimetric method ELISA HPLC	Good	Measures generic oxidation; does not differentiate between those protein carbonyl arising directly from protein oxidation and those formed by adduction of other oxidised products	[143, 153, 179]

TABLE 1 Continued.

Type of measurement	Biomarker	Biological sample	Laboratory technique	Sensitivity and specificity	Comments	[Ref.]
Other	GSH	Sputum Plasma Saliva BAL EBC	Spectrophotometry Reverse phase HPLC HPLC /with fluorescence detection	Good Good Good	GSH is a protective antioxidant against oxidative stress Level of GSH depends on biological sample	[159, 180–184]
	GSH/GSSG ratio	Plasma Serum	Colourimetry HPLC NL	Good	Decrease in GSH/GSSG indicates chronic oxidative stress	[153, 185]
	H_2O_2	EBC	Spectrophotometry Fluorometry Chemiluminescence	Poor: high variation	Concentration appears to be expiratory flow rate dependent Wide variability in mean exhaled H_2O_2 concentration in healthy nonsmoking adults Other factors: exercise, food, beverage intake	[159, 186–188]
	CC16	Serum BALF	Latex immunoassay ELISA	Good	These tests evaluate the integrity of respiratory tract Peripheral marker CC16 protects the respiratory tract against oxidative stress and inflammation	[189–192]
	Thioredoxin	Serum	ELISA	Good	Thioredoxin is induced by oxidative stress and secreted by cells	[193–195]

TAC: total antioxidant capacity; TRAP: total radical trapping antioxidant parameter; R-PE: R-phycoerythrin; TBARS: thiobarbituric acid-reactive substances; MDA-TBA: malondialdehyde-thiobarbituric acid; HPLC: high performance liquid chromatography; MS: mass spectometry; EBC: exhaled breath condensate; UV/Vis: UV/visible detection; HPCE: high performance capillary electrophoresis; HNE: 4-hydroxynonenal; GC/MS: gas chromatography/MS tandem; ROS: reactive oxygen species; CD: conjugated dienes; LDL: low-density lipoprotein; BDC: baseline diene conjugation; CEOOH: cholesteryl ester hydroperoxides; PG: prostaglandin; LTB_4: leukotriene B_4; BAL: bronchoalveolar lavage; NO: nitric oxide; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; ECD: electrochemical detection; 8-oxoGua: 8-oxo-7,8-dihydroguanine; FPG: fasting plasma glucose; SCGE: single cell microgel electrophoresis; 8-oxodGuo: 8-oxo-7,8-dihydro-2′-deoxyguanosine; HmdU: 5-hydroxymethyl-2′-deoxyuridine; GSH: reduced glutathione; GSSG: oxidised glutathione (disulfide form); NL: nasal lavage; BALF: BAL fluid(s). $^{\#}$: $r=0.93$, $p<0.01$.

atopic mothers) might provide some insight into the role of antioxidants and n-3 PUFA as modulators of the air pollution effect. In these studies, a major challenge is the accurate assessment of air pollution exposure, oxidative stress, biomarkers of nutritional status and health outcomes. Standardisation of these factors within and between studies is crucial to allow comparability of results. In the following section some issues to be considered in future studies will be discussed.

Air pollution exposure

Contrasts in exposure need to be maximised to be able to distinguish between effects in the placebo group and smaller or no effects in the supplemented groups. Depending on the study design and hypotheses tested, either temporal or spatial contrast should be large. Multicentre studies including areas with contrasting air pollution levels and the enrolment of random samples of participants within each centre might be an option. Moreover, the design of the exposure assessment must take into account the relationship between measured or measurable markers of oxidant pollution and personal exposure to the pollutant relevant to the hypothesis. For example, there are often large indoor/outdoor ratios in O_3 concentrations and these can be very heterogeneous across homes. Personal O_3 concentration may be very poorly correlated with ambient levels in certain areas. It might be useful to measure the redox activity of ambient pollutants or the antioxidant depletion rates, as these may be the most relevant characteristics in the hypothesised pathways of redox imbalance. Various assays have been developed to measure the redox activity of particles, such as OH radical formation or antioxidant depletion rates [137]. However, the measurement methods may need further development to be applicable in epidemiological studies, in particular, for personal exposure assessment.

Biomarkers of oxidative stress

The advantage of using biomarkers is that they integrate both the effects of oxidant exposure and the full range of antioxidant protective mechanisms *in vivo* [30]. However, samples can be oxidised during handling, processing and analysis, so there is potential for artefacts in estimates of baseline levels of oxidation markers. The magnitude of this problem varies between biomarkers [31, 138]. Most of these biomarkers include measures of lipid, DNA and protein oxidation. Recent review articles provide broad coverage of this topic [30, 139]. Table 1 presents a summary of oxidative stress biomarkers useful for clinical and epidemiological studies including: the type of marker; the biological media for measurement; the laboratory techniques most frequently used; an appreciation of its

TABLE 2 Biomarkers of nutrient intake most commonly used in clinical and epidemiological studies

Type of measurement	Biological sample	Laboratory technique	Comments	Characteristics and sources	[Ref.]
Carotenoids	Serum	HPLC	Poor bioavailability in raw food, improved by mild cooking or heating (*e.g.* lycopene in tomato juice)	Liposoluble	[143, 196–198]
β-Carotene	Plasma		Reflect short-term intake	Red, orange and yellow fruits and vegetables (sweet potato, carrots, winter squash)	
α-Carotene	Induced sputum		Need to control for cholesterol level	Green vegetables	
Lycopene	Adipose tissue		Adipose tissue reflects long-term exposure		
Lutein			May not reflect concentration in target tissue		
Xanthine					
β-Cryptoxanthin					
Tocopherols	Serum	HPLC	Serum and plasma reflect short-term intake	Liposoluble	
α-Tocopherol	Plasma		Need to control for cholesterol level	Vegetable and seed oils (corn, safflower, soy)	[143, 199]
γ-Tocopherol	Adipose tissue		Adipose tissue reflects long-term exposure	Beans, eggs, green vegetables	
Vitamin C	Serum	HPLC	Vitamin C in food can be destroyed by exposure to high temperature, oxidation or cooking in large amount of water	Hydrosoluble	
	Plasma		Response to intake up to 50–90 mg·day^{-1}, then eliminated by renal clearance	Fruits: papaya, canteloupe, citrus fruits, strawberries	[143, 200]
			Reflects short-term intake	Vegetables: cauliflower, broccoli, brussel sprouts, kale, sweet peppers	
			Predicts intake at low level of vitamin intake		
Selenium	Plasma	Atomic absorption spectrophotometry	At higher levels of intake, the correlation between plasma selenium concentration and dietary intake depends on the chemical form of selenium in the diet	Cereals and grains	[143, 201–204]
	Toenail	HPLC	Selenium content of cereals and grains depends on the soil content	Animal products, especially organ meats and seafood	
			Plasma reflects short-term intake		
			Nail and whole blood reflect long-term exposure (>26–56 weeks)		
Flavonoids	Serum	HPLC	Measures the usual dietary intake over 1 week	Apples, lemons, oranges	[205, 206]
	Urine			Potatoes, cauliflower	
				Tea	
				Skin of tubers and roots	
				Red wine	
Isoflavonoids	Serum	GC/MS	Sex differences in metabolism and excretion	Legumes: soybeans, beans, lentils, chickpeas.	[207–209]
	Urine	HPLC			

TABLE 2 Continued.

Type of measurement	Biological sample	Laboratory technique	Comments	Characteristics and sources	[Ref.]
Lignans	Serum	HPLC	Sex differences in metabolism and excretion	Oil seeds (flax seed, soybean, rapeseed)	[207–209]
	-24–72 h urine			Whole-grain cereals (wheat, oats, rye), legumes, vegetables; fruits	
PUFA	Free fatty acids in serum or plasma	HPLC	Samples are temperature and oxygen sensitive	Fish oils	[210–212]
n-3 PUFA		GC/MS	Potential for oxidation and degeneration over time	Fish and shellfish	
n-6 PUFA	Components of circulating triglycerides	GLC	Free fatty acids, phospholipids and cholesterol esters represent the intake over the last few days or meals	Soy and canola oil	
	Phospholipids		Serum fatty acids appear to be sensitive to changes in diet; high fluctuation (10–12%) and lab error <5%		
	Cholesterol esters		Components of triglycerides represent intake over the past few hours		
	Red blood cell membranes		RBC reflect longer term intake (half-life of RBC: 120 days)		
	EBC		RBC sample: collected whole blood is suspended in phosphate buffer and centrifuged; packed red cells are stored at -80°C		
	Adipose tissue		RBC: may contain lower levels of n-3 and n-6 PUFA		
			Adipose tissue reflects long-term intake if no severe weight loss has occurred		
Folate	Serum	ELISA	Serum: short-term folate	Leafy vegetables	[213, 214]
	RBC		RBC: dietary intake over last 120 days	Dry beans and peas, fortified cereal	
				Some fruits	
Zinc	Plasma	Atomic absorption spectrometry	Plasma: most frequently used	Oysters	[202, 215–218]
	Cells		Possibility of no association between zinc intake and plasma zinc	Animal proteins	
	Erythrocyte, monocyte, neutrophil, platelet		Cells: complex sample preparation	Beans	
			Poor sensitivity, imperfect specificity	Nuts	
	Hair			Pumpkin and sunflower seeds	
	Nails				
	Urine				

HPLC: high performance liquid chromatography; GC: gas chromatography; MS: mass spectrometry; PUFA: polyunsaturated fatty acids; GLC: gas liquid chromatography; EBC: exhaled breath condensate; RBC: red blood cells.

sensitivity and specificity based on the literature review; and some additional comments [140–195].

Biomarkers of exposure to antioxidant nutrients and n-3PUFA

These biochemical indicators have the advantage of integrating different food sources and providing a better estimation of the internal dose, *i.e.* a closer indication of the amount of nutrient available after absorption and metabolism [33]. They can also be used in intervention studies to monitor compliance with the supplement. However, they are subject to measurement errors and sampling, storage, handling and laboratory analysis and temporality issues need to be carefully considered [30]. Table 2 presents a summary of biomarkers of antioxidant and n-3 PUFA intake used in clinical and epidemiological studies including: the type of marker; the biological media for measurements; the laboratory techniques most frequently used; the characteristics and food sources of these nutrient biomarkers; and some additional comments [196–218].

Health end-points

The limited validity of symptoms of respiratory or cardiac diseases has been extensively discussed [219, 220]. Objective outcomes, such as lung function, nitric oxide in exhaled breath, carotid intimae-media thickness, electrocardiographic abnormalities or HRV, are less prone to bias and may be a good alternative but their long-term predictive value is uncertain. Biological indicators, such as pro-inflammatory markers (*e.g.* IL-6, IL-4, TNF-α, IFN-γ) in sera, exhaled breath and nasal lavage, and peripheral inflammatory markers (*e.g.* cell counts, fibrinogen, C-reactive protein, von-Willebrand factor, prostaglandin E2, plasminogen activator inhibitor, cell adhesion molecules) might provide useful information about potential mechanisms of air pollutant exposure. However, they are subject to large within-person variability and limited specificity as they are common to different end-points; therefore, serial measurements over the study period are required. In addition, intra-individual variability and the temporal frame need to be considered for any of the transient end-points. A mechanistic approach that includes evaluation of several end-points at the clinical and biological levels seems most appropriate. Further understanding of the crucial role of transcription factors, DNA methylation and RNA control of gene expression will provide new perspectives on the complex interaction of air pollutants and nutritional factors.

CONCLUSION

Oxidative stress is one of the main mechanisms by which air pollutants affect respiratory and cardiovascular health. Short-term randomised supplementation trials suggest that antioxidant vitamins and n-3 polyunsaturated fatty acids might protect against the acute effect of these pollutants, particularly in vulnerable subgroups [80, 96, 106]. However, the evidence is still limited because of the small sample size in most studies and the lack of comprehensive assessment of baseline nutritional status and oxidative stress response. Future studies should include randomised control trials of antioxidant or n-3 polyunsaturated fatty acid supplementation in susceptible populations and measure clinical, as well as intermediate, outcomes and biomarkers of oxidative stress and nutrient intake considering factors, such as reproducibility, inter- *versus* intra-person variability, detection limits and specificity and sensitivity of these markers. Doses and duration are still under debate but harmonisation between studies is desirable for comparison purposes.

ACKNOWLEDGEMENTS

The authors would like to thank G. Evans for reviewing the English of the manuscript.

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Toxicologic Pathology, 36:289-310, 2008

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623307313011

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

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Abstract

Air pollution is a serious environmental problem. We investigated whether residency in cities with high air pollution is associated with neuroinflammation/neurodegeneration in healthy children and young adults who died suddenly. We measured mRNA cyclooxygenase-2, interleukin-1β, and CD14 in target brain regions from low (n = 12) or highly exposed residents (n = 35) aged 25.1 ± 1.5 years. Upregulation of cyclooxygenase-2, interleukin-1β, and CD14 in olfactory bulb, frontal cortex, substantia nigrae and vagus nerves; disruption of the blood-brain barrier; endothelial activation, oxidative stress, and inflammatory cell trafficking were seen in highly exposed subjects. Amyloid β42 (Aβ42) immunoreactivity was observed in 58.8% of apolipoprotein E (APOE) 3/3 < 25 y, and 100% of the APOE 4 subjects, whereas α-synuclein was seen in 23.5% of < 25 y subjects. Particulate material (PM) was seen in olfactory bulb neurons, and PM < 100 nm were observed in intraluminal erythrocytes from lung, frontal, and trigeminal ganglia capillaries.

Exposure to air pollution causes neuroinflammation, an altered brain innate immune response, and accumulation of Aβ42 and α-synuclein starting in childhood. Exposure to air pollution should be considered a risk factor for Alzheimer's and Parkinson's diseases, and carriers of the APOE 4 allele could have a higher risk of developing Alzheimer's disease if they reside in a polluted environment.

Keywords: α-synuclein; Alzheimer's disease; air pollution; amyloid β42; neuroinflammation; Parkinson's disease; ultrafine particulate matter.

Introduction

Air pollution is a complex and dynamic mixture of gases, particulate matter (PM), and organic compounds present in outdoor and indoor air. Exposure to air pollution is associated with respiratory, cardiovascular, and stroke-related sickness and death (Banauch et al. 2006; Brunekreef and Holgate 2002). Children living in Mexico City (MC) exhibit evidence of chronic inflammation of the upper and lower respiratory tracts, alterations in circulating inflammatory mediators, and breakdown of the nasal epithelial barrier (Calderón-Garcidueñas et al. 2001; Calderón-Garcidueñas, Franco-Lira et al. 2007; Calderón-Garcidueñas, Mora-Tiscareño et al. 2003). These children also have heart rhythm alterations and decreased vagal responses associated with sustained high plasma endothelin-1, a potent vasoconstrictor peptide involved in the homeostatic regulation of vascular smooth muscle tone, and upregulated after exposure to air pollutants including PM (Thomson et al. 2004, 2005; Calderón-Garcidueñas et al. 2006; Calderón-Garcidueñas, Vincent et al. 2007). Dogs exposed to the polluted environment in MC exhibit chronic respiratory tract inflammation; early expression of neuronal nuclear NFκB and endothelial/glial inducible nitric oxide synthase; disruption of the nasal and olfactory barriers and the blood-brain barrier (BBB); accumulation of amyloid β42 (Aβ42) in neurons; and increased olfactory bulb (OB) and hippocampal apurinic/apyrimidinic sites, indicators of oxidative DNA damage (Calderón-Garcidueñas et al. 2001, 2002; Calderón-Garcidueñas, Maronpot et al. 2003).

Breakdown of the nasal respiratory and olfactory epithelium and the BBB facilitates the access of systemic inflammatory mediators and components of air pollution to the central nervous system (CNS) (Calderón-Garcidueñas et al. 2004). Chronic inflammatory processes in the CNS play an important role in the progressive neuronal death seen in neurodegenerative diseases such as Alzheimer's (Akiyama et al. 2000; McGeer et al., 2006; Selkoe 2001, 2002). A coherent pathway linking exposure to air pollution and brain damage includes a chronic inflammatory process involving the respiratory tract, which results in a systemic inflammatory response with the production of inflammatory mediators capable of reaching the brain; continuous expression of crucial inflammatory mediators in the CNS at low levels; and the formation of reactive oxygen species (ROS) (Calderón-Garcidueñas et al. 2002, 2004; Calderón-Garcidueñas, Maronpot et al. 2003; Calderón-Garcidueñas, Mora-Tiscareño et al. 2003). Ultrafine PM (UFPM), particulate-matter–associated lipopolysaccharides (PM-LPS), and metal uptake could take place through olfactory neurons, cranial nerves such as the trigeminal and vagus, the systemic circulation, and macrophage-like cells loaded with PM from the lungs (Calderón-Garcidueñas et al. 2001, 2002, 2004; Calderón-Garcidueñas, Maronpot et al. 2003; Calderón-Garcidueñas, Mora-Tiscareño et al. 2003). Activation of the brain innate immune responses could follow the interaction between circulating cytokines and constitutively expressed cytokine receptors located in endothelial brain capillary cells, followed by activation of cells involved in adaptive immunity (Nguyen et al. 2002; Simard and Rivest 2006). Monocytes are the main innate immune response mediator cells, producing and secreting TNFα, IL-6, and interleukin-1β (IL-1β), which in turn recruit and increase the activity of other immune cells (Simard and Rivest 2006). In the sustained upper and lower respiratory tract chronic inflammatory process elicited on exposure to significant concentrations of air pollutants in megacities such as MC, particularly fine and ultrafine PM could serve as the crucial trigger for a chain of events leading to endothelial activation, disruption of the BBB, altered response of the innate immune system, neuroinflammation, and neurodegeneration. We previously reported that adult residents of highly polluted urban areas, average age 54.7 ± 4.8 years, exhibit significantly higher expression of cyclooxygenase-2 (COX2)—a powerful inflammatory gene—in brain target areas when compared with matched age/gender/educational level subjects from cities with low pollution levels (Calderón-Garcidueñas et al. 2004). Highly exposed subjects also exhibited a significant neuronal and astrocytic accumulation of the 42 amino acid-isoform (Aβ42) of β amyloid, which is more hydrophobic and prone to aggregation than other Aβ isoforms (Selkoe 2001, 2002). Given that pollutant levels in MC vary within a relatively narrow range throughout the year, its residents are exposed all year long to a significant burden of air pollutants. The pollution levels have been sustained or have worsened in the past twenty years (Bravo-Alvarez and Torres-Jardón 2002), so the exposure of today's children and teenagers is truly life long, as it began in utero. Moreover, there is a relatively low mobility of MC residents, so individuals tend to be exposed to the same environment for long periods, thus allowing for the opportunity to study chronic health effects associated with prolonged sustained exposure to severe air pollution.

The primary purpose of the present work was to measure by real-time polymerase chain reaction two key inflammatory genes, COX2 and IL-1β, and the LPS receptor CD14; this selection was based on the increasing evidence that neuroinflammatory processes contribute to the cascade of events that lead to neurodegeneration. These markers of neuroinflammation were measured in target brain areas including the OB, frontal cortex, hippocampus, substantia nigrae, periaqueductal gray, and vagus nerves in a cohort of cognitively intact Mexican children, adolescents, and young adults who died suddenly and were residents from low- or high-polluted urban areas in Mexico. Given that inflammatory responses involve the microvasculature and the trafficking of inflammatory cells, we also explore the integrity of the tight junctions in the brain capillaries, the nature of the inflammatory responsive cells, and the expression of endothelial inflammatory markers. We assessed zonula occludens-1 (ZO-1), a scaffolding protein marking tight and adherens junctions. Immune cells were identified immunohistochemically using antibodies to CD68, surface HLA-DR antigens, and CD163 (a macrophage scavenger receptor that identifies brain perivascular macrophages). Leukocyte adhesion molecules investigated included vascular adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). Since we have seen the transfer of UFPM from alveolar type I cells to the alveolar epithelial basement membrane, to endothelial cells, and finally to macrophage-like cells in the lumen of exposed MC dog lung capillaries

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This work was supported in part by the National Science Foundation 0346458, the Montana Board of Research and Commercialization Technology 04-06, 1KO1 NS046410-01A1, 1R21-ES013293-01, and 5 P20 RR015583 from the National Center for Research Resources (NCRR). Advice and support from Jerrold Abraham, MD, SUNY Upstate Medical University, are deeply appreciated. We appreciate the technical assistance of Sarah Ulatowski and Rodolfo Villarreal-Calderón. Lilian Calderón-Garcidueñas and William Reed contributed equally to this work.

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Abbreviations: Aβ42, beta amyloid; AD, Alzheimer's disease; APO E, apolipoprotein E; APP, amyloid precursor protein; BBB, blood-brain barrier; COX2, cyclooxygenase 2; GFAP, glial fibrillary acidic protein; HLA-DR, human leukocyte antigen-DR; IL-1β, interleukin-1β; ICAM-1, intercellular adhesion molecule-1; IHC, immunohistochemistry; LPS, lipopolysaccharide; MC, Mexico City; MTBE, methyl-ter-butyl ether; NFκB, transcription factor nuclear factor kappa-B; NSE, neuron specific enolase; O_3, ozone; OB, olfactory bulb; PD, Parkinson's disease; PM, particulate matter; PNS, peripheral nervous system; PT, prothrombin; RBC, red blood cells; SNC, substantia nigrae pars compacta; TLR, toll-like receptor; UFPM, ultrafine PM; VCAM-1, vascular adhesion molecule-1; ZO-1, zonula occludens-1.

(Calderón-Garcidueñas et al. 2001; Calderón-Garcidueñas, Franco-Lira et al. 2007), we did extensive electron microscopy in samples from the lungs and brains of both control and exposed MC subjects to look for PM. The accumulation of Aβ42 and α-synuclein was also investigated. The trigeminal ganglia were examined given the evidence by Lewis et al. of trigeminal uptake and clearance of inhaled manganese in rodents. In addition, the cohorts were genotyped for the APOE alleles and allelic frequencies of the Asp299Gly TLR4 polymorphism to determine if subjects had a known risk factor for Alzheimer's disease (i.e., APOE ε4 allele carriers) and if they were capable of responding to lipopolysaccharides (one of the major organic components in MC PM).

Methods

Study Cities and Air Quality Data

We selected a large, polluted megacity and two control cities. Mexico City (MC) was the selected megacity, and Tlaxcala and Veracruz were the low-polluted cities. Mexico City represents an extreme of urban growth and environmental pollution (Bravo-Alvarez and Torres-Jardón 2002). Mexico City is a megacity that covers an area of 2000 km^2 surrounded by a series of volcanic and discontinuous mountain ranges that limit the natural ventilation of the basin. The basin has more than 30,000 industrial facilities and 4 million vehicles, with an estimated annual emission of 2.6 million tons of particulate and gaseous air pollutants. The critical air pollutants are ozone (O_3), and PM. The climatic conditions in MC are relatively stable through the seasons, thus air pollutant concentrations are relatively consistent. Residents in MC have been chronically exposed to significant concentrations of O_3, PM, and LPS for the past 2 decades. The marked increase in O_3 concentrations initially started in the fall of 1986, coinciding with the introduction of a new gasoline with lower tetraethyl lead concentration and higher levels of short-chain aliphatic hydrocarbons and aromatic compounds (Bravo-Alvarez and Torres-Jardón 2002). The change in gasoline composition led to an increase in reactive hydrocarbon emissions and O_3 ambient concentrations. By the end of 1989, in an apparent move to further reduce atmospheric carbon monoxide and hydrocarbon emissions, methyl-ter-butyl ether (MTBE) was introduced as an additive in gasoline. However, the use of MTBE in the absence of catalytic converters on motor vehicles led to a further increase in reactive hydrocarbons (i.e., isobutene and formaldehyde). As a result, O_3 production chemistry changed, leading to an additional rise in ambient O_3 concentrations. Around the same time, MC authorities imposed a regulation banning residents from driving cars on specific days of the week. This measure significantly increased total driving in MC, because many people bought an additional car because of the inefficient public transportation. The resulting effect of the greater use of old cars not equipped with catalytic converters, overcrowded streets, and increased weekend driving was a serious boost in vehicular emissions, which, combined with the use of MTBE in gasoline, led to very high O_3 levels that peaked in 1991 (Bravo-Alvarez and Torres-Jardón 2002). Citizen concerns about air pollution and car market pressure to introduce new cars equipped with catalytic converters forced authorities to consider the distribution of reformulated gasoline free of tetraethyl lead. As a consequence, beginning with 1991 car models, catalytic converters were required in Mexico, although the turnover rate to new converter-equipped cars was slow because of the weak economic situation. A slight reduction in O_3 ambient levels started in 1992. Additional measures, such as the vehicle emission inspection program and more strict control of hydrocarbon emissions from gas stations, helped to reduce O_3 levels. However, the growth of the population and the number of cars in MC, the continuing usage of MTBE in reformulated gasoline, and the very high levels of volatile organic compounds have slowed and delayed the reduction of O_3 to acceptable levels. A serious problem in MC is the contribution of aromatic compounds to secondary organic aerosol formation through atmospheric transformation and the formation of oxidation products that are partially absorbed into organic films on pre-existing $PM_{2.5}$. Concentrations of $PM_{2.5}$ and PM_{10} in MC are above the current annual standards. Lipopolysaccharides (LPS) detected in PM_{10} samples show a range of 15.3 to 20.6 nanograms per milligram of PM_{10}, and PM samples from South Mexico City show the highest endotoxin concentrations at 59 EU/mg PM_{10} (Bonner et al. 1998). Mexico City has significant sources of environmental endotoxins, including open-field waste areas, waste disposal dust, waste water treatment plants, open sewer channels, and daily outdoor deposits of 500 metric tons of animal and human fecal material.

Control Cities: The control cities included Tlaxcala and Veracruz. Because of the combination of the relatively few contributing emission sources from industry and cars and the good ventilation conditions by the regional wind, criteria pollutants (O_3, PM_{10}, SO_2, NO_2, CO, and Pb) levels in control cities are below the current US standards. Three additional factors for the selection of the control cities included: (1) altitude above sea level similar to Mexico City (i.e., Tlaxcala); (2) dog necropsies from these cities have shown minimal pathology in lungs and hearts (Calderón-Garcidueñas et al. 2001); and (3) clinical studies in children in these cities have shown healthy children with no evidence of air-pollution–associated pathology (Calderón-Garcidueñas et al. 2003).

Autopsy Selection: The study protocol was approved by the Institutional Review Boards for Human Studies at the institutions involved. We studied 47 subjects from 2 cohorts of clinically healthy, cognitively and neurologically intact children and adults, ages two to forty-five years, with an average age of 25.1 ± 1.5 y. The control cohort included subjects from low-polluted cities (n = 12) and the exposed cohort (n = 35) from MC. The forty-seven subjects had complete autopsies and neuropathological examinations and were included in the immunohistochemistry (IHC) and the real-time polymerase chain reaction (RT-PCR) studies. Data available for all subjects included age, gender, place of birth, place of residency, occupation, smoking habits, clinical histories, cause of death, and time between death and autopsy. Cause of death was considered for all subjects to rule out the possibility that infection, inflammatory events, drug exposure, brain ischemia, and hypoxia might impact the mRNA levels of the inflammatory markers measured in the study. Therefore, the selected cohorts had no clinical history or pathological evidence of short- or long-term inflammatory processes, administration of drugs, anti-inflammatory medications, hormones, or events such as cerebral ischemia or epilepsy.

Necropsy and Tissue Preparation: Autopsies were performed 3.9 ± 1.1 hours after death. The postmortem period was similar for controls and pollution-exposed subjects. The skull was opened, and the OBs, trigeminal ganglia, and brain were removed. The right and left vagus nerves were exposed and dissected at the neck level, and a 10-cm section was cut along the OBs and selected areas from alternating right and left cerebral hemispheres, then quickly frozen and kept at -80°C. Frozen tissues for the RT-PCR were taken from the cortex and the white matter, taking care to make a perpendicular cut to the brain surface and keeping similar amounts of cortex and white matter for each method. In the midbrain section taken at the level of the superior colliculi, we dissected the substantia nigrae and the central grey stratum around the cerebral aqueduct. The right side was selected for the RT-PCR studies, and the left side was fixed in formaldehyde. Brain sections adjacent to the frozen material were immersed in 10% neutral formaldehyde, fixed for 48 hours, and transferred to 70% alcohol. Sections were taken from the OB, superior frontal gyrus, anteriomedial temporal lobe, hippocampus, basal ganglia, midbrain at the level of the superior colliculi, pons, medulla, neocerebellum, and trigeminal ganglia. Sections from lungs (upper-right lobe), peribronchial lymph nodes, heart (left and right ventricles), kidney, and liver were also taken. Paraffin sections 8 μm thick were cut and routinely stained with hematoxylin and eosin (H & E).

Immunohistochemistry (IHC) was performed on sections from the OB, frontal lobe, hippocampus, midbrain, pons, trigeminal ganglia, heart, and lungs. The sections were deparaffinized and immunostained as described previously (Calderón-Garcidueñas et al. 2004). Negative controls included omission or substitution of primary antibodies by nonspecific, isotype-matched antibodies. Positive and negative controls were included for each antibody. In double IHC, detection of β amyloid$_{1–42}$ was followed by GFAP staining, and CD163 was combined with glucose transporter type 1 (Glut-1). The brain histopathologic parameters evaluated included: vascular changes; the presence of histological elements characteristic of neuronal, glial necrosis, or apoptosis; and the distribution and characteristics of astrocytes. Sections were read blindly by one neuropathologist and one general pathologist with no access to the codes regarding the subjects' data. Electron microscopy was performed in frontal, trigeminal ganglia, and lungs of control and MC samples. Samples were fixed in 2% paraformaldehyde, 2% glutaraldehyde in sodium phosphate buffer (0.1M, pH 7.4), post-fixed in 1% osmium tetraoxide, and embedded in Epon. Semithin sections (0.5–1 μm) were cut and then stained with toluidine blue for light microscopy examination. Ultrathin sections (60–90 nm) were cut and collected on slot grids previously covered with formvar membrane. Sections were stained with uranyl acetate and lead citrate and examined with a Carl Zeiss EM109T (Germany) or a JEM-1011 (Japan). For immunofluorescence staining, prior to staining, 10- to 20-μm paraffin-embedded tissue sections were dewaxed, rehydrated, and pretreated by incubation with warm (37°C) trypsin 0.1% in phosphate-buffered saline (PBS) with $CaCl_2$ (PBS-$CaCl_2$) for ten minutes. Sections were then washed in PBS and incubated with the primary antibodies overnight at 4°C. After washing, incubation with secondary antibodies was done for four hours at room temperature. Primary antibodies were diluted as follows in PBS with 0.5% BSA: rabbit anti-Glut-1, mouse CD163, VCAM-1, and ZO-1. Secondary antibody included goat antirabbit cyanine 5 and goat anti mouse Alexa fluor 488 and 568 at 1:100 (InVitrogen). Sections were mounted in PBS/glycerol (2:1) containing 170 mg/mL Mowiol 4–88 (Calbiochem, VWR International). For the confocal microscopy using the ZO-1 antibodies, we prepared smears of frontal fresh brain of seventeen cases, six controls, and eleven MC (APOE 3/3 and 4) subjects, fixed them in cold acetone for ten minutes, and air-dried the slides. Vessel diameters and tight juntion (TJ) abnormalities were assessed by two independent observers, and vessels were scored as normal or abnormal on the basis of the ZO-1 staining of their TJs. Selected areas with blood vessels were examined, and an average of one hundred vessels were visualized for the integrity of the ZO-1 staining. Fluorescence was examined using a BioRad Radiance 2000 laser scanning confocal on an inverted Nikon TE 300 microscope. Images were processed and visualized with LaserSharp software (version 2000, BioRad Microscience, Hertfordshire, UK).

Estimation of mRNA abundance was by real-time RT-PCR. Total RNA was extracted from frozen tissues including lungs, OB, frontal cortex, hippocampus, substantia nigrae, periaqueductal grey, and vagus nerves, using Trizol Reagent (Invitrogen Corp, Carlsbad, CA) according to the manufacturer's instructions. Random-primed first-strand cDNAs were generated as described (Calderón-Garcidueñas et al. 2004). Relative abundances of mRNAs encoding COX2, IL-1β, and CD14 were estimated by quantitative fluorogenic 5' nuclease (TaqMan) assay of the first-strand cDNAs as described (Calderón-Garcidueñas et al. 2004). Primers and fluorophore-labeled TaqMan probes targeting human COX2, IL-1β, and CD14 were designed using Primer Designer software (Scientific and Educational Software, Durham, NC) based on sequence information in GenBank.

For Asp299Gly and APOE genotyping, Asp299Gly genotype was determined using an allelic discrimination assay protocol according to Applied Biosystems (ABI). The aspartic-acid-to-glycine change at residue 299 results from the substitution of an adenosine to glycine at nucleotide 896 from the start codon of the TLR4 cDNA.The portion of the TLR4 gene containing the polymorphism was amplified using the PCR on the ABI Prism 7700 instrument. For the APOE genotyping, DNA was isolated from the frontal cortex as described and genotyped for the HhaI restriction site polymorphism in the APOE gene.

Statistics: Statistics were performed using Stata statistical software (College Station, TX). We applied the parametric procedure that considers the differences among variances of the variables of interest—COX2, IL-1β, and CD14 mRNA abundance in controls and exposed subjects. Significance was assumed at $p < .05$. Data are expressed as mean values ± SD.

Results

Air Quality Data

Residents in Mexico City have been chronically exposed to significant concentrations of O_3 and PM for the past two decades (Figure 1). The climatic conditions in Mexico City are relatively stable, thus pollutants concentrations are consistent year after year. Figure 1A illustrates the long-term trend (1986–2006) of the number of exceedances per year of the eight-hour O_3 air quality standard (0.085 ppm over any eight-hour period, not to be exceeded in three years) average concentrations as well as their 90th and 50th percentiles for eight-hour averages determined for the whole Mexico City Metropolitan Area (MCMA). The higher eight-hour average O_3 concentrations coincide with the times children and teens are outdoors during the school recess and physical education periods as well as when they play outdoors at home (Villarreal-Calderón et al. 2002). Figure 1B shows the trends of the number of days above the PM_{10} (10 μm or less in aerodynamic diameter) twenty-four-hour average air quality standard (150 μg/m^3, not be exceeded more than once per year), the maximum of the daily PM_{10} average concentrations, and the 50th percentile for 24-hour PM_{10} concentration data registered in the whole MCMA from 1990 to 2006. Because of the existing high correlation between secondary organic aerosols and photochemical processes, PM_{10} concentrations in Mexico City also tend to peak during the midafternoon hours, coinciding with children's activities (Villarreal-Calderón et al. 2002). Figure 1C illustrates $PM_{2.5}$ (2.5 μm or less in aerodynamic diameter) twenty-four-hour and annual concentrations for five different regions in MC for the years 2003–2006. Residents of MC are exposed to concentrations of $PM_{2.5}$ above the standards year after year. The air pollutant data from MC were obtained from the MC Ambient Air Monitoring Network.

Study Population

The primary cause of death was accidents resulting in immediate death. The average age for the study cohorts of twelve controls and thirty-five highly exposed subjects was 26.4 ± 3.7 and 24.6 ± 1.6 years, respectively ($p = .66$) (Tables 1 and 2). The cohorts included thirteen children aged two to seventeen

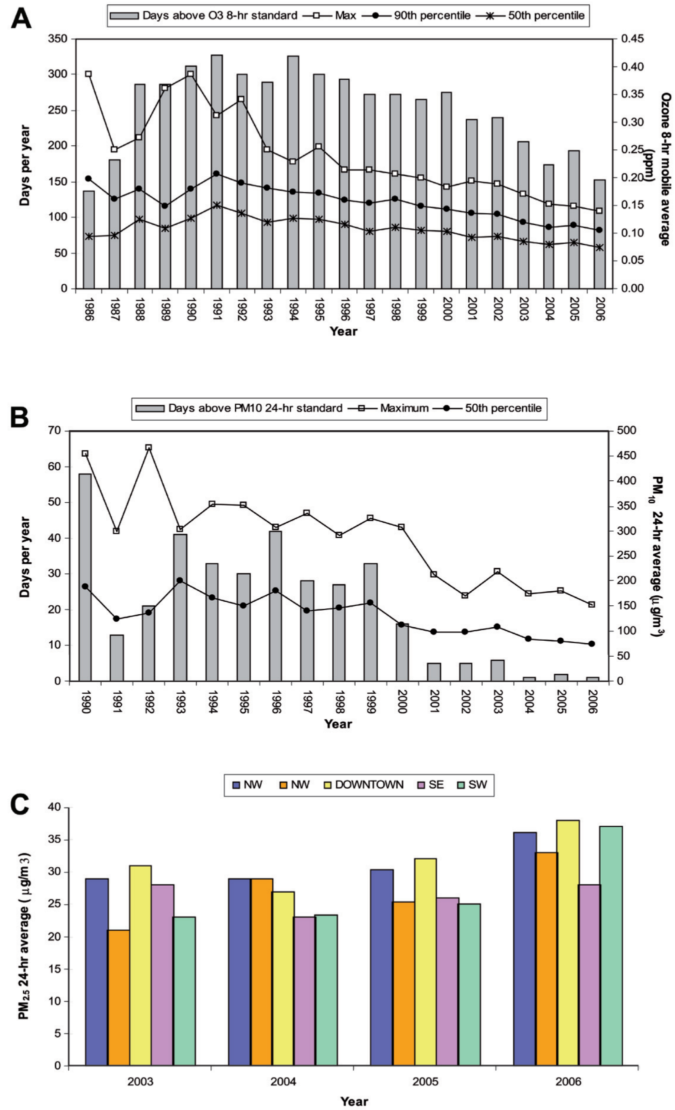

FIGURE 1.—A. Ozone eight-hour mobile average concentrations for Mexico City (MC) for the years 1986–2006. We illustrate the variations in the yearly number of days above the O_3 eight-hour mobile average air quality standard (0.08 ppm), the maximum, and the 90th and the 50th percentiles registered in all the O_3 monitoring sites in MC.
B. PM_{10} exceedences above the twenty-four-hour air quality standard (150 μg/m^3) for MC for the years 1990–2006 and the variations in maximum and 50th percentiles of the whole PM_{10} daily average levels registered in all the MC PM_{10} monitoring sites during the same period.
C. $PM_{2.5}$ twenty-four-hour and annual average concentrations for five different regions in MC for the years 2003–2006. All five regions including downtown, NW, NE, SW, and SE have annual average concentrations of $PM_{2.5}$ above the respective annual standard (15 μg/m^3). (All graphs constructed with data available from the Mexico City Ambient Air Monitoring Network, http://www.sma.df.gob.mx/simat)

TABLE 1.—Results of APOE and TLR4 genotyping, Aβ 42 and α-synuclein immunoreactivity by immunohistochemistry, disruption of the BBB as shown by abnormal ZO-1 tight junctions, and trafficking of inflammatory cells expressing CD163, CD68, and HLA-DR in Controls and Mexico City residents younger than 25 years.

Genotype APOE TLR4	Age/gender	Residency	Aβ42 immunoreactivity (OB, frontal, hippocampus)	α-synuclein immunoreactivity (OB, brain stem)	Disruption of the BBB (abnormal ZO-1)	Trafficking inflammatory cells (CD163, CD68, HLA-DR)
APOE 3/3 TLR4 +	2y M	MC	—	—	yes	yes
APOE 3/3 TLR4 +	2y F	Control	—	—	no	no
APOE 3/3 TLR4 +	7y M	MC	—	—	no	no
APOE 3/3 TLR4 +	11y M	MC	OB, frontal	OB	yes	yes
APOE 3/3 TLR4 +	14y M	MC	OB, frontal	—	yes	yes
APOE 3/3 TLR4 +	15y M	MC	OB	—	yes	yes
APOE 3/3 TLR4 +	16y M	MC	frontal	—	yes	yes
APOE 3/3 TLR4 +	17y M	Control	—	—	no	no
APOE 3/3 TLR4 +	17y M	Control	—	—	no	no
APOE 3/3 TLR4 +	17y M	MC	frontal	OB spinal lemniscus	yes	yes
APOE 3/3 TLR4 +	17y M	MC	OB, frontal diffuse plaques	SNC	yes	yes
APOE 3/3 TLR4 +	17y M	Control	—	—	no	no
APOE 3/3 TLR4 +	19y M	MC	—	—	yes	no
APOE 3/3 TLR4 +	20y M	MC	—	OB	yes	yes
APOE 3/3 TLR4 +	20y M	MC	—	—	yes	yes
APOE 3/3 TLR4 +	21y F	Control	—	—	no	no
APOE 3/3 TLR4 -	22y F	MC	—	—	yes	yes
APOE 3/3 TLR4 -	22y F	MC	frontal	—	yes	yes
APOE 3/3 TLR4 +	22y F	MC	OB, frontal	—	yes	yes
APOE 3/3 TLR4 +	24y F	Control	—	—	no	no
APOE 3/3 TLR4 +	24y M	MC	OB, frontal, hippocampus	—	yes	yes
APOE 3/3 TLR4 +	24y M	MC	frontal	—	yes	yes
APOE 3/3 TLR4 +	24y M	MC	—	—	yes	yes

Abbreviations: Aβ42, beta amyloid; APOE, apolipoprotein E; BBB, blood-brain barrier; HLA-DR, human leukocyte antigen-DR; MC, Mexico City; OB, olfactory bulb; SNC, substantia nigrae pars compacta; TLR, toll-like receptor; ZO-1, zonula occludens-1.

years (n = 4 in the control and n = 9 in the MC group), average age 13.2 ± 3.7 and 12.6 ± 1.7 respectively (p = .33), and within both cohorts there were twenty-three subjects younger than twenty-five years (Table 1). The occupations in both cohorts included elementary, middle, and high school as well as college students and blue- and white-collar workers. Based on the careful evaluation of the medical information available and the results of the autopsy, each subject was considered to be clinically healthy and cognitively and neurologically intact prior to his or her demise.

Real-time PCR mRNA Analysis of COX2, IL-1β, and CD14

Real-time, rapid-cycle PCR analysis of COX2, IL-1β, and CD14 in lungs, OB, frontal cortex, hippocampus, substantia nigrae, periaqueductal gray, and vagus nerves from 47 subjects indicated that the corresponding mRNA was present in each of the samples analyzed (Table 3). When samples were stratified according to the subject's residency (MC vs. low-polluted cities), there was a significant difference in mRNA for COX2 in lung (p = 0.01), OB (p = .0002), frontal cortex (p = .008), substantia nigrae (p = .03), left vagus (p = .03), and right vagus (p = .0002), whereas it was not significant for hippocampus (p = .1) and periaqueductal gray (p = .1) (Table 3). When MC subjects were graphed by age for OB mRNA COX2 values, there were five subjects (APOE ε 3/3) identified with the highest mRNA COX2 values; these subjects ranged in age between seven and thirty-four years, and four of them were teenagers. Three of these teens already exhibited Aβ42 in their OBs, and one of them also exhibited α-synuclein. The youngest child with the high OB COX2 value did not have Aβ42 or α-synuclein in his OBs. Age graphs for the substantia nigrae pars compacta SNC/COX2 dataset showed a cluster of four subjects with the highest mRNA COX2 values ranging in age from two to forty-five years; three of these subjects, including an eleven-year-old boy, had α-synuclein in OB and/or neurons in brain stem nuclei. When frontal mRNA COX2 samples were graphed by age, the higher values were seen in subjects in the third decade and older. The higher values of lung COX2 were seen in eight MC subjects aged two to forty-five years; these subjects, with the exception of a two-year-old boy, exhibited significant deposition of PM in interstitial spaces, alveolar macrophages, and subpleural regions. For the vagus nerves, the subjects with the higher COX2 values for the left were different—except for one twenty-year-old male APOE ε 3/4 subject—from the subjects with the higher COX2 right vagus values, and two of the higher COX2 vagus subjects also had the higher IL-1β values. The subject with the higher COX2 values for the left vagus, a thirty-four-year-old male APOE ε 3/3, exhibited α-synuclein in the dorsal nucleus of the vagus and in neuronal groups in the pons and medulla. For IL-1β, the frontal cortex (p = .0002) and

TABLE 2.—Results of APOE and TLR4 genotyping, Aβ42 and α-synuclein immunoreactivity by immunohistochemistry, disruption of the BBB as shown by abnormal ZO-1 tight junctions, and trafficking of inflammatory cells expressing CD163, CD68, and HLA-DR in Controls and Mexico City residents older than 25 years.

Genotype (APOE TLR4)	Age/gender	Residency	Aβ42 immunoreactivity (OB, frontal, hippocampus)	α-synuclein immunoreactivity (OB, brain stem)	Disruption of the BBB (abnormal ZO-1)	Trafficking inflammatory cells (CD163, CD68, HLA-DR)
APOE 3/3 TLR4 +	27y M	Control	—	—	+	—
APOE 3/3 TLR4 +	27y M	Control	—	—	—	—
APOE 3/3 TLR4 +	28y M	MC	Frontal, hippocampus	—	+	+
APOE 3/3 TLR4 +	29y M	MC	—	—	+	+
APOE 3/3 TLR4 +	30y M	MC	—	—	+	+
APOE 3/3 TLR4 +	31y M	MC	Frontal diffuse plaques	—	+	+
APOE 3/3 TLR4 +	34y M	MC	frontal	Dorsal nucleus vagus, locus ceruleus, medulla	+	+
APOE 3/3 TLR4 +	35y M	MC	—	Brain stem nuclei	+	+
APOE 3/3 TLR4 +	37y M	MC	frontal	—	+	+
APOE 3/3 TLR4 +	38y M	MC	—	—	+	+
APOE 3/3 TLR4 +	40y M	Control	—	—	+	—
APOE 3/3 TLR4 +	45y M	MC	Frontal, hippocampus	midbrain	+	+
APOE 3/3 TLR4 +	45y M	MC	—	—	+	+

Abbreviations: Aβ42, beta amyloid; APOE, apolipoprotein E; BBB, blood-brain barrier; HLA-DR, human leukocyte antigen-DR; MC, Mexico City; OB, olfactory bulb; TLR, toll-like receptor; ZO-1, zonula occludens-1.

TABLE 3.—RT-PCR sample results from Control vs MC lung, CNS, and PNS tissues, and their statistical significance.

Anatomical region and gene	Controls	Mexico City residents	Statistical significance
COX2 lung[a]	$15.9 \pm 6.7 \times 10^6$	$42.3 \pm 7.4 \times 10^6$	.015
IL-1β lung[a]	$3.08 \pm 1.87 \times 10^6$	$4.51 \pm 2.6 \times 10^6$	.60
COX2 OB[a]	$12.9 \pm 3.0 \times 10^5$	$38.7 \pm 5.5 \times 10^5$	.0002
IL-1β OB[a]	$3.4 \pm 0.8 \times 10^4$	$7.7 \pm 1.0 \times 10^4$	.003
CD14 OB[b]	0.01 ± 0.001	0.04 ± 0.01	.04
COX2 frontal[a]	$2.6 \pm 0.4 \times 10^5$	$5.0 \pm 0.7 \times 10^5$	.008
IL-1β frontal[a]	$0.6 \pm 0.2 \times 10^4$	$6.2 \pm 1.3 \times 10^4$	.0002
COX2 hippocampus[a]	$1.9 \pm 0.5 \times 10^5$	$1.6 \pm 8.7 \times 10^5$	.1
IL-1β hippocampus[a]	$1.8 \pm 0.2 \times 10^4$	$3.0 \pm 0.5 \times 10^4$	.06
COX2 substantia nigrae[a]	0.16 ± 0.06	0.97 ± 0.2	.03
IL-1β substantia nigrae[b]	0.01 ± 0.005	0.09 ± 0.03	.06
CD14 substantia nigrae[b]	0.02 ± 0.005	0.03 ± 0.007	.7
COX2 periaqueductal gray[b]	0.10 ± 0.03	0.45 ± 0.12	.12
IL-1β periaqueductal gray[b]	0.009 ± 0.003	0.07 ± 0.02	.09
COX2 left vagus[b]	0.65 ± 0.18	2.68 ± 0.82	.03
COX2 right vagus[b]	0.43 ± 0.09	3.68 ± 0.8	.0002
IL1β left vagus[b]	0.1 ± 0.03	1.3 ± 0.73	.06
IL1β right vagus[b]	0.15 ± 0.09	0.87 ± 0.53	.66
CD14 left vagus[b]	0.07 ± 0.01	0.79 ± 0.41	.01
CD14 right vagus [b]	0.05 ± 0.01	0.31 ± 0.1	.02

Abbreviations: CNS, central nervous system; MC, Mexico City; OB, olfactory bulb; PNS, peripheral nervous system; RT-PCR, real-time polymerase chain reaction.

The amount of COX2, IL-1β and CD14 cDNA in each sample was normalized to the amount of GAPDH cDNA, yielding an index (molecules per femtomol[a] or molecules/uEq[b] GAPDH rRNA) proportional to the relative abundance of each mRNA in each sample.

the OB ($p = .003$) were significantly higher in MC subjects vs. controls, whereas it was not significant for lung, hippocampus, substantia nigrae, periaqueductal gray, and vagus nerves. The higher IL-1β mRNA values for both OB and frontal cortex corresponded to teens and young adults. Significant upregulation of CD14 was present in the OB ($p = .04$), and the right ($p = .02$) and left ($p = .01$) vagus in MC subjects. The left vagus had the highest CD14 values across all subjects.

Clinical and Gross Pathological Observations

Non-CNS Findings: Tracheal epithelium showed patchy areas of squamous metaplasia and submucosal chronic inflammatory infiltrates in MC subjects over the age of twenty-five years. Nonperfused lungs from MC subjects displayed patchy clusters of alveolar macrophages filled with PM, bronchiolar smooth muscle cell hyperplasia, chronic mononuclear cell infiltrates,

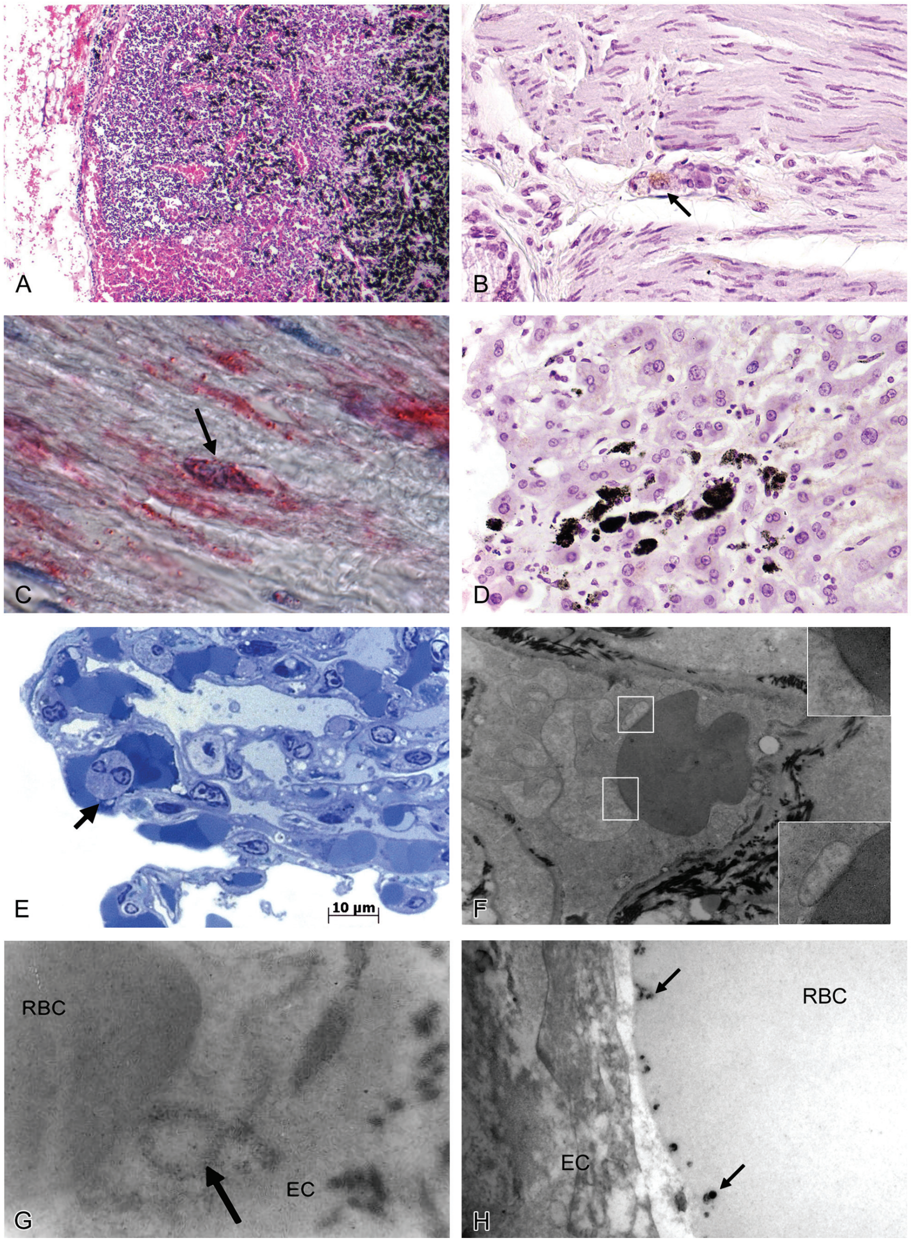

FIGURE 2.—A. Peribronchial lymph node in a seventeen-year-old male MC nonsmoker. There are numerous macrophages in the cortical zone loaded with black particulate matter. The afferent lymphatics also exhibit abundant PM-loaded macrophages.
B. Bronchial ganglion cells with positive α-synuclein granular punctuate cytoplasmic deposits (arrow) (brown product). (α-synuclein IHC)
C. Mexico City eleven-year-old boy APOE ε 3/3 exhibits granular punctuate deposits in the cytoplasm of Schwann cells in parenchymal lung nerves (arrow) (red product). (α-synuclein IHC)
D. Kupffer cells loaded with PM in the liver of a thirty-two-year-old MC resident. (Hematoxylin stain)
E. One-micron toluidine blue section of lung in a thirty-three-year-old male MC resident. PMNs are seen attached to endothelial cells (arrow) in lung capillaries, in keeping with endothelial activation and the significant decrease of circulating PMNs observed in young MC residents. (Toluidine blue 1-µm section)
F. Electron micrographs of lung capillaries in a twenty-four-year-old female MC resident. The endothelial cell lining of the lung capillary exhibits elongated fronds that surround a luminal erythrocyte. The endothelial fronds completely embrace the erythrocyte on the plane of the picture. The inserts display the close association between the cytoplasm of the endothelial cell and the erythrocyte, with aggregation of particulate material at the interphase. (EM x 12,000 inserts x 25,000)
G. Same lung capillary as Figure 2F, showing the relationship between the endothelial cell membrane-bound structure (arrow) with ultrafine PM and the erythrocyte (RBC) surface. (EM x 50,000)
H. An erythrocyte (RBC) in the lumen of a lung capillary exhibits numerous nanosized particulate material. EC is the endothelial cell. (EM x 50,000)

and macrophages filled with PM surrounding the bronchiolar walls and extending into adjacent vascular structures. In nine MC subjects there was extensive deposition of PM-laden macrophages in the subpleural regions along with mononuclear inflammatory infiltrates, smooth muscle cell hyperplasia of the pulmonary veins, and clusters of macrophages in the submucosa of the medium-sized bronchi. Peribronchial lymph nodes were grossly black in subjects over the age of twenty-five years and were loaded with PM (Figure 2A). Subjects from control cities exhibited small numbers of alveolar macrophages and rare foci of inflammatory cells in association with either terminal bronchioles or pulmonary blood vessels. Peribronchial lymph nodes showed small clusters of PM-containing macrophages. The higher lung values of mRNA COX2 were seen in eight of nine subjects, with the higher loads of PM in subpleural regions. Ganglion cells present in the bronchial walls, as well as Schwann cells in bronchial nerves, exhibit punctuate α-synuclein (Figures 2B and 2C). Nerve fibers in large bronchi also exhibit foci of mononuclear cells. Heart sections in MC residents showed clusters of perivascular partially degranulated mast cells, whereas nerve fibers on the epicardial surface exhibit positive α-synuclein punctuate pattern not seen in the control subjects. Liver sections from six MC residents showed PM in Kupffer cells (Figure 2D), and in macrophage-like cells in the portal spaces. These six subjects also had the most PM in their lungs. No liver abnormalities were seen in the control cohort.

Lung Electron Microscopy: One-micrometer–thick toluidine blue sections from MC teenagers and young adults showed neutrophils attached to alveolar capillary endothelial cells (Figure 2E). The alveolar walls exhibited collagen interstitial fibers, and the endothelial cells exhibited numerous fronds surrounding red blood cells (RBC) (Figure 2F). The RBC exhibited aggregation of particles along the cytoplasmic membrane and established discrete contacts with endothelial cell cytoplasmic vacuoles lined by particulate material (Figure 2G). Higher magnifications of RBC in lung capillaries revealed ultrafine PM (Figure 2H).

CNS Gross Findings: Gross brain examination was unremarkable in all subjects.

Brain Histopathology: For the olfactory nerve and bulb, four of the thirty-five MC subjects, including a fourteen-year-old boy, exhibited a significant amount of black PM in the cytoplasm of neuron-specific enolase (NSE)-positive cells at the glomerular region (Figure 3A). COX2 stained the cytoplasm of mitral and tufted neurons and olfactory ensheathing cells. Aβ42 was seen in ensheathing cells, astrocytes in the olfactory nerve, and in OB neurons in six of eighteen MC APOE ε 3/3 subjects younger than twenty-five years (Table 2), the youngest an eleven-year-old boy (Figure 3B). Corporae amylacea were numerous along the length of the olfactory nerves starting in the late teens. Reactive gliosis (GFAP-positive astrocytes) was present in all layers of the OB in all exposed subjects (including external and internal plexiform, mitral cell layers, and the olfactory glomeruli). Alpha-synuclein was present in the form of Lewy neurites, as well as granular punctuate cytoplasmic deposits in NSE-positive cells in the glomerular, mitral, and granular cell layers in four of eighteen MC subjects younger than twenty-five years old (Table 1, Figure 3C); the youngest was an eleven-year-old boy (Figure 3D). In the trigeminal ganglia and nerves, partially degranulated mast cells were seen in close proximity to the ganglion cells (Figure 3E). Perineurial blood vessels exhibited vacuolated endothelial cells and marginal WBCs.

Cortical Sections: As to vascular changes, teens exhibited significant amounts of lipofuscin in endothelial cortical capillaries cells. Perivascular hemosiderin-laden macrophages were seen around small venules and arterioles in both gray and white matter, the latter being foremost; these changes were already prominent in the eleven-year-old MC boy in this series. Intact RBCs inside macrophages were identified alongside the hemosiderin-laden macrophages (Figure 3F). In five MC subjects, cortical blood vessels exhibit platelet thrombi (Figure 3G). Exposed subjects exhibited positive prothrombin (PT) staining outside blood vessel walls, predominantly in the white matter (Figure 3 H). Perivascular macrophages as well as reactive astrocytes were positive for prothrombin in the proximity of blood vessels with PT outside the walls. No PT outside of blood vessels was seen in the controls. Clusters of mononuclear cells around blood vessels in the frontal and temporal cortex, subicular area, and the brain stem were a frequent finding in MC subjects regardless of age (Figure 4A). These mononuclear cells were positive for CD68, CD163, and HLA-DR. CD163-positive cells were present predominantly in perivascular locations in the cortex and to a lesser degree in the neuropil as activated positive microglia (Figure 4B). CD68 stained numerous white matter microglia-like cells in highly exposed individuals. Positive CD68 and HLA-DR cells were seen predominantly in the white matter (Figures 4C and 4D), and positive perivascular cells were seen in the cortex in MC subjects as young as two years of age. In MC subjects, numerous partially degranulated mast cells exhibit positive tryptase granules (Figure 4E), particulary in the white matter, whereas frontal neurons exhibited positive staining in their cytoplasm. In controls, however, only occasional tryptase positive perivascular cells were seen, and the neurons were negative. VCAM-1 strongly stained cortical endothelial cells in MC subjects (Figure 4F), whereas ICAM-1 was positive for astrocytes and microglia cells in both the cortex and the white matter. Nitrotyrosine (NT) positive cells were present in all exposed individuals. NT immunorectivity was present as diffuse cytoplasm neuronal staining in frontal neurons as well as inclusions in glial cells, including astrocytes and microglia. Abundant NT-positive, macrophage-like cells were seen in perivascular white matter locations (Figure 4G), as well in endothelial cells. Control subjects exhibited an occasional perivascular positive cell. NFκB was positive in the nuclei of endothelial cells in cortical capillaries (Figure 4H) and perivascular macrophages in MC residents. NFκB nuclear positivity was not seen in control subjects. iNOS-positive cells included astrocytes and neurons in cortical regions and the OB of MC residents. COX2 immunoreactivity was seen in neuronal cell bodies and dendrites, as well as endothelial cells

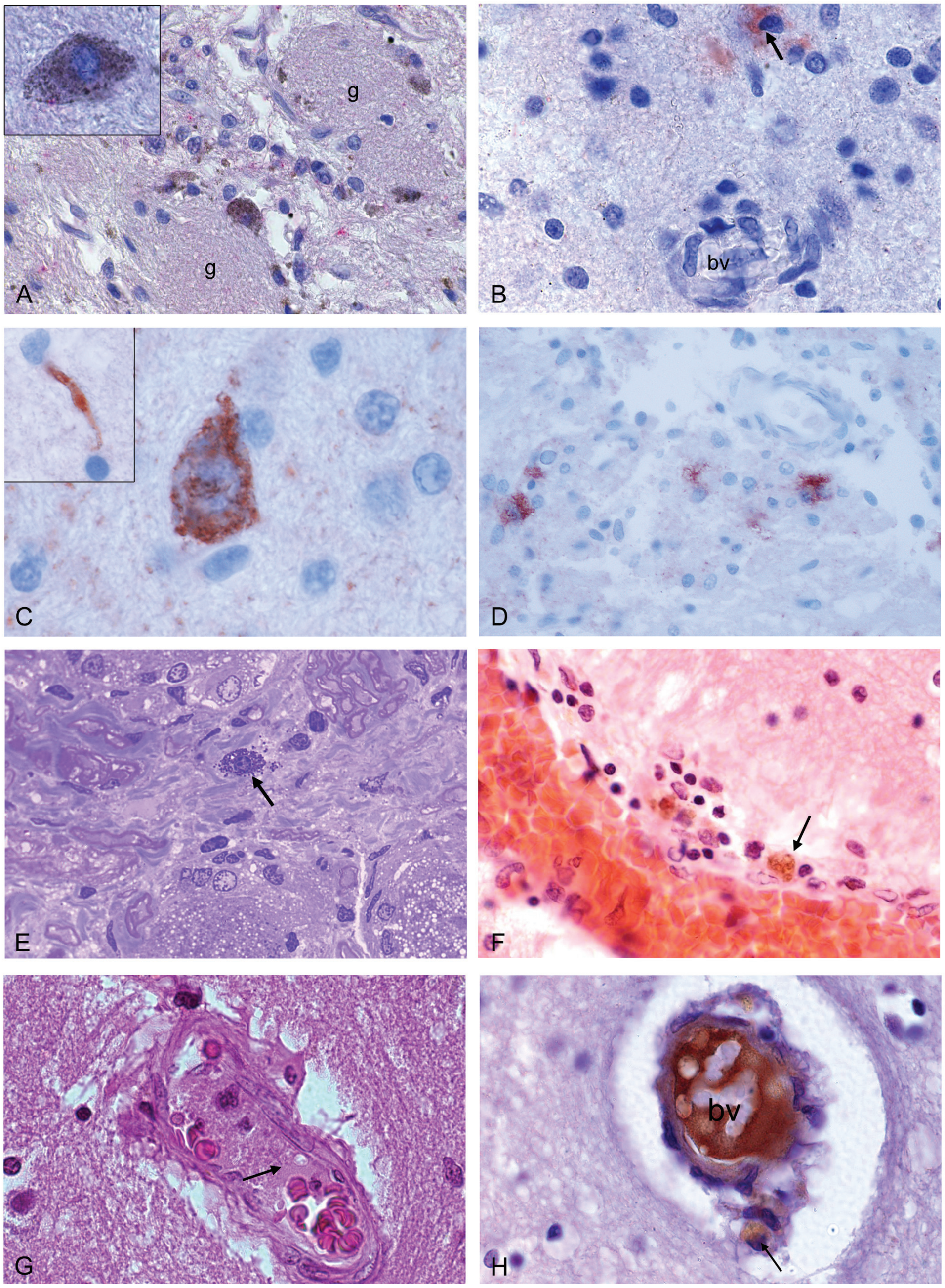

FIGURE 3.—A. Olfactory bulb (OB) neurons (enolase-positive) in the glomerular region (g) exhibit abundant particulate matter (PM) in their cytoplasm in a fourteen-year-old Mexico City (MC) boy. Upper-left insert: a close-up of one PM-loaded neuron with positive Aβ42 red product in its cytoplasm. (Aβ42 IHC counterstained with hematoxylin)

B. OB in an eleven-year-old MC boy APOE β 3/3 showing Aβ42 immunoreactivity in glial cells (arrow, red product). The blood vessel (bv) in the lower central area is free of amyloid. (Aβ42 IHC counterstained with H)

C. Olfactory bulb in a forty-two-year-old MC male, α-synuclein granular positive neurons are seen along Lewy neurites (insert).

D. OB in the same eleven-year-old boy as Figure 3B showing granular positive staining for α-synuclein in olfactory neurons (enolase-positive, not shown). (α-synuclein IHC)

E. One-micron toluidine blue section from a trigeminal ganglia in a twenty-year-old MC male. A partially degranulated mast cell (arrow) is seen in the perineural space. (Toluidine blue 1μm section)

F. Frontal white matter blood vessel in a thirty-two-year-old MC female. The blood vessel shows numerous hemosiderin-laden perivascular macrophages (arrow) and mononuclear cells. (H & E stain)

G. Frontal cortex vessel from a seventeen-year-old MC boy with platelet thrombi (arrow) partially obstructing its lumen. (H & E stain)

H. A frontal blood vessel from an eleven-year-old MC boy exhibits positive prothrombin reaction within the vessel lumen (bv) and in extravascular location, including positive perivascular macrophages (arrow). (PT IHC counterstained with H)

TABLE 4.—Results of APOE and TLR4 genotyping, Aβ42 and α-synuclein immunoreactivity by immunohistochemistry in Control and Mexico City subjects with the APOE 4 allele.

Genotype	Age	Gender	Residency	Aβ 42	α-synuclein
E4/E4 TLR4+	32	F	MC	Olfactory bulb, blood vessels, and cortical neurons	+ substantia nigrae, mesencephalic V
E3/E4 TLR4+	15	M	MC	Cortical neurons and diffuse plaques	—
E3/E4 TLR4-	20	M	MC	Olfactory bulb, blood vessels, and cortical neurons	—
E3/E4 TLR4+	22	M	MC	Cortical neurons and diffuse plaques	—
E3/E4 TLR4+	25	M	MC	Olfactory bulb and cortical neurons	+ olfactory bulb
E3/E4 TLR4+	32	M	MC	Cortical neurons	—
E3/E4 TLR4+	34	M	MC	Cortical neurons	—
E3/E4 TLR4+	36	M	MC	Olfactory bulb, cortical neurons, diffuse and mature plaques	—
E3/E4 TLR4+	36	F	Control	Plaques diffuse and mature	—
E3/E4 TLR4+	44	M	Control	—	—
E3/E4 TLR4+	45	M	Control	Olfactory bulb and cortical neurons	—

Abbreviations: APOE, apolipoprotein E; MC, Mexico City; RT-PCR, real-time polymerase chain reaction; TLR, toll-like receptor.

of small capillaries and arterioles in the frontal cortex. Exposed subjects exhibited strong endothelial COX2 staining in both cortex and white matter. In control subjects, the staining was confined to neurons. 8-0HdG positivity was present predominantly in pyramidal frontal cells and, to a lesser degree, in astrocytes in the white matter of MC subjects. Astrocytes with a small amount of cytoplasm were seen around blood vessels and neurons in the frontal cortex; a few of these astrocytes were positive for GFAP. Patchy cortical GFAP-positive astrocytes were prominent in MC children (present in the youngest, two years old) and teens. GFAP-positive astrocytes increased in the cortex with age. Reactive astrocytes were focally prominent in subpial areas and perivascular deep white matter of all exposed individuals. Immunoreactivity for Aβ42 was seen in the cytoplasm of neurons in the frontal and temporal cortices, in the smooth muscle cells of cortical vessels, and in both diffuse and mature senile plaques. In MC residents, Aβ42 selectively accumulated in the perikaryon of pyramidal frontal neurons as discrete granules and was present in cortical and white matter astrocytes and in subarachnoid and cortical blood vessels. Neuronal Aβ42 was identified in APOE ε 3/3 children as young as eleven years old, whereas diffuse plaques were first seen in seventeen-year-olds (Figure 5A). Mature Aβ42 plaques were abundant in subjects in the fourth decade (Figure 5B). In the cohort of APOE ε 3/3 MC subjects under twenty-five years of age, nine of seventeen exhibited Aβ42 positivity in the frontal cortex (Table 1). In sharp contrast, in the cohort of APOE ε 4 MC subjects (Table 4), the four youngest subjects (ages fifteen, twenty, twenty-two, and twenty-five) all exhibited Aβ42 in the OB, blood vessels, cortical neurons, and/or in diffuse plaques. There were three controls who were heterozygous for APOE 4 (ages thirty-six, forty-four, and forty-five), and two of these subjects had Aβ42 immunoreactivity. None of the forty-seven subjects fulfilled morphological Alzheimer's criteria as described in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Braak stages, and NIA-Reagan Institute criteria (Lilian Calderón-Garcidueñas, unpublished data).

Confocal Microscopy for Tight Junctional Abnormalities Zonula Occludens Ab (ZO-1). The majority of examined vessels were < 100 μm in diameter. In the control group APOE β 3/3 (n = 4, age = 16 ± 4.88 years), there were 3.8 ± 1.08% of vessels with abnormal ZO-1 TJs. Mexico City subjects APOE β 3/3 (n = 8, age 13.25 ± 2.36 years) exhibited 30.8 ± 5.9%, whereas APOE β 4/4 and 3/4 (n = 5, including 2 controls) had 62.2 ± 7.36% of the vessels with discontinuous or punctuate staining in the frontal cortex (Figure 5C). There was a significant difference in the number of abnormal tight junctions between APOE β 3/3 controls and MC subjects ($p = .01$) and vs APOE β 3/4 ($p = .0002$), whereas there was also a significant difference between MC APOE β 3/3 vs. 3/4 ($p = .007$).

Brainstem: vascular changes in the brainstem, including the midbrain, were similar to the ones described for the neocortex. Exposed subjects exhibit significant VCAM-1 staining of endothelial cells in capillaries and small venous and arteriolar vessels in the midbrain. CD163 and HLA-DR strongly stained mononuclear perivascular cells, whereas CD68 stained microglia-like cells in the substantia nigrae pars compacta (SNC) region, superior colliculus, red nucleus, tegmental tract, and medial lemniscus. A few tryptase-stained perivascular cells were seen in some of the exposed subjects. There was a significant degranulation of SNC in subjects in their twenties and early thirties. The degranulation was accompanied by numerous macrophages loaded with melanin pigment around the degranulated neurons and in perivascular locations. These changes were also seen in the Asp299Gly TLR4 polymorphism subjects. The MC woman APOE ε 4/4 exhibited α-synuclein positivity in substantia nigrae neurons and mesencephalic V neurons and displayed significant degranulation of SNC pigmented cells with

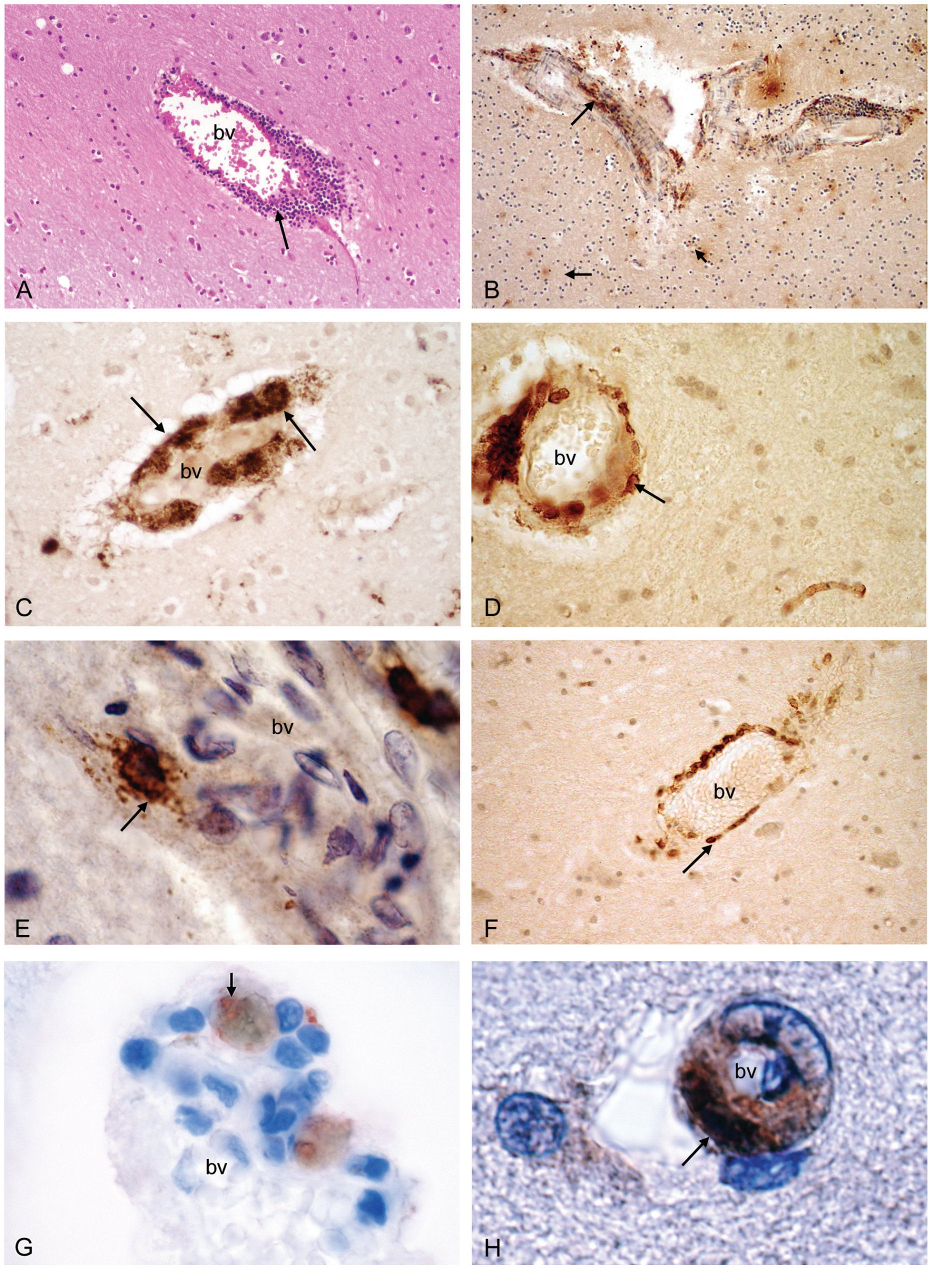

FIGURE 4.—A. Entorhinal area (Broadman 28) blood vessel (bv) with significant number of perivascular mononuclear cells (arrow) in a twenty-two-year-old female from Mexico City (MC). (H & E stain)

B. Frontal white matter from a fourteen-year-old MC male stained with anti-CD163 antibody shows CD163 immunoreactivity in perivascular cells (long arrow) and microglia-like cells scattered in the neuropil (short arrows) (DAB, brown product). (CD163 IHC)

C. Frontal white matter in a twenty-four-year-old MC male. There are several strongly CD 68 positive perivascular cells (arrows), as well as scattered positive microglia-like cells (DAB, brown product). (CD68 IHC)

D. Midbrain bv showing strongly positive staining for HLA-DR in perivascular cells (arrow) in a thirty-four-year-old MC male. (HLA-DR IHC)

E. Frontal cortex in a twenty-four-year-old MC male showing perivascular bv tryptase + partially degranulated mast cells (arrow) (DAB, brown product). (Tryptase IHC)

F. Midbrain bv in a twenty-five-year-old MC male showing strong expression of VCAM-1 in endothelial cells (arrow) (DAB, brown product). (VCAM-1 IHC)

G. Frontal cortex in a twenty-four-year-old MC male stained with anti-3 nitrotyrosine (NT) antibody. Positive macrophage-like cells (arrow) are positive in the perivascular spaces (Fast Red, red product). (NT IHC)

H. Frontal white matter capillary in a fifteen-year-old MC boy showing strong nuclear endothelial expression (arrow) for NFκB. An adjacent glial cell exhibits weak staining in the cytoplasm (DAB, brown product). (NFκB Aminoterminal domain p65 IHC)

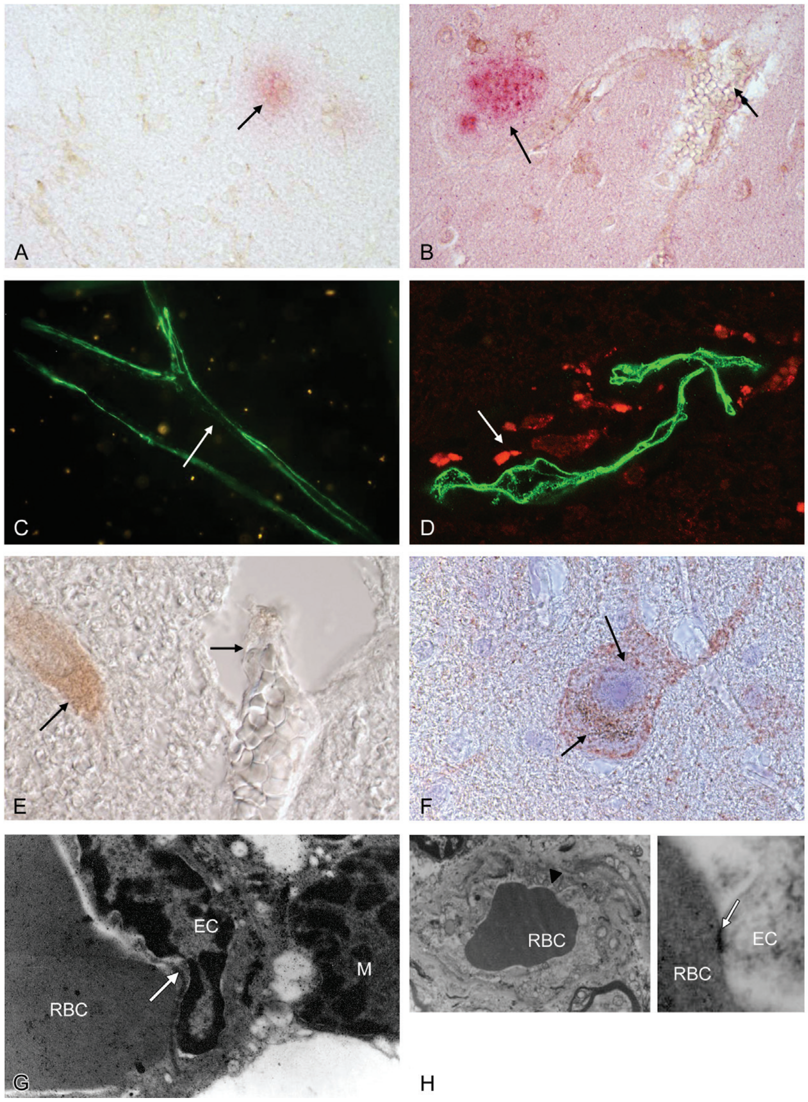

FIGURE 5.—A. Frontal cortex in an APOE β 3/3 seventeen-year-old Mexico City (MC) boy. A diffuse amyloid plaque is seen (arrow, red product). A stain for glial fibrillary acidic protein (GFAP) for reactive astrocytes is negative (brown product) (Fast Red, red product; and DAB, brown product). (Dual immunohistochemistry for Aβ42 and GFAP)
B. Frontal cortex in a thirty-six-year-old APOE 3/4 MC male with leaking blood vessels (short arrow) and mature Aβ42 plaques (long arrow, red product). Reactive astrocytes are numerous (cytoplasmic GFAP+) (brown product) (Fast Red, red product; and DAB, brown product). (Dual IHC for Aβ42 and GFAP)
C. Confocal micrograph of a frontal cortical blood vessel in an eleven-year-old stained with antibodies against Zonula occludens-1 (ZO-1). ZO-1 stains microvascular tight junctions (TJ). Vessels exhibit areas with discontinuous or punctate TJ staining (arrow).
D. Frontal white matter blood vessel in a twenty-year-old MC male, a dual staining for glucose transporter type 1 Glut1 (green product, endothelial cells), and CD163-positive perivascular macrophages (red product). (Dual staining for Glut 1 and CD163)
E. Seventeen-year-old MC boy midbrain section showing a gigantocellular reticular nucleus neuron (long arrow), strongly positive for 8-hydroxydeoxyguanosine adjacent to a leaky blood vessel with a weak positive endothelial cell (short arrow) (Fast Red, red product). (8-hydroxydeoxyguanosine IHC)
F. Substantia nigrae pars compacta pigmented neuron in an eleven-year-old MC boy showing a few neuromelanin granules (short arrow, black granules) and α-synuclein-positive granular stain (long arrow, red product) (Fast Red, red product). (α-synuclein IHC)
G. Frontal cortex capillary electron micrograph in a twenty-seven-year-old MC male. A RBC with ultrafine particles in its cytoplasm is seen forming discrete contact with the endothelial cell (EC) cytoplasm. Aggregation of intramembrane particles is seen at both the interphase between the RBC and the endothelial cell (arrow) and between the mononuclear cell (M) outside the blood-brain barrier (BBB) and the capillary. (EM X 12000)
H. Electron micrographs of a trigeminal ganglia capillary in a nineteen-year-old MC male shows the presence of discrete contact regions (arrow head) between the luminal RBC with ultrafine particles in its cytoplasm and the endothelial cell. The area of the contact region (arrow) between the RBC and the EC is shown on the right frame picture. (EM X 12000 and 30000)

numerous melanin-laden macrophages. In MC residents, NT and 8-0HdG positivity were present in raphe neurons, mesencephalic V neurons, and glial cells in the medial raphe (Figure 5E). 8-0HdG-positive neurons were also seen in the trigeminal thalamic ventral tract. Alpha-synuclein granular cytoplasmic neuronal staining involved neurons in the trigeminal thalamic tract, mesencephalic V, reticular and raphe nuclei, the glossopharyngeal-vagus complexes, and the SNC (Figure 5F) in exposed subjects as young as seventeen years of age (Table 1). Perivascular macrophages with hemosiderin pigment and intact RBC were seen in capillaries throughout the brain stem, including the ones in the regions of cranial nerve nuclei (i.e., mesencephalic trigeminal neurons). Fibrin thrombi were seen at all levels of the brain stem in small blood vessels in exposed subjects.

Evaluation of APOE ε 3/4 and 4/4 Subjects: All MC APOE ε 4 either heterozygous or homozygous subjects had Aβ42 in neurons and blood vessels in the frontal cortex and the hippocampus, including the twenty-year-old male with a mutant TLR4 genotype (Table 4). Vascular changes, cortical reactive GFAP-positive astrocytes and white matter gliosis were more prominent than in the APOE ε 3/3 age-matched MC cohort. The only APOE ε 4/4 subject, a thirty-two-year-old MC woman, had scattered foci of perivascular monuclear cells in the hippocampi, as well as platelet thrombi in small blood vessels. This woman had Aβ42 in her OBs, cortical neurons, and cortical and subarachnoid blood vessels, in addition to α-synuclein immunoreactivity in the substantia nigrae and neurons from the mesencephalic trigeminal nerve. Subjects with the APOE ε 4 allele displayed ZO-1 discontinuous or punctuate staining in 62.2% of their vessels throughout the frontal cortex, in sharp contrast to the 30.8% in APOE ε 3/3 subjects ($p = .007$). Assessment of accumulation of Aβ42 and α-synuclein as a function of age and residency (Tables 5 and 6) showed that 58.8% of APOE ε 2/3, 3/3 subjects under the age of twenty-five who were residents of MC exhibit Aβ42 accumulation (average age 17.4 years), whereas in the same group 23.5% already had α-synuclein detectable by IHC. Accumulation of both Aβ42 and α-synuclein starts in the teen years in MC residents (Tables 5 and 6).

Electron Microscopy: Frontal capillaries exhibited RBC with ultrafine particles in their cytoplasm, along with aggregation of intramembrane UFPM and establishment of discrete contacts with endothelial cell cytoplasmic membranes (Figure 5G). Mononuclear cells established a close contact with the capillary outside the BBB, and UFPM was seen frequently at the interphase. Trigeminal ganglia capillary sections also revealed the presence of discrete contacts between the RBC and the endothelial cells and increased caveoli (Figure 5H with insert).

Discussion

Clinically healthy, cognitively and neurologically intact children, teenagers, and young adults with a lifetime exposure to significant concentrations of air pollutants including O_3, PM, and PM-LPS exhibit an upregulation of mRNA COX2, IL-1β, and a key innate immunity receptor CD14 in the OB, frontal cortex, substantia nigrae, and/or vagus nerves, as well as early disruption of the tight junctions in frontal blood vessels. These subjects exhibit nuclear NFκB in brain endothelial cells as well as evidence of an activated inflamed cerebral endothelium, with an altered BBB and trafficking of inflammatory cells in perivascular areas and in the neuropil. The OB mRNA COX2 upregulation, the frontal disruption of the BBB, and the endothelial nuclear NFκB are early key findings in the highly exposed cohort. Inflammatory cell trafficking and Aβ42 accumulation in the OB and frontal cortex are seen in prepuberal children with no known risk factors for Alzheimer's disease. Alpha-synuclein Lewy neurites and punctuate α-synuclein neuronal accumulation are seen in the OB in children as young as eleven years of age, and in teens and young adults the α-synuclein immunoreactivity was also identified in the dorsal nucleus of the vagus, mesencephalic V, trigeminal thalamic tract, substantia nigrae, and in lung and heart autonomic ganglia and nerves.

The presence of PM in olfactory bulb neurons, in luminal erythrocytes from capillaries in lung, frontal and trigeminal ganglia, and in Kupffer cells, along with the translocation of UFPM from RBC to endothelial cells in capillary lungs, and from RBC to endothelial cells and to perivascular macrophage-like cells in frontal capillaries are very important observations in these highly exposed individuals. The fact that PM is directly reaching the brain parenchyma, along with the early disruption of the BBB and the vagal upregulation of CD14 capable of activating inflammatory processes in the brain stem, are key findings that need to be analyzed in terms of their potential impact on neuroinflammation and neurodegeneration.

There has been a growing interest in the identification of fine and ultrafine PM in urban air and their health effects (Donaldson 2003; Oberdorster et al. 2002), as well as how these particles reach the brain (Dorman et al. 2002; Henriksson et al. 1997). Moreover, neurodegenerative effects have been reported in experimental animals using UFPM (Block et al. 2004; Peters et al. 2006), and in dogs and human beings exposed to urban environments (Calderón-Garcidueñas et al. 2002; Calderón-Garcidueñas, Maronpot et al. 2003; Peters et al. 2006). Fine and ultrafine PM exhibit biological activities that are detrimental to cells, including induction of oxidative stress with the consequent depletion of cell antioxidants, direct cytoxicity including mitochondrial dysfunction and altered phagocytic function, alteration of cell signaling pathways, and DNA and lipid damage (Donaldson 2003). Portals of entry of PM are of utmost importance in highly exposed subjects in MC, particularly children, since we have documented breakdown of the nasal barrier with significant accumulation of PM in and around nasal epithelial cells (Calderón-Garcidueñas et al. 2001; Calderón-Garcidueñas, Franco-Lira et al. 2007) and the transport of metals associated with PM to OB neurons (Calderón-Garcidueñas, Maronpot et al. 2003). Factors such as age, gender, weight, race, nostril shape, exercise level, minute ventilation, and outdoor time all contribute to the particle deposition and to lesser or higher risk from inhalation of pollutant PM in ambient air (Bennett et al. 2005; Villarreal-Calderón et al. 2002).

Early disruption of the BBB and translocation of UFPM likely contribute to damage of the BBB. An intact BBB is necessary

TABLE 5.—Distribution of subjects with expression of Aβ42 as a function of age and residency.

Groups/number of cases	Aβ42 Number of cases IHC+	% of cases	Average age
Controls < 25 y APOE 3/3 N: 6	0	0	16.33 ± 3.09
Controls > 25 y APOE 3/3 N:3	0	0	31.3 ± 4.3
MC E2 or E3 < 25 y N:17	10	58.82	17.41 ± 1.51
MC E2 or E3 > 25 y N:10	8	80	35.2 ± 1.9
MC E4 N:8	8	100	27 ± 7.5
Controls E4 N:3	2 (36 y, 45 y)	66	41.67 ± 2.85

Abbreviation: APOE, apolipoprotein E; IHC, immunohistochemistry; MC, Mexico City.

TABLE 6.—Distribution of subjects with α-synuclein as a function of age and residency.

Groups/number of cases	α-synuclein Number of cases IHC+	% cases	Average age
Controls < 25 y APOE 3/3 N: 6	0	0	16.33 ± 3.09
Controls > 25 y APOE 3/3 N:3	0	0	31.3 ± 4.3
MC E2 or E3 < 25 y N:17	4	23.5	17.41 ± 1.51
MC E2 or E3 > 25 y N:10	3	30	35.2 ± 1.9
MC E4 N:8	2	25	27 ± 7.5
Controls E4 N:3	0	0	41.67 ± 2.85

Abbreviation: APOE, apolipoprotein E; MC, Mexico City.

for the proper functioning of the CNS by actively controlling cellular and molecular trafficking between the systemic circulation and the brain parenchyma (Abbott 2005). Brain capillaries represent the largest surface area blood–CNS interface where tight intercellular junctions constitute the morphological basis of the BBB (Lossinsky et al. 2004). The issue of a damaged BBB is important, since this barrier has the ability to respond to LPS, IL-1β, TNFα, and IL-6 (Nadeau and Rivest 1999; Rivest 2001). LPS and IL-1β upregulate adhesion molecules, increase leukocyte migration across the CNS endothelial cells, and regulate BBB permeability (Hickey 2001; Rothwell and Luheshi 2000), whereas TNFα and IL-6 disrupt the BBB through the release of endothelial nitric oxide or, in the case of a transgenic animal overexpressing IL-6, the lack of BBB development (Brett et al. 1995; Farkas et al. 2006). Clinically healthy children in MC have evidence of systemic inflammation with increased sustained levels of prostaglandin E metabolite, IL-6, IL-1β, and a systemic response to their LPS-PM exposure through upregulation of mCD14 and two transporting LPS proteins: lactoferrin and heat shock protein 60 (Calderón-Garcidueñas Mora Tiscareño et al. 2003; Calderón-Garcidueñas, Franco-Lira et al. 2007; Calderón-Garcidueñas, Vincent et al. 2007). Since brain blood vessels express receptors for TNFα, IL-1β, and IL-6 (Nadeau and Rivest 1999), and TNFα and IL-1β can evoke expression of inflammatory mediator genes, such as COX2 (Rivest 2001) within the brain capillary endothelium, our findings of an early BBB disruption and CD14 upregulation suggest that systemic cytokines could be key early CNS vascular aggressors. Moreover, circulating cytokines can gain access to the brain by being transported across the BBB (Nguyen et al. 2002; Rivest 2001; Pan and Kastin 2001) and are able to evoke additional inflammatory mediator expression by vascular-associated microglia (Griffin et al. 2002), further increasing the permeability of the BBB (Blamire et al. 2000). Systemic and local brain production of cytokines are implicated in contributing to the initiation, propagation, and regulation of immune and inflammatory circuits (Benveniste 1998; Cunningham et al. 2005). IL-1β is the most important molecule capable of modulating cerebral functions during systemic and localized inflammation (Ferrari et al. 2006; Griffin et al. 2002; Rothwell and Luheshi 2000). Zhang and Rivest proposed that circulating LPS and cytokines could bind to their cognate receptors onto endothelial and/or monocytic cells lining the BBB, which in turn will lead to proinflammatory signaling and transcription of the receptors for different proinflammatory ligands that can stimulate NFκB kinases and mitogen-activated protein (MAP) and the enzymes responsible for PGE2 formation in the cerebral tissue (Zhang et al. 2003). Zhang and Rivest proposed responses to systemic immune stimuli likely apply to our chronically air-pollution–exposed subjects.

A critical finding is the endothelial nuclear NFκB activation present in the brain capillaries of young exposed subjects. NFκB activation depends on varied stimuli such as cytokines, LPS, and DNA damage (Pahl 1999); activation is tightly regulated and quickly shortened through feedback inhibition following the initial activating stimulus (Xiao et al. 2006). However, persistant activation (i.e., continuous exposure to significant levels of cytokines, UFPM, and/or PMLPS) results in deleterious effects.

Once the BBB is disrupted, significant leaking of RBC and proteins such as prothrombin may follow. There is an increment in the number of perivascular macrophages and microglia that expresses CD163, a scavenger receptor mediating the removal of hemoglobin-heptaglobin complexes, that is increased in inflammatory disorders (Kim et al. 2006). CD163 perivascular macrophages were common in the deep frontal and temporal white matter of MC subjects. Concomitantly with the increment in CD163, immunoreactivity for CD68 and HLA-DR in microglia, perivascular macrophages and endothelial cells were observed, in keeping with the inflammatory response. Intact and degranulated mast cells identified by means of tryptase monoclonal antibodies were seen in perivascular locations in frontal and temporal cortices, as well in trigeminal ganglia, and in peripheral autonomic nerves innervating the lungs and hearts in MC subjects, whereas in the control subjects mast cells were very rare and intact. Mast cells in the brain are normally observed in small numbers around the third ventricle, thalamus, hypothalamus, and meninges, and in the peripheral nervous system in association with inflammatory processes (Dropp 1979; Theoharides 1990). Mediators released by activated mast cells contribute to local inflammatory responses, regulating BBB permeability and angiogenesis and playing an active role in neuroinflammation (Ibrahim et al. 1996). More importantly, their presence in the context of the disruption of the BBB relates to their arrival in the CNS and PNS via the bloodstream following the trafficking of other inflammatory cells (Ibrahim et al. 1996). The identification of prothrombin in extravascular spaces and perivascular macrophages is a crucial finding in keeping with the BBB disruption (Mhatre et al. 2006), and it could be a contributing factor in the increased apolipoprotein immunoreactivity observed in MC dogs (Calderón-Garcidueñas et al. 2002), and as described by Mhatre et al. in a rat model of intraventricular infusion of prothrombin (Mhatre et al. 2006). The seminal work of Grammas et al. has shown that neurotoxic thrombin and inflammatory proteins are elevated in AD microvessels, a finding that is very relevant to our work. Rupture of the vascular basement membrane and leakage of prothrombin are described in the prefrontal cortex of Alzheimer's patients (Zipser et al. 2007).

Perivascular mononuclear cells are active and efficient antigen-presenting cells (Lossinsky et al. 2004). In a healthy brain the endothelial cells express very low levels of adhesion molecules required for leukocyte emigration (Lossinsky et al. 2004), a central pathogenic event in CNS inflammation (Hickey 2001). Leukocyte adhesion to endothelial cells is a crucial step to facilitate selective and effective capture of leukocytes (Hickey 2001), and for leukocytes to cross the BBB, they must first roll along the luminal endothelial cell (EC) surfaces to establish the initial cell–cell communication (Abbott 2005; Hickey 2001; Lossinky et al. 2004). In in vitro adhesion assays, binding of lymphocytes to inflamed brain vessels is mainly mediated by leukocyte function-associated antigen-1 and intracellular adhesion molecule-1, the late-activation antigen-4, and the vascular cell adhesion molecule-1 (Hickey 2001). EC activation is seen after the injection of TNFα and LPS (Nadeau and Rivest 1999; Pan and Kastin 2001; Rivest 2001), the latter of which represents an important component of PM in MC. In MC subjects including children, the luminal EC exhibit strong immunoreactivity for adhesion molecules such as VCAM-1 and ICAM-1 both in supra- and infratentorial regions. In keeping with the EC activation, two critical observations were described in this human study: the presence of UFPM in RBCs and the aggregation of intramembrane particles with the formation of patterned discrete contact points between endothelial cells and RBCs in the CNS, trigeminal ganglia, and lung capillaries of highly exposed people. The establishment of contact points between ECs and RBCs could represent a pathway for the exchange of PM between the activated endothelial cell and the UFPM-loaded RBCs, in keeping with the capacity of ultrafine PM to penetrate RBC, as elegantly shown by Geiser and Rothen-Rutishauser (Geiser et al. 2005; Rothen-Rutishauser et al. 2006). Ultrafine particles are not membrane bound, which allows for direct access to intracellular proteins, organelles, and DNA, enhancing their toxic potential (Geiser et al. 2005). Further, the passage of PM to the brain following the RBC-activated EC is likely to be increased in subjects exposed to pollutants owing to the disruption of the BBB as described in previous lines, and it is likely related to the production of NO (Calderón-Garcidueñas et al. 2002; Thiel and Audus 2001). Plasmodium infected RBCs induce endothelial upregulation of ICAM-1 and give rise to endothelial cell microvilli or cytoplasmic fronds that touch the infected RBCs (Tripathi et al. 2006). The formation of endothelial fronds surrounding the RBC in the malaria-infected model is remarkably similar to our findings in the lung and trigeminal ganglia capillaries. Of utmost importance, the endothelial fronds/microvilli in the malaria model interfered with blood flow even after lysis of the infected RBCs (Tripathi et al. 2006), an indication that in our subjects the endothelial frond formation could account for a decreased blood flow in the involved areas.

Breakdown of the nasal barrier in pollution-exposed subjects may also contribute to brain inflammation by increasing the access of PM to the brain through the olfactory and trigeminal pathways. The finding of PM in the glomerular region of the OBs of MC residents indicates that particles are readily transported from the nasal cavity to the brain via the olfactory nerve, a pathway very well known in experimental animals exposed to metals (Dorman et al. 2002; Henriksson et al. 1997). Moreover, there is an early and significant upregulation of COX2, IL-1β, and CD14 in the OB, which is indicative of an ongoing inflammatory process. Further, the accumulation of Aβ42 and α-synuclein in the OB is associated with significant upregulation of mRNA COX2, whereas the presence of α-synuclein in the brain stem is related to COX2 upregulation in the substantia nigrae. The upregulation of COX2 is particularly relevant in these subjects already exhibiting Aβ42 accumulation, since COX2 potentiates β-amyloid peptide generation through alterations in γ secretase activity and apoptotic cell death and is indeed associated with the accumulation of Aβ42 (Qin et al. 2003; Xiang et al. 2002) and α-synuclein (Jellinger 2003). Both Aβ42 and α-synuclein are proteins capable of aggregation and misfolding, leading to progressive neurodegeneration that develops insidiously over the lifetime of the individual (Jellinger 2003; McGeer et al. 2006; Nguyen et al. 2002; Selkoe 2001, 2002). Given that axons from the olfactory sensory neurons project to the OB, and the primary axons of the projection neurons send off collateral branches to the olfactory nuclei, piriform cortex, entorhinal cortex, and amygdaloid nuclei, and then to the hippocampal formation and the parahippocampal gyrus, it is expected that significant inflammatory process in the OB in these highly exposed subjects may translate into olfactory dysfunction, which is indeed the case in young adults (L. Calderón-Garcidueñas and M. Franco-Lira, pers. comm. 2007). Olfactory dysfunction is an early clinical finding in several neurodegenerative disorders, including Alzheimer and Parkinson's diseases (Hawkes 2003).

We have shown that the OB and the substantia nigrae are early targets of air pollution in young people, since the greater upregulation of mRNA COX2 was documented in teens and young adults. Alpha-synuclein accumulated as Lewy neurites and/or punctuate deposits in the OB, trigeminal thalamic tract, mesencephalic V, reticular and raphe nuclei, the glossopharyngeal-vagus complexes, and lung and heart autonomic ganglia in subjects as young as eleven years of age for the OB and the lung ganglion cells, and seventeen years for the brain stem findings.

The brain stem findings in teens and young adults bring up three crucial issues: (1) the role the vagus nerves play in the brain stem inflammation development; (2) the accumulation of α-synuclein in target areas as a risk factor for the development of Parkinson's disease in exposed populations; and (3) the accumulation of α-synuclein as a neuroprotective or neurotoxic effect. We know that systemic cytokines could affect the CNS via sensory nerves such as the vagus. This could be a consequence of exposure to air pollutants, because IL-1β is recognized by chemosensory receptors located in vagal paraganglia in the vagus nerve at several levels, including the cervical, thoracic, and abdominal regions (Elmquist et al. 1997). Activation of the peripheral immune system drives viscerosensory pathways originating in the brain stem nucleus of the solitary tract and ventrolateral medulla in response to cytokine signaling in the vagus nerve (Elmquist et al. 1997). The vagus and glosopharyngeal nerves, with their chemosensitive afferent fibers, are major neural pathways that establish communication between the immune system and the brain, generating responses to pro-inflammatory mediators (Elmquist et al. 1997). Moreover, indirect activation of the vagus nerve can be accomplished by paraganglia activation (Goehler et al. 1999). Paraganglia are located in the thorax and abdomen and are positioned to sense immune products released in lymph nodes and visceral organs, and they express binding receptors for IL-1β (Goehler et al. 1999). Indeed, the vagus nerves play a role in the lung inflammation caused by diesel-soot rodent exposures (McQueen et al. 2007), further emphasizing their potential to extend the inflammatory response into the brain stem. The upregulation of COX2 in the vagus nerves was an expected finding, given the extensive innervation coverage of the vagus nerves in target organs exposed to PM and endotoxins (i.e., lung, heart, and liver) (Kukanova and Mravec 2006; Uyama et al. 2004). Moreover, the presence of PM in Kupffer cells—the liver-resident macrophages (Uyama et al. 2004; Wake et al. 1989) responsible for the clearance of foreign material arriving from the circulation and the gut (Wake et al. 1989)—is a very interesting finding, given that the liver and the digestive tract are preferred sites for extrapulmonary translocation of ultrafine particles in human beings and rats (Oberdorster et al. 2002). Thus, the mRNA COX2 right vagus nerve's significant upregulation when compared to the left in MC residents could be an indication of the role the liver plays in the detoxification and clearance of foreign and altered-self substances including PM and LPS-PM in the parenchyma (Nolan 1975). The issue is important from the clinical point of view, since in Parkinson's disease there is substantial asymmetry of symptoms from the onset, with a marked preference for the right side (Djaldetti et al. 2006). Thus, the asymmetry could be explained for the PM factor, by the type and size of particles people are exposed to, and their fate in the lung and extrarespiratory anatomical areas (Daigle et al. 2003). Thus, in MC residents with a disrupted and ineffective nasal barrier, major concentrations of PM would be swallowed and thus enter the digestive system, the liver pathway, and the right vagus. Interestingly, whereas the substantia nigrae in the highly exposed subjects exhibited an upregulation of COX2 (p = .03), IL-1β did not reach significance (p = .06). In contrast, the periventricular grey adjacent to the SNC but not involved in the same neural pathways did not show upregulation of any of the selected inflammatory genes. Based on these findings we concluded that in subjects exposed to air pollution, the brain stem is taking part in the inflammatory process, either through local pathways or systemic inflammation or both, and the brain stem participation likely also depends on the PM entry pathways (i.e., digestive and lower respiratory systems).

Alpha-synuclein—an abundant brain 140 residue protein—is the culprit in Parkinson's disease (PD) (Braak et al. 2003; Eriksen et al. 2003; Fink 2006; Jellinger 2003). Synucleins are developmentally expressed, and α-synuclein is present in presynaptic terminals and in both soluble and membrane-associated brain fractions (Fink 2006; Eriksen et al. 2003; Jellinger 2003). Substantial evidence suggests that α-synuclein aggregation is a critical step in PD and other synucleopathies (Fink 2006; Jellinger 2003), and a pathway going from normal soluble to abnormal misfolded filamentous proteins is a key process regardless of the primary disorder (Fink 2006; Jellinger 2003). Factors affecting the kinetics of α-synuclein fibrillation include oxidative stress, pesticides, metals, glycosaminoglycans, lipids, and macromolecular crowding (Fink 2006). Linse et al. demonstrated that nanoparticles enhance the rate of protein fibrillation by decreasing the lag time for nucleation, a novel mechanism that could be applicable to both Aβ42 and α-synuclein in the scenario of air pollution. Oxidative stress is present in the brain stem of these MC subjects, as evidenced by the presence of cells positive for 8-OHdG and NT and the upregulation of COX2 in the substantia nigrae, which could result in the production of ROS (Choi et al. 2006; Minghetti 2005). Early and sustained production of COX2 results in the production of free radicals in the process of converting arachidonic acid to precursors of vasoactive prostaglandins (Choi et al. 2006; Minghetti 2005). The presence of aggregated α-synuclein in target CNS and PNS regions in these high-air-pollution–exposed young cohorts follows the characteristic topographical distribution of early PD lesions, as described by Braak and colleagues (Braak et al. 2003, 2006; Del Tredeci et al. 2002), that is, OB, lower brain stem, and ganglionic autonomic cells. These prepuberal teens and young adults can be identified by their aggregated α-synuclein as being in Braak stages 1 and 2, the presymptomatic PD stage. Recent observations among MC pediatric cardiologists of an increased number of otherwise healthy children with syncope could offer evidence of heart autonomic and lower brain stem involvement as we have shown here (Dr. Alfredo Bobadilla-Aguirre, pers. comm., November 14, 2006). We strongly suggest that the Braak et al. proposal (2003) about a "putative environmental pathogen capable of passing the gastric epithelial lining might induce α-synuclein misfolding and aggregation" could indeed be related to PM gaining access to the brain through the respiratory and gastrointestinal vagus pathway in subjects exposed to significant PM concentrations for long periods of time. A controversial issue has to be addressed in this scenario: is the aggregation of α-synuclein neuroprotective or toxic in these young subjects? (Quilty et al. 2006; Sidhu et al. 2004) It appears that in tissue culture and with relatively low levels of oxidative stress, increased α-synuclein offers neuroprotection (Quilty et al. 2006), and it is also clear that the level of expression is crucial to confer either protection or toxicity (Sidhu et al. 2004). Given that the potential factors (oxidative stress, COX2 upregulation, vascular inflammation, nanoparticles) likely accounting for the aggregation of α-synuclein in these air-pollution–exposed subjects are both intense and prolonged, we favor the idea that α-synuclein acquires neurotoxic properties in these cohorts.

Chronic oxidative stress is a major contributing factor in the pathogenesis of both Alzheimer's and Parkinson's diseases (Nunomura et al. 2006; Quilty et al. 2006). We previously described significant oxidative DNA damage (genomic DNA apurinic/apyrimidinic sites) in both MC dogs and human beings in the OB and the frontal cortex (Calderón-Garcidueñas et al. 2002; Calderón-Garcidueñas, Maronpot et al. 2003). Our human data support previous work from Nunomura et al., Forero et al., and Zhu et al. stating that oxidative stress is early and precedes neuropathological manifestations of AD. We could add that brain oxidative stress starts in childhood and the teen years and is accompanied by accumulation of both Aβ42 and α-synuclein in the scenario of air pollution exposure.

Apolipoprotein E is the susceptibility gene with the clearest link to late-onset Alzheimer's disease, although the ε 4 genotype alone is insufficient to predict an individual's risk for AD (Wishart et al. 2006). In this work we have shown that carriers of an ε 4 allele residing in MC accelerate their Aβ42 accumulation by one decade compared to 3/3 carriers (Table 5). On the other hand, there is Aβ42 brain immunoreactivity in 58.8% of young MC residents (17.41 ± 1.5 years) with ε 3 alleles, and 80% in the older cohort (>25 years [35.2 ± 1.9 years]). These results suggest that cumulative exposures and age are key factors. It is interesting to point to this observation, because the deposits of Aβ42 start in childhood and the teen years in MC residents, and we know that these subjects do not fulfill current morphological AD criteria, thus these younger years constitute a time frame that is important in terms of pharmacological protection of our exposed populations. Alpha-synuclein accumulation also starts in the teens in highly exposed subjects, moreover, as expected we found no differences in APOE 4 carriers (Table 6).

Given that all ε 4 MC subjects—including the fifteen-year-old boy—had accumulation of Aβ42 obligates us to entertain the possibility that in the context of exposure to severe air pollution, the presence of an ε 4 accelerates the AD-like pathology. Since regional brain atrophy in the right medial temporal and bilateral frontotemporal regions (Wishart et al. 2006) and altered fractional anisotrophy (Persson et al. 2006)—a marker of white matter integrity—have been described in cognitively intact adults with homozygous or heterozygous ε 4 status, it is possible than MC APOE ε 4 teens already display similar alterations, a major issue because maturation of white-matter pathways is crucial in cognitive, behavioral, emotional, and motor development during childhood and the teen years.

There is no doubt that some subjects in this highly exposed MC cohort responded mainly with supratentorial pathology, deposition of Aβ42, and formation of diffuse amyloid plaques, whereas for others the response was mainly infratentorial, with the substantia nigrae and the vagus upregulation of COX2 and the deposition of α-synuclein in brain stem nuclei. A small group of subjects displayed both supra- and infratentorial pathology. This pattern of findings pointing toward Alzheimer's and/or Parkinson's-like pathology resembles the distribution of AD/PD patients with overlaps (Kurosinski et al. 2002). Given the common denominators between these two major neurodegenerative diseases, our findings are expected.

The age issue of detection of Aβ42 in teens is important, given that higher mRNA IL-1β expression is seen in frontal cortex in teens and young adults under the age of twenty-five, whereas the higher values for mRNA COX2 were seen in adults over the age of thirty. Thus, teens' frontal cortices exhibit early IL-1β upregulation. Cytokines play a central role in the self-propagation of neuroinflammation, with IL-1β having a prominent function (Minghetti 2005). The early upregulation of IL-1β in the frontal lobe of young subjects is of utmost importance, because this proinflammatory cytokine has been associated with BBB disruption; recruitment of inflammatory cells into the CNS (Ferrari et al. 2006); sustained upregulation of IL-8, VCAM-1, and ICAM-1 in astrocytes (Moynagh 2005); and with neuronal, glial, and endothelial injury through strong activation of the classical IL-1 signaling pathway, activation of MAPKs and NFκB (reviewed in Allan et al. 2005). Equally crucial is the role of IL-1β in the transformation of diffuse Aβ in mature plaques (Akiyama et al. 2000). NFκB is a crucial mediator in the IL-1β signal, and NFκB activation is sustained in astrocytes in response to IL-1 stimulation (Moynagh 2005).

The upregulation of CD14 may significantly contribute to the neuroinflammatory response in air-pollution–exposed subjects, particularly those exposed to significant amounts of PM-associated LPS, hence the upregulation of mRNA CD14 in the OBs and vagal nerves could indicate a brisk response of the innate immune system to LPS. Interestingly, although mCOX2 was significantly upregulated in the right vagus (p =.0002) versus the left (p = .03), CD14 expression was less, presumably reflecting the liver capacity to inactivate LPS. Fassbender et al. showed that CD14 binds Aβ and mediates Aβ-induced microglial and monocytic activation and toxicity for neurons. Further, they demostrated CD14 in Alzheimer's brains but not in control subjects by immunohistochemistry (Liu et al. 2005). Letiembre et al. showed an altered regulation of innate immune receptors in older nondemented people. Given that TLR4 is necessary to engage the innate immune responses in the brain (Fassbender et al. 2004; Letiembre et al. 2007; Liu et al. 2005), we had hypothesized that TLR4-mutant subjects will have fewer brain inflammatory responses. However, that was not the case; trafficking of inflammatory cells and accumulation of Aβ42 were also observed in the 3 TLR4-mutant subjects, thus suggesting that factors other than TLR4 are also playing a crucial role in cell trafficking and amyloid accumulation observed in these megacity pollution-exposed subjects.

We would like to propose that sustained exposures to significant levels of air pollutants including UFPM, $PM_{2.5}$, and PM-LPS produce brain neuroinflammation and neurodegeneration through at least four pathways.

1 Induction of upper respiratory, lung epithelial, and endothelial injury leading to persistant chronic inflammation in the respiratory tract and systemic inflammation. The systemic imflammation is accompanied by the production of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1β (all of which are upregulated in MC children), for which brain blood vessels exhibit constitutive and induced expression of receptors. These cytokines can activate endothelial cells in the BBB, disrupt the BBB (early findings in highly exposed subjects and dogs), upregulate COX2 (target brain regions in MC subjects), and trigger cascades leading to activation of MAP kinases/NFκB (nuclear transduction of NFκB in endothelial brain cells in exposed subjects). A high level of activation of NFκB in astrocytes results in increased expression of nitric oxide synthase (seen in three-month-old MC dogs), and nitric oxide production that opens the BBB (seen in dogs, children, and teens). The early disruption of the BBB is followed by leaking of RBC and proteins such as prothrombin (neurotoxic protease, increases APP) (Grammas et al. 2006; Mhatre et al. 2006; Zipser et al. 2007) and trafficking of inflammatory cells expressing CD163, CD68, and HLA-DR, as well as mast cells in keeping with the inflammatory response. A dysregulated inflammatory response involves neural-immune interactions including the upregulation of CD14 that further activate immune cells, glial cells, and neurons (Fassbender et al. 2004; Letiembre et al. 2007; Liu et al. 2005; Minghetti 2005). Chronic oxidative stress is an early component of the brain responses, as evidenced by DNA oxidative damage present in different target brain areas as well as outside the CNS (Calderón-Garcidueñas, Maronpot et al. 2003).
2 We strongly support the importance of the olfactory pathway, especially in children, since olfactory neurons are loaded with PM and a strong early upregulation of COX2, IL-1β, and CD14 is present. Early damage to the OB and its connections and the accumulation of Aβ42 and α-synuclein will potentially translate into an abnormality in the limbic system, including the hippocampus and the parahippocampal gyri, as well as a decrease in the number of stem cells existing in the OB (Bédard et al. 2004).
3 The vagus/trigeminal (Lewis et al. 2005) pathways are also crucial, given that PM enters the respiratory and digestive systems (i.e., the liver). PM-LPS is likely to play an important role in these pathways, as shown by the vagal upregulation of CD14.
4 Direct access of UFPM to the brain, further accentuating an inflammatory response in the brain parenchyma (ROS production in activated microglia and perivascular macrophages), damaging components of the BBB, and potentially enhancing the rate of protein fibrillation affecting Aβ42 and α-synuclein (Linse et al. 2007).

All four pathways are clearly demonstrated in MC children, teens, and young adults, and based on the long-standing view that chronic inflammation, altered innate immune responses, and oxidative stress are detrimental, we propose that inflammatory interactions that take place at the blood-endothelium interface along with early oxidative stress are the bases for the early Alzheimer's and Parkinson's-like changes we observed in these populations. Oxidative stress in AD and PD is involved at the earlier stages of the pathological cascades with aggregation of the target proteins: amyloid β, tau and α-synuclein as an initial compensatory response (Eriksen et al. 2003; Fink 2006; Forero et al. 2006; Minghetti 2005; Nunomura et al. 2006; Quilty et al. 2006; Sidhu et al. 2004; Zhu et al. 2006). Persistance of the initial damaging factors translates into a neurodegenerative response.

In summary, exposure to significant concentrations of air pollutants including UFPM and $PM_{2.5}$ produces neuroinflammation and altered innate immune responses in crucial brain target anatomical areas in children and young adults. Ultrafine PM could play a role in the enhancement rate of protein fibrillation affecting Aβ42 and α-synuclein (Linse et al. 2007). We strongly propose that neuroinflammation as a result of exposure to air pollution could have a causative role in both Alzheimer's and Parkinson's diseases and that sustained brain inflammation confers a higher risk for the development of these two frequent neurodegenerative disorders. In the United States, 158 million people live in areas where O_3 exceeds the eight-hour standard, 29 million are exposed to $PM_{10,}$ and 88 million are exposed to $PM_{2.5}$ (http://www.epa.gov/oar/oaqps/greenbk/03co.html). Neuroinflammation provides a mechanistic link between inhalation/ingestion of air pollutants and neurodegeneration as seen in AD and PD. Neuroinflammation and accumulation of Aβ42 and α-synuclein in key target brain areas start in healthy children with no known risk factors for neurodegenerative diseases. Long-term exposure to air pollution should be considered a risk factor for both Alzheimer's and Parkinson's diseases, and APOE ε 4 allele carriers could have a higher risk of developing AD if they reside in a polluted environment.

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Emissions from an International Airport Increase Particle Number Concentrations 4-fold at 10 km Downwind

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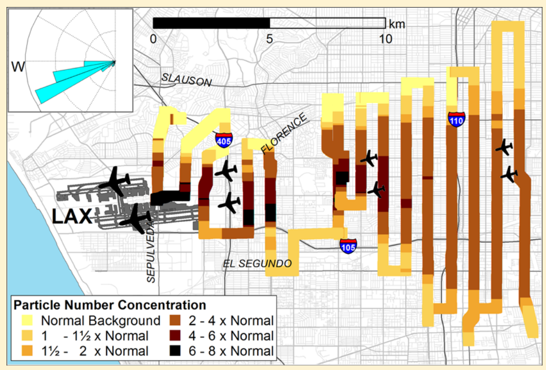
Supporting Information

ABSTRACT: We measured the spatial pattern of particle number (PN) concentrations downwind from the Los Angeles International Airport (LAX) with an instrumented vehicle that enabled us to cover larger areas than allowed by traditional stationary measurements. LAX emissions adversely impacted air quality much farther than reported in previous airport studies. We measured at least a 2-fold increase in PN concentrations over unimpacted baseline PN concentrations during most hours of the day in an area of about 60 km^2 that extended to 16 km (10 miles) downwind and a 4- to 5-fold increase to 8–10 km (5–6 miles) downwind. Locations of maximum PN concentrations were aligned to eastern, downwind jet trajectories during prevailing westerly winds and to 8 km downwind concentrations exceeded 75 000 particles/cm^3, more than the average freeway PN concentration in Los Angeles. During infrequent northerly winds, the impact area remained large but shifted to south of the airport. The freeway length that would cause an impact equivalent to that measured in this study (i.e., PN concentration increases weighted by the area impacted) was estimated to be 280–790 km. The total freeway length in Los Angeles is 1500 km. These results suggest that airport emissions are a major source of PN in Los Angeles that are of the same general magnitude as the entire urban freeway network. They also indicate that the air quality impact areas of major airports may have been seriously underestimated.



■ INTRODUCTION

Previous studies that directly measured the impact of aviation activity on air quality have mostly conducted measurements in close proximity of airports. Few studies have reported significant air quality impacts extending beyond a kilometer.[1−4] Carslaw et al. 2006[1] analyzed differences in pollutant concentrations by wind speed and direction along with differences in aircraft and ground traffic activity at Heathrow Airport in London. They found airport contributions of up to 15% of total oxides of nitrogen (NO_x) at a site 1.5 km downwind of the nearest runway. At Hong Kong International Airport, Yu et al. 2004[2] used nonparametric regression analysis on pollutant concentrations by wind speed and direction. They calculated that aircraft nearly doubled sulfur dioxide concentrations 3 km away and also increased concentrations of carbon monoxide and respirable suspended particles under similar wind speeds and directions. Fanning et al. 2007[3] measured particle numbers concentrations in the 10–100 nm range and found significant increases above background at 1.9, 2.7, and 3.3 km downwind of the Los Angeles International Airport (LAX) blast fence. Although measurements were stationary and not concurrent, they also noted that takeoffs produced high concentrations and downwind gradients within 600 m of the blast fence. Dodson et al. 2009[4] found that aircraft activity at a regional airport in Warwick, RI contributed 24–28% of the total black carbon (BC) measured at five sites 0.16–3.7 km from the airport.

Several other airport and aviation emissions studies focused on quantifying the air quality impacts from jet takeoffs[5,6] and measured air pollutant concentrations very close to runways. Of particular relevance to this study, Hsu et al. 2013[7] linked flight activity at LAX with 1 min average PN concentrations. Their models suggested that aircraft produced a median PN concentration of nearly 150 000 particles/cm^3 at the end of the departure runway. PN concentrations decreased rapidly with distance to 19 000 particles/cm^3 at a location 250 m downwind and to 17 000 particles/cm^3 at a location 500 m further downwind. The rapid drop-off in concentration, however, may have reflected an increasing offset from the centerline of impacts with greater downwind measurement distance. Similar magnitude PN concentrations and correlations

Received: January 22, 2014
Revised: May 12, 2014
Accepted: May 14, 2014
Published: May 29, 2014

with departures were reported by Westerdahl et al. 2008[8] and Zhu et al. 2011[9] at sites located within 100−200 m of the Hsu et al. 2013[7] measurements.

Our study was motivated by mobile monitoring platform (MMP) based observations of large but gradual increases in PN concentrations as we approached locations under LAX jet landing trajectories on multiple transects up to 10 km downwind of LAX. We hypothesized that emissions from LAX activities were increasing PN concentrations over much larger areas and longer downwind distances than previously observed in studies that focused on near freeway and jet takeoff impacts to air quality. An extensive monitoring campaign confirmed that LAX-related emissions increased PN concentrations downwind at least 2-fold to 16 km. This large, previously undiscovered spatial extent of the air quality impacts downwind of major airports may mean a significant fraction of urban dwellers living near airports likely receive most of their outdoor PN exposure from airports rather than roadway traffic.

■ MATERIALS AND METHODS

Monitoring Area. LAX is the sixth busiest airport in the world and third busiest in the United States. About 95% of flights take off and land into the prevailing westerly/west-southwesterly (W/WSW) onshore winds[10] (i.e., 263 degrees, the direction of runway alignment[2]) using two sets of parallel runways separated by about 1.5 km. In the busiest hours, 40−60 jets per hour arrive during hours 0700−1900 and depart during hours 0800−2100. Reduced activity is typical for the early morning and late evening hours. 20−40 jets per hour arrive during hours 0600 and 1000−0100 and depart during hours 0700 and 2200−2300. During other hours typically fewer than five jets per hour arrive or depart.[10]

The airport complex is about 4.5 km east to west (E-W) and about 2.5 km north to south (N−S) and is surrounded by major roadways and freeways, as highlighted in Figure 1 (Figure S.1 in Supporting Information (SI) shows a map of this area with street name labels). The Federal Aviation Administration noise contours of the modeled annual 65 dB A-weighted equivalent (L_{Aeq}) noise threshold are shown[11] extending eastward along the predominant downwind direction and reflect the jet trajectories used for landing. They also extend west of the airport over the Pacific Ocean (not shown).

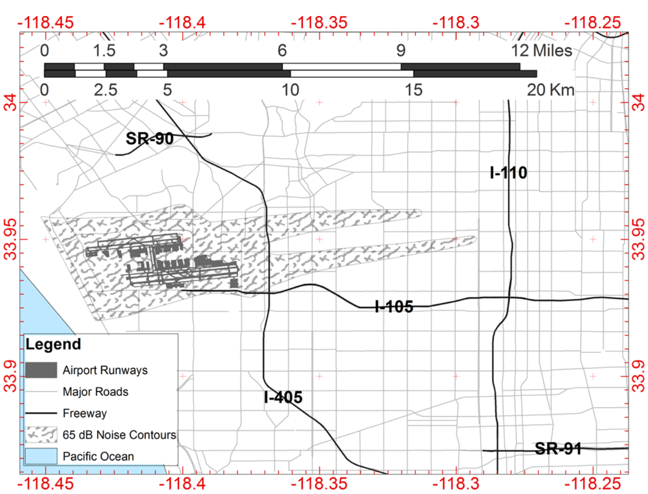


Figure 1. Los Angeles International Airport and 65 dB noise contours indicating eastern jet trajectories.

Mobile Monitoring. Monitoring consisted of transects 4−16 km in length, nearly perpendicular (i.e., N−S) to the direction of the prevailing winds, at varying downwind distances. Different monitoring routes were required to fully capture the changes in impact locations due to shifts in wind direction. A general downwind direction was chosen based on meteorological predictions but transect lengths and locations were determined during the monitoring run based on observations of the rate of change of PN concentrations. For each transect, monitoring was extended several hundred meters beyond the location where baseline PN concentrations appeared stable.

Measurements were conducted over 29 days with the University of Southern California (USC) MMP, a gasoline-powered hybrid vehicle. A second MMP, the University of Washington (UW) MMP, a gasoline-powered minivan, joined the monitoring on 3 days (June 22, 27 and July 1, 2013). Table 1 gives monitoring dates and times.

Most measurements were conducted during times of onshore westerly winds, typically strongest during 1100−1600, but we also conducted measurements during early morning and late night hours when air traffic was low and onshore winds were reduced (August 13, 16, 23, 24 and 25, December 03, 09, 15 and 16, 2013). Monitoring focused on the area east of LAX (i.e., the predominant downwind direction) but included several runs along the boundary of the airport in the upwind direction and south of the airport complex during occasions of northerly winds in winter months.

Instrumentation. Concentration measurements included PN, BC, NO, NO_2, NO_x, and particle surface UV-photoionization potential (measured using Ecochem Photoelectric Aerosol Sensor [PAS] that responds to elemental carbon and particle-bound polycyclic aromatic hydrocarbons [PB−PAH]). Instrument details are provided in SI (Table S.1 and S.2). Instruments were powered by two deep-cycle marine batteries via DC-to-AC inverter. Our power arrangement allowed for 5 h of run time if all instruments were running. For sampling runs that were anticipated to exceed 5 h, several instruments were shut down to extend battery life and the Condensation Particle Counter (CPC) was run on the vehicle's 12 V cell phone power outlet. If other instruments were turned on later, the required warm-up time was 25 min.

Instrument clock times were regularly synchronized to be within 1 s of the global positioning system device time, which also recorded speed and location. Measurements from instruments with a delayed response time were advanced to match the instantaneous instruments and the GPS time and location recorded at 1 s intervals. For pollutant measurements recorded at 10 s intervals, all locations within the recording interval were assigned the pollutant value reported for that interval.

Meteorological Data. Minute and hourly wind speed and wind direction data were obtained from the Automated Surface Observing Systems monitor at LAX airport (latitude 33.943 and longitude −118.407). Due to the 16 km distance between eastern edge of the study area and the meteorological station located at LAX, we could not assume that wind speed and direction were identical to those measured at LAX, but wind direction in this region of Los Angeles tends to be similar over large areas during daytime.[12]

The average wind direction at LAX is WSW (252°).[12] Daytime southwesterly sea breezes typically occur 16 h per day in the summer (0900−0100 for June−August), decreasing to 6

Table 1. Sampling Days, Time Periods and Meteorological Conditions during Sampling

date[a]	time	sampling distance from LAX (km)	WD[b]	WS (m/s)	urban background PN[c]	ratio of impacted to unimpacted baseline PN, 10 km downwind
4/6/2011	14:30–16:45	8–12	WSW, **W**	5.0 ± 1.8	15 000	2.0
4/10/2011	15:00–17:30	8–12	**W**	6.9 ± 1.2	10 000	4.5
5/24/2011	09:00–11:00	8–12	**Calm**, W	1.0 ± 2.5	10 000	3.0
5/27/2011	12:15–14:45	8–12	WSW, **W**	6.3 ± 1.3	10 000	4.7
1/26/2012	17:28–20:22	8–12	WSW, **W**	2.9 ± 2.1	20 000	6.0
9/29/2012	13:30–17:30	0–8	**W**	6.1 ± 1.1	10 000	3.7
9/30/2012	15:45–18:30	0–8	**W**	6.1 ± 0.4	5000	5.2
6/11/2013	14:14–15:14	2.5–8.5	**WSW**, W	6.7 ± 0.0	15 000	5.0
6/12/2013	13:30–16:30	2.5–10.5	**W**	4.0 ± 0.4	15 000	4.0
6/22/2013	11:47–18:50[d]	0–8	WSW, **W**	5.7 ± 0.4	10 000	4.4
6/27/2013	11:49–18:00[d]	0–8	WSW, **W**	5.3 ± 0.7	10 000	4.0
7/01/2013	10:30–18:30[d]	0–8	**W**, ESE	3.8 ± 1.0	15 000	3.8[e]
8/6,7/2013	23:56–02:45	0–8	WSW, W, S	3.3 ± 0.7	10 000	3.3
8/13/2013	06:30–15:00	0–8	Calm, WSW, **W**, NNE, NE, ENE, E, ESE[f]	3.0 ± 2.0	10 000	4.0
8/15/2013	08:30–15:30	0–16	Calm, WSW,**W**	2.5 ± 2.1	20 000	3.8
8/16/2013	09:45–20:50	0–16	SW, WSW,**W**, WNW	4.4 ± 1.3	10 000	3.0
8/23,24/2013	12:00–01:30	0–16	SSW, WSW,**W**	4.4 ± 2.2	20 000	4.0, 5.0
8/24,25/2013[g]	17:30–01:00	0–16	Calm, SSW, SW, WSW,**W**, ESE	3.1 ± 2.1	15 000	6.0
11/1/2013	16:00–19:50	0–12	SSE, W, **WSW**	3.7 ± 0.7	10 000	3.8[e]
12/3/2013	19:45–00:20	0–12	**WSW, W, WNW**	8.8 ± 1.4	5000	6.0
12/5/2013	13:00–18:30	0–12	WSW, **W**, WNW	5.5 ± 0.6	10 000	2.8
12/9/2013	16:00–00:00	0–10	**N**, NNE	2.7 ± 0.6	20 000	n/a
12/10/2013	15:30–21:30	0–10	**WNW,N**, NW	3.1 ± 1.1	20 000	5.0
12/14/2013	17:00–20:30	0–10	W, Calm	2.1 ± 0.5	20 000	data lost
12/15,16/2013	22:00–02:00	0–10	N, **NE**, ESE	2.9 ± 1.0	17 500	n/a
12/16/2013	10:00–16:00	0–12	**N, W**	2.8 ± 1.6	10 000	4.5
12/18/2013	17:30–20:30	0–10	**WSW**, SSW, SSE	3.3 ± 1.3	10 000	6.0
12/20/2013	16:30–20:00	0–10	**WSW, Calm**, E	2.6 ± 1.3	15 000	4.0
12/23/2013	15:15–19:00	0–12	**W**, Calm, E	2.8 ± 1.3	10 000	11.0

[a]The runs for which maps are presented are formatted in bold. [b]Predominant wind direction is formatted as bold. [c]Urban background value concentrations are reported to nearest 2500 particles/cm^3 and are the average baseline values in the unimpacted areas away from local traffic sources [d]Concurrent MMP sampling times: June 22:1320–1720, June 27:1325–1510, July 1:1240–1640. [e]Monitoring route did not cover the full N–S extent of the impact on Western Av (10 km downwind) on these days, values have been reported for Crenshaw Blvd. (8 km downwind). [f]Easterly flow was recorded in morning hours (until 1000) and westerly later morning to afternoon [g]08/25/2013 was not counted as an additional monitoring day because only 1 h of monitoring (0000–0100) was conducted on this date

h in the winter (1200–1800 in December). Only during the winter months (November–February, 0000–0900) are light easterly off-shore winds common.[12] Wind speed and direction during the monitoring periods are summarized in Table 1. Wind roses based on 1 min data are shown in Figure S.2 and S.3 of the SI.

Data Processing. MMP measurements included a localized traffic emissions signal representing microscale and middle scale variations (10–100 m and 100–500 m, respectively) and an underlying "baseline" pollutant concentration that varied gradually over the neighborhood scale (500 m–4 km).[13] Watson et al. 1997[13] derived these categories by considering the spatial scales of impact of various types of air pollution sources. We adopted a smoothing methodology to estimate baseline PN concentrations that excluded the microscale and middle scale impacts due to local sources, usually specific vehicles.

Baseline PN concentrations were derived from our mobile measurements by taking a rolling 30-s fifth percentile value of the 1-s concentration time series, and assigning that value to the measured location. This removed the microscale and middle scale impacts from traffic sources such as specific vehicle plumes. Baseline concentrations for a run were relatively spatially uniform outside of the LAX impact areas, with coefficients of variation (CV) of less than 5%. In comparison, the raw PN concentrations on roadways outside the LAX impact areas had CVs on the order of 40%. On rare occasions, the MMP was behind a high emitter for longer than 30 s. Such events, only if verifiable by video and field notes, were censored. However, less than 0.5% of data were censored in this manner, generated from about a dozen instances of prolonged influence from high emitting vehicles. An illustration of both raw and smoothed concentration time series is presented in the SI (Figures S.4–S.7). The figures in this text are based on smoothed data.

RESULTS AND DISCUSSION

Spatial Pattern and Extent of Elevated PN Concentrations. Downwind of LAX we observed gradual but large increases in baseline PN concentrations occurring over transect distances of multiple kilometers. PN concentrations were elevated 4-fold or more above nearby unimpacted baseline concentrations up to 10 km in the downwind direction from

dx.doi.org/10.1021/es5001566 | Environ. Sci. Technol. 2014, 48, 6628–6635

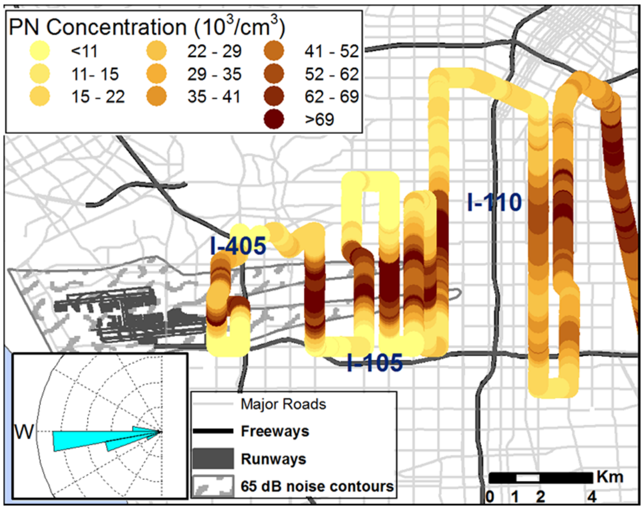


Figure 2. Spatial pattern of PN concentration (colored by deciles) for the afternoon and evening hours of August 23, 2013.

LAX. Figure 2 shows an example of the spatial pattern of the elevated PN concentrations.

The size of the impacted areas with high PN concentration increases was remarkable. At 16 km downwind, a 2-fold increase in PN concentration over baseline concentrations was measured across 6.5 km. Assuming a trapezoidal shaped plume with parallel edges of length 1.5 and 6.5 km, PN concentrations were at least doubled over an area of 60 km^2. Eight km downwind, a 5-fold increase in PN concentrations over baseline concentrations extended across 3 km and covered a total area of 24 km^2. (Concentrations in this large area exceeded 71 000 particles/cm^3, the average concentration on Los Angeles freeways.[14]) Within 3 km of the airport boundary, concentrations were elevated nearly 10-fold, exceeding 100 000 particles/cm^3, with concentrations of 150 000 particles/cm^3 occurring over a several km^2 area.

This pattern of elevated PN concentrations over large areas east of LAX was consistently observed during periods when there were both westerly winds and high air traffic volumes, typically all daylight hours and well into the night. Figure 3

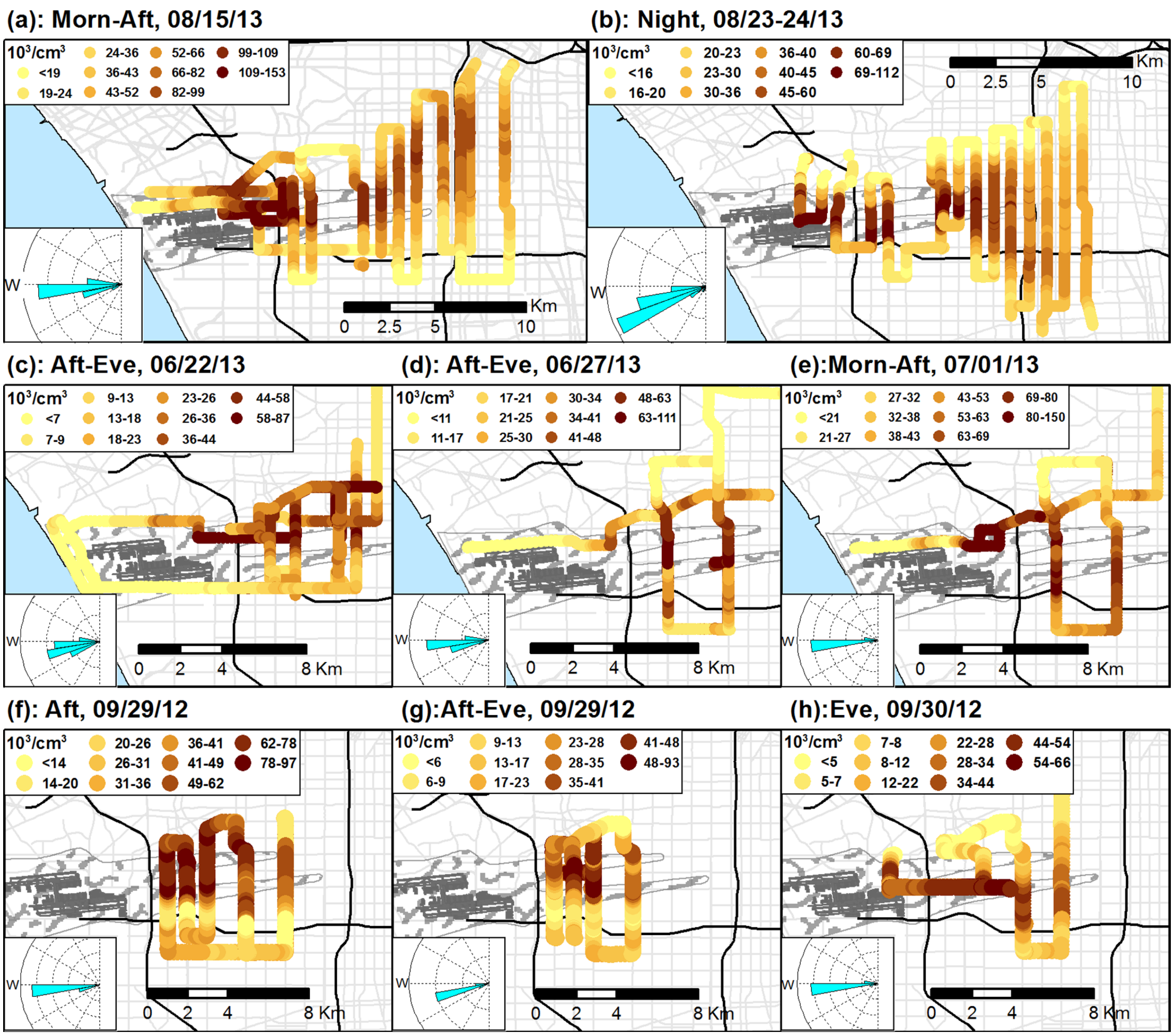


Figure 3. Spatial pattern of impact during different monitoring events. Wind direction during monitoring is shown in insets on bottom left. PN concentrations are classified and colored by deciles.

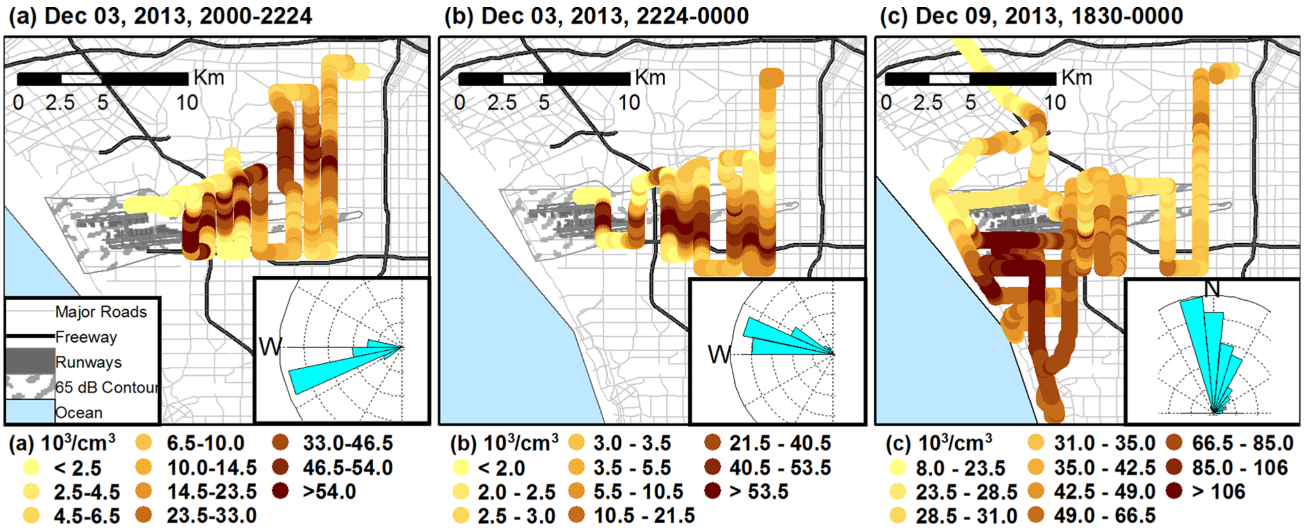


Figure 4. Change in location of impact due to shift in wind direction. Wind direction during monitoring is shown in insets on bottom left. PN concentrations are classified and colored by deciles.

shows the consistency of the patterns over eight monitoring runs at various times of day, displayed in each row by similarity of spatial scale.

In directions other than the downwind direction, no large areas of elevated PN concentrations were observed. Figures 3(c)−(e) include concentrations measured upwind of the LAX boundary (these are indicated by faint yellow lines within the noise contour); the concentrations recorded were typical of the coastal baseline concentrations, less than 10 000 particles per cm^3 (also see Figure S.8 in SI). Of possible other PN sources, a large refinery is located south of the airport but we did not observe elevated PN or other pollutant concentrations directly downwind of this source. In general, industrial point sources of pollution in the Los Angeles Air Basin are very tightly regulated by the South Coast Air Quality Management District.

We did not observe distinct day versus night differences, as might be expected based on the large change in meteorologically driven dilution between day and night for ground level sources. It appeared that the distant impacts we observed downwind of LAX required sufficient wind speeds for the jet climbing and landing emissions to reach the ground, as observed in Yu et al., 2004[2] at LAX and Hong Kong International Airports and Carslaw et al. 2006[1] at Heathrow Airport. At LAX, this probably corresponded to the development of the on-shore sea breezes that typically started 4−6 h after sunrise and lasted until 3−6 h after sunset.[12]

We also did not see the impacts of individual jets at the distances monitored, but the merging of individual jet impacts is not unexpected at distances of multiple km. Considering the frequency of landings and takeoffs (>90 per hour from 0900−2100[10]), at an average wind speed of 4 m/s, for example, an incoming parcel of air will travel only about 160 m before another jet landing or takeoff occurs. Under normal daytime air turbulence and the enhanced turbulence produced by jets,[15,16] significant mixing is expected over a 5−10 km distance (20−40 min). The generally smooth increases and decreases observed across the length of transects at such distances are additional evidence that mixing of plumes occurs. Examples of these smooth concentration increases for individual transects are shown in Figures S.6 and S.7 in the SI.

The consistent and distinctive spatial pattern of elevated concentrations was aligned to prevailing westerly winds and landing jet trajectories, and roughly followed the shape of the contours of noise from landing jets, indicating that landing jets probably are an important contributor to the large downwind spatial extent of elevated PN concentrations. As defined by the International Civil Aviation Organization, typical engine thrust during landing is 30%, as compared to 100% for takeoff and 85% for the climbing phase.[6] Stettler et al. 2011[6] calculated 18% of total NO_x emissions from landings, with 12% from taxiing and holding, 18% from takeoff, and 52% from the climb and climb out phases, respectively. When the extra upwind distance of the climb and climb out phases are taken into account, the landing approach emissions likely produce a significant fraction of the increased PN concentrations observed downwind.

Influence of Wind Direction on Location of Impact. The downwind location of the impact changed with shifts in the prevailing wind direction, although significant shifts in wind direction during the daytime are not typical of this area of Los Angeles.[12] Figure 4(a) and (b) illustrate one such change in impacted locations due to a shift in wind direction on a gusty day with frontal weather that also resulted in cleaner upwind baseline PN concentrations of less than 5000 particles/cm^3. The impacted locations were aligned along the NE direction during 2000−2220 h when winds were from W to WSW (250−280°). The impact then moved southwards between 2220−0000 h as winds turned more W to WNW (280−330°). During this shift, the impact centerline moved by 5.5 km on transects 8−10 km east of LAX.

Monitoring was also conducted during N to NE prevailing winds that tend to occur late at night in November and December (2100−2300).[12] This N to NE wind direction resulted in impacts that were centered south of the airport (Figure 4(c)). The PN concentrations in this southerly impact were roughly twice as high as on other days, in part because the baseline PN concentrations reflected urban air from northerly winds instead of marine air from westerly winds.

Diurnal wind patterns change little by season in Los Angeles basin.[12] Onshore westerly winds are common during midday hours, even in winter. As a result, areas of elevated PN

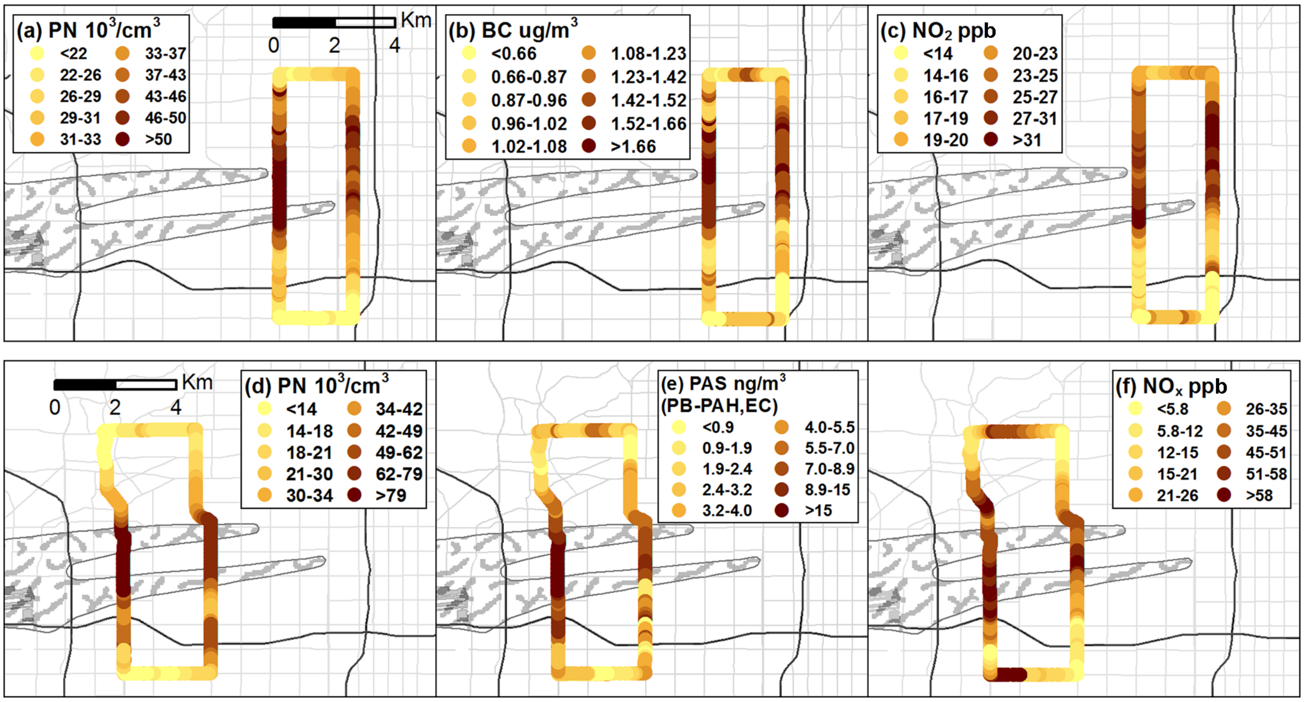


Figure 5. Spatial pattern of simultaneously measured pollutants during 1400–1530 on June 27, 2013. Concentrations are classified and colored by deciles. Panels (a)–(c) show data measured by the UW MMP and (d)–(f) show data measured by the USC MMP.

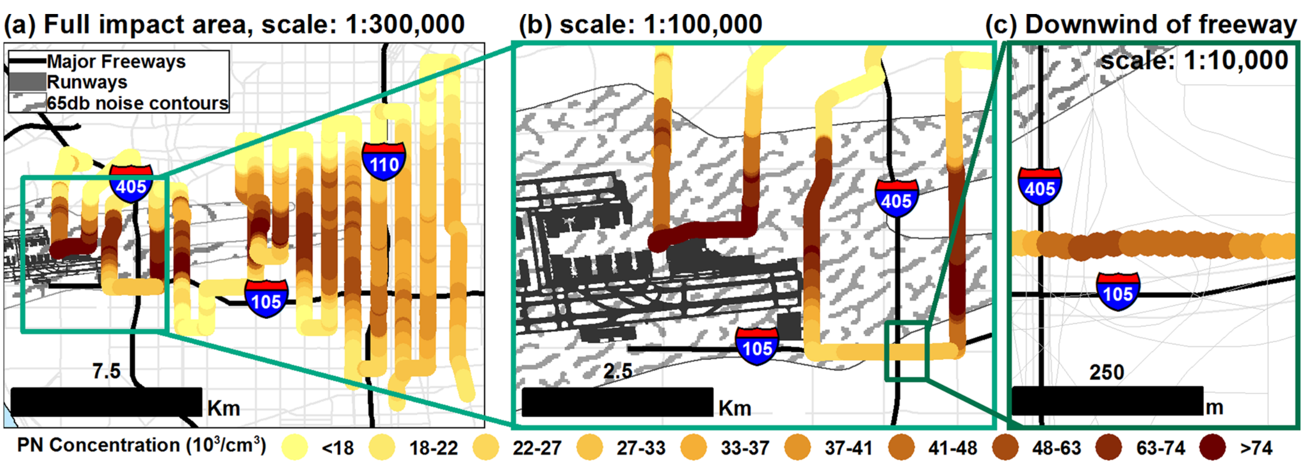


Figure 6. Comparison of the spatial scale of freeway impacts compared to airport impacts for monitoring during nighttime on August 23–24, 2013.

concentrations downwind and east of LAX likely occur in all seasons. Monitoring in different seasons demonstrated the consistent year round presence of this impact. Examples of similarly extensive impacts in non-summer months are shown in the SI (Figures S.8 and S.9).

Other Pollutants. Over large areas downwind of LAX, concentrations of pollutants other than PN were also elevated. Figure 5(a)–(c) show nearly indistinguishable spatial patterns for PN, BC, and NO_2 concentration measured simultaneously at distances of 9.5–12 km from LAX. This suggests a common source for these pollutants, although the BC concentration increases were not large when compared to PN and NO_x, about 0.5–1 $\mu g/m^3$ at 8–10 km downwind. While jet aircraft are not known to produce large amounts of BC, two studies found elevated BC from plane takeoffs at LAX. Zhu et al. 2011[9] measured an increase of about 1 $\mu g/m^3$ of BC due to plane activity 140 m downwind of the runway. Westerdahl et al. 2008[8] measured increases in BC concentration of several $\mu g/m^3$ during takeoff events near the eastern LAX boundary, but also observed elevated BC concentrations at all times. At a smaller airport, Dodson et al. 2009[4] found median contributions of about 0.1 $\mu g/m^3$, about one-quarter of total BC measured at five sites ranging in downwind distance from 0.3–3.7 km, and also observed departures producing about twice the impact as arrivals. Therefore, it appears some jets at LAX are capable of producing measurable increases in BC, particularly at takeoffs.

Spatial patterns of simultaneously measured PN and PAS response (PB–PAH and EC) were also similar on transects 4.5–7.5 km from LAX (Figure 5(d)–(e)). The NO_X elevation pattern was less regular (Figure 5(f)). This was likely due to smaller LAX related contributions compared to baseline concentrations, thus reducing the signal-to-noise ratio.

dx.doi.org/10.1021/es5001566 | Environ. Sci. Technol. 2014, 48, 6628–6635

Overall, the top quartile concentrations (highly impacted) of all pollutants were about three times higher than the lowest quartile within 7.5 km from LAX and two times higher at 12 km distance. In addition, concurrent sampling with the two mobile platforms demonstrated high temporal (SI Figure S.10) and spatial consistency (SI Figure S.11) for PN measurements.

Comparison of LAX and Freeway PN Impacts. PN concentration increases from ground level line sources such as freeways, under conditions of daytime crosswind dilution, decrease exponentially with increasing downwind distance and return to baseline concentrations within 200−300 m.[17] The two N−S freeways (I-405 and I-110 that run perpendicular to the prevailing winds) did not contribute appreciably to elevated PN concentrations in areas where we observed large impacts from LAX on PN concentrations. This is illustrated in Figure 6, which contains two enlargements to show the increase in PN number concentrations over approximately 250 m distance downwind of I-405, a distance and an increase in PN concentration that is not discernible at the scale of Figures 2 and 3. The panel in Figure 6(c) at 1:10 000 scale shows the PN concentration increase of about 24 000/cm^3. The maximum PN concentration was not immediately downwind of the freeway because at this location there is an elevated overpass and some distance is needed for emissions to reach the ground.

To put into further perspective the extent of the elevated PN concentrations observed downwind of LAX, we estimated the freeway length necessary to produce an equivalent impact in terms of PN concentration-weighted area of impact assuming typical daytime dilution conditions for freeways.

For the days we captured the fullest downwind extent of the impact under typical daytime wind conditions (August 15, 23, and 24), we calculated an integrated PN impact above baseline PN concentrations of 2.3, 1.6, and 1.1 × 10^6 (particles/cm^3) × km^2, respectively. See Table S.3(a)−(c) of SI for calculations. Impacted areas were calculated using ArcGIS spatial analysis tools and were conservatively defined as areas where increased PN concentration were at least double the baseline concentrations measured north and south of the impact zone. The resulting impact areas were 30−65 km^2. For comparison, a less conservative criterion for defining the impact area such as a 50% or 33% increase over baseline PN concentrations increased the impacted area by 40% and 80%, respectively.

To calculate PN impacts downwind of freeways, we combined the exponential regression fit of near-freeway measurements made downwind of I-405 by Zhu et al. 2002a[18] with updated average daytime on-freeway PN concentrations taken from Li et al. 2013[14] (71 000 particles/cm^3). PN concentrations were at least double the baseline PN concentrations of 15 000−20 000 particles/cm^3 for 90−130 m downwind.[3] This resulted in a concentration-weighted impact area of 2930−3930 (particles/cm^3) × km^2 per km of freeway length.

Based on these concentration-weighted impact areas, 280−790 km of freeway are needed to produce the equivalent PN-concentration-weighted impact area of LAX. (The less conservative criteria resulted in ranges of freeway length of 340−1000 km and 430−1100 km for thresholds of 50% and 33%, respectively.) There are only about 1500 km of freeways and highways in Los Angeles County.[19] Therefore, LAX should be considered one of the most important sources of PN in Los Angeles. For comparison, within the 60 km^2 area of elevated PN concentrations downwind and east of LAX, the 15−25 km of freeways contributed less than 5% of the PN concentration increase.

Recommendations for Other Studies. LAX is in a region of Los Angeles with highly consistent wind direction. This provided the several hours necessary for a single mobile platform to monitor a sufficient number of transects to cover the large area impacted by LAX emissions. At airport locations where the prevailing wind direction frequently shifts during the day, multiple platforms would be necessary to quickly capture the full spatial extent of emissions impacts to surrounding air quality.

The emissions from LAX are likely not unique on a per-activity basis. The large area of impact from LAX suggests that air pollution studies involving PN, localized roadway impacts, or other sources whose impacts are in the influence zone of a large airport should carefully consider wind conditions and whether measurements are influenced by airport emissions.

Source apportionment of specific airport sources or activities was beyond the scope of our study but would be necessary to evaluate the effectiveness of possible mitigation options. Differing NO_2 to NO_x ratios at different levels of engine thrust[20] might be used to distinguish the contributions of jet landing, idling or takeoff activities. Takeoff and idling emission also differ in surface properties (i.e., the ratio of active surface area to surface bound photoionizable species)[21] and particle size distributions differ between aircraft and ground support equipment emissions.[21]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Map of monitoring area (Figure S.1), the instruments used (Tables S.1−S.2), wind roses (Figures S.2 and S.3), illustration of data processing (Figures S.4−S.7), additional maps illustrating the spatial pattern (Figures S.8 and S.9), concurrent sampling with two mobile measurement platforms (Figures S.10 and S.11) and calculations for comparing freeway impact (Table S.3 (a)−(c)) are presented in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by National Institute of Environmental Health Sciences (NIEHS) Grant 1K25ES019224-01 and 5P30ES007048 to the University of Southern California and by US EPA Grant RD-83479601-0. This publication's contents are solely the responsibility of the grantee and do not necessarily represent the official views of NIEHS or US EPA. Further, NIEHS and U.S. EPA do not endorse the purchase of any commercial products or services mentioned in the publication. We thank Andrea Hricko of USC for helpful comments.

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Interim Manifesto

Policies for the People

UK Independence Party
September 2018

Contents

Introduction

Under my leadership I want UKIP to be a **'populist party'** in the real sense of the word – a party whose policies are popular with the voters. In recent times the word populist has been turned into a derogatory term. This is because the political and media establishments across the western world stand for and promote so much that is deeply unpopular with their own peoples. These unpopular policies include: government from Brussels by the EU, open-border uncontrolled immigration, and imposing an alien politically correct cultural agenda on their peoples.

This Interim Manifesto cannot possibly include every policy area or every detail, it represents a summary of where UKIP is now. It is a dynamic document, and policies will be developed further in the future.

UKIP is always at its best when it's at its most radical. It is strongest when it is bold and leading the political agenda. We have done this on numerous occasions in the past. UKIP set the agenda on leaving the European Union, on introducing a limited and controlled immigration system, and opposing Islamic literalist and fundamentalist extremism. UKIP will set the agenda on going forward into a post-Brexit world. UKIP remains the only party willing to discuss the issues of real importance to most people. **UKIP is the only real opposition.**

UKIP will promote and defend our national and individual freedoms. We stand for freedom from the European Union and the right to live once again under our own traditional freedoms and liberties, together with the right once again to be proud of our great country. We are determined to protect our freedom of speech and the right to speak our minds without fear of the politically correct thought-police knocking on our doors.

UKIP has stuck to its principles year in, year out, in the sure knowledge that the solutions we offer are sound. We believe in Britain and we make no apologies to anyone for doing so. We say what we mean and we mean what we say. We ask you to support and join UKIP and to vote for us in local or Parliamentary elections whenever you have the chance. We need your support, and our country needs UKIP.

[redacted]

Gerard Batten MEP

UKIP Leader.

1. Brexit

UKIP stands for a complete and total withdrawal from the European Union. UKIP was the only party to publish a Brexit plan, entitled, ***'Brexit Must Mean Exit. Taking Control. The UKIP Plan for Leaving the European Union'*** (July 2017). This is available to read or download from the UKIP website, www.ukip.org

- In short, UKIP stands for: no more money to be paid to the EU, no more EU laws imposed upon us, no more jurisdiction over us by the European Court and no more open-border EU immigration.
- Irrespective of whatever 'Withdrawal Agreement' HM Government agrees with the EU, UKIP will continue to fight for the UK's total independence from the EU, and to fully restore the UK's former status as an independent, self-governing, sovereign state.
- A clean exit from the EU will include withdrawing post-Brexit from PESCO (Permanent Structure Cooperation), the EU's 'Defence Union', or nascent Army, which the Government agreed to prior to Brexit.
- Britain's international standing will be enhanced by leaving the EU as it will be able to act independently, whilst retaining its membership of the UN Security Council, the World Trade Organisation, the Five Eyes intelligence alliance, and over 100 other international organisations of which we are a member.
- **Outside the European Union Britain will be a more prosperous nation. It will regain control of its trade policy, free business from unnecessary regulation, regain control of its agricultural industry and restore its fishing industry. Increased prosperity will mean more jobs, and more tax revenue to pay for the things we all want for the British people.**

2. NHS Policy in England

UKIP believes in an NHS free at the point of delivery. The NHS is in crisis, not just from a lack of adequate funding but because of the inefficient use of funds, Private Finance Initiative (PFI) contract liabilities, and ever-increasing demand from foreign nationals who should have no entitlement to use its services free of charge.

- The current Purchaser/Provider purchasing system should be replaced wherever possible by more centralised purchasing systems designed to capitalise on cost savings.
- The NHS is a national health service and not an international health service. The NHS is open to widespread abuse by non-UK citizens. We will end 'health tourism' by foreign nationals. An **NHS Health Card** will entitle British citizens to use the NHS, whilst foreign visitors, unless specifically provided for by reciprocal agreements, will be required to have private health insurance.
- EU open borders have created a major drain on resources by bringing in around **3.8 million** additional people. Many of these people will have no history of contributing significant tax revenue to help pay for the NHS but have the same entitlement as British citizens. When Britain leaves the EU, this entitlement must not be extended to any new arrivals from the EU (unless national reciprocal agreements are negotiated with individual nations).

- The **PFI** scandal (introduced by the Tories and expanded by Labour), is draining much needed funds out of our NHS. PFI contracts financed £11.8 billion to build hospitals in England but will cost £71 billion to pay back over 31 years. **UKIP will terminate these contracts by Act of Parliament where possible.**

- American style litigation is out of control, with an estimated £78 billion worth of claims in the system with the potential to destroy the NHS.[1] UKIP would adopt the 'no automatic lump sum' compensation policy and only pay for criminal negligence, similar to the Australian system. Where applicable, support payments should be paid monthly.

- We will address the shortage of GPs, nurses and midwives by waiving tuition fees in exchange for a minimum five-year period to be worked in the NHS. This would dramatically increase the number of training places for British doctors, nurses and paramedics. British nursing applicants are being rejected because it is cheaper to recruit already qualified foreign applicants, and in some cases thereby lowering acceptable standards. We will prioritise training our own NHS workers, rather than relying on recruiting medical staff from abroad.

- UKIP will scrap hospital car parking charges wherever possible (as is currently being done in Wales); these are a tax on patients and visitors.

3. Social Care and Mental Health in England

There is an increasing proportion of older people in the population whose care issues are not being addressed.

- UKIP will increase social care funding by **£2bn** per annum to pay for additional residential, nursing and home care services.

- An increasing number of younger people are suffering from mental health issues and this needs to be addressed. We will introduce practical policies to improve the delivery of mental health services and increase mental health funding by **£500m** per annum.

4. Welfare and Disability Policy in England

UKIP is committed to maintaining a strong and robust supportive safety net for those in genuine need, but which will not be a soft-touch on welfare.

- UKIP will end the unfair ATOS-style work capability assessments and replace it with a system using qualified medical practitioners.

- UKIP is committed to protecting the rights of disabled people and we support their inclusion in the workplace whenever that is possible.

- UKIP would scrap the bedroom tax – which adversely affects many disabled people.

- UKIP will stop child benefit being paid for non-UK resident children of foreign citizens.

- UKIP would not pay benefits to foreign nationals resident in the UK until they have paid tax for 5 years.

1 Estimated by Angus Dalgleish FRCP, FRCPath, FMedSci, Professor of Oncology, St George's, University of London.

5. Immigration

Mass uncontrolled immigration has been extremely damaging to Britain. We have imported cheap labour by the million. This not only exploits migrants but depresses the wages and living standards of those at the bottom end of the economic scale, and drives up property prices and rental costs. In 1997 the official British population figure was **58 million** people. The figure in 2017 was **66 million**. A recent report showed that the **6.6 million** population growth between 2000-2016 was **80%** due to migrants and births to migrants [2]. Such a rate of increase is simply unsustainable in one of the most densely populated countries in the world.

- UKIP believes that the age of uncontrolled mass-immigration must come to an end. We have open borders with the EU but successive British governments have also failed to control immigration from outside of the EU. UKIP will introduce a selective and limited Australian style points-based immigration system. Immigration for permanent settlement must be strictly limited.
- Temporary immigration for workers on work permits and students will be both strictly controlled and time-limited.
- UKIP will develop the UK Border Force into a **Migration Control Department** directly responsible to a Minister. This department will oversee the immigration system and border control.
- Migrants will not be able to claim public housing or benefits until they have been a tax paying resident in UK for a continuous five years.
- Workers on permits and students will be expected to possess private health insurance as a condition of entry to the UK (unless covered by a reciprocal medical treatment agreement).
- UKIP will rescind the UK's assent to the **Barcelona Declaration** (1995) and the **Marrakesh Declaration** (2018). Both of these documents pave the way for yet more uncontrolled and unlimited immigration from Africa, the Middle East and beyond.

6. Housing

The UK does not have a housing problem - it has a demand problem, with demand being fuelled by mass uncontrolled immigration. Supply of housing simply cannot keep up with demand. We cannot stabilise the housing problem until we have controlled immigration.

- One of the most significant problems has been that immigrants from the European Union have enjoyed access to social housing on the same basis as British citizens. Post Brexit, UKIP would end this.
- Overseas investors now purchase approximately **60%** of residential new-build properties in central London, and around **30%** overall,[3] thereby driving up property prices. These properties are often left vacant. UKIP will introduce a **five-year** residency qualification for any non-UK citizen buyer of residential property in designated areas in England. Rich foreigners will try to find loopholes no doubt, and government will have to try and close them.

2 Migration Watch UK. Impact of Migration on UK Population Growth. MW 452. August 2018.

3 The role of overseas investors in the London new-build residential market. Final Report for Homes for London. Keith Scanlon, Christine Whitehead and Fanny Blanc with Ulises Moreno-Tabarez. London School of Economics May 2017.

- It should be possible to build **one million** new houses on brownfield sites. We will offer grants to bring this land into use.
- We will increase the supply of housing by identifying long-term dormant land held by central and local government that can be released.
- To ease the immediate problem, we will encourage the building of modular housing, made by British companies, which is inexpensive to build and highly energy efficient.
- UKIP will abolish Stamp Duty (see section 21. Taxation) thereby saving house buyers £16.2bn per annum.[4]

7. Education and Training

- It is a matter of great concern that the state education system is turning out a large number of children who are functionally innumerate and illiterate.
- Teachers must be able to concentrate on what's important by cutting down on bureaucratic assessments and appraisals. Education needs to re-focus on teaching children the basics.
- UKIP will encourage the establishment of new grammar schools, which are a proven path to social mobility for working class children.
- UKIP will push for a range of different types of school, including grammar schools, technical, vocational, general and specialist secondary schools within a geographical area. This will make our secondary school system more responsive to the differing aptitudes, capabilities and speed of development of our children.
- We will waive tuition fees for further and higher education in subjects vital to our national life: science, technology, engineering, mathematics and medicine subjects (STEMM) at university, dependent on graduates working in the UK for five years.
- UKIP will support real trade apprenticeships and apprentice degree courses.
- UKIP will drop the artificial target of 50% of people going to higher education.
- UKIP opposes gender confusion ideologies and the implementation of compulsory LGBT-inclusive relationships education in primary schools, due to be introduced from September 2019.

8. Transport

Britain is a nation of commuters, for work and for pleasure. Whether our journeys take us on the daily commute to work, on a cross country commercial delivery haul, or the school run, everyone needs a comprehensive and reliable transport network.

- UKIP will scrap HS2. At an estimated cost of **£100bn** this vanity project is not affordable [5]. HS2 will

4 Office for National Statistics April 2018

5 Estimated by the Institute of Economic Affairs.

destroy people's lives and will have a huge environmental impact. UKIP will invest in the existing railways to improve capacity and journey times.

- The problem of failing rail operators could be solved by taking control by means of a new government owned company to run the franchises. All options would be considered.
- UKIP opposed the expansion of Heathrow Airport. UKIP will encourage investment in regional airports. The current Heathrow plan will destroy many villages and listed buildings as well as add to pollution in the locality.
- UKIP will scrap all road tolls. Tolling increases costs to business and the public. Road users are already overtaxed and should not be paying twice to use our roads. We will also block any introduction of pay-as-you-go road pricing.
- UKIP will abandon the current rollout of smart motorways and instead divert the funding to road maintenance with a priority for fixing potholes. Smart motorways are perceived by the public as being money-making scams, and removing the hard shoulder is dangerous.
- UKIP will stop diesel drivers from being penalised through discriminatory parking fees or zone charging. Modern diesels are far cleaner today and many people bought their vehicles in good faith on Government advice.
- UKIP supports the transition to electric vehicles, but the electric charging infrastructure is not keeping pace. We will support the installation of charging stations by diverting funds from the electric car subsidy. We will also encourage off-street parking and charging provision in all new housing and industrial developments through the local planning process.
- UKIP supports the development of driverless car technology.
- UKIP will scrap the EU derived law for the **Certificate of Professional Competence** (CPC) which has been severely damaging to the UK haulage industry. This unnecessary qualification has led to a shortage of HGV drivers in the UK.

9. Foreign Affairs and Overseas Aid

Post Brexit, Britain's foreign policy no longer needs be linked to the EU's Common Security and Defence Policy, which would inevitably involve us in the EU's planned armed forces and embroil us in its foreign policy ambitions. We should put the needs of our own citizens first. Our foreign aid budget is often wasted on corrupt regimes, or given to countries that can afford their own atomic weapon and space programmes.

- Under former Labour and Conservative governments, we have been engaged in wars that have not brought peace, but instead have made the world a more dangerous place. Britain's foreign policy should be strictly framed from the view-point of what is in the UK's national interest. We should not allow ourselves to be swept into war on someone else's coat tails.
- David Cameron committed the UK to **0.7%** (currently £14bn) of GNI (Gross National Income) to Overseas Aid. This is a purely artificial construct and much of this money goes to corrupt governments and is lost in fraud. The Department for International Development (DfID) spends and wastes money, purely to meet its artificial target.

- UKIP will scrap the target of 0.7% GNI for Overseas Aid and return £14 billion to HM Treasury to assist our own citizens in our own country.
- UKIP supports government providing genuine disaster relief and humanitarian aid, as appropriate. UKIP would return to the old system in which DfID was a small directorate of the Foreign Office responsible for disaster relief on an 'as and when' basis.
- UKIP supports existing systems whereby citizens can donate to foreign aid charities and receive tax relief.

10. Defence and Security

UKIP believes that we should not get involved in international conflicts unless it can be clearly shown to be in the national interest.

- UKIP is committed to **NATO** for our collective defence. UKIP expects all NATO members to honour their commitment to contribute a minimum of 2% GDP.
- UKIP will withdraw the UK from the EU's attempts to create its own armed forces, e.g. through **PESCO** (Permanent Structured Cooperation), already committed to by the Conservative Government prior to Brexit, and from Mrs May's proposed new EU Security Treaty.
- Britain's Royal Navy, Army and Royal Air Force have been so reduced in size that they struggle to meet their commitments. UKIP is committed to adequately funding Britain's armed forces.
- UKIP will initiate a defence review to consider our future defence requirements and the size and shape of our armed forces. UK manufacturers should get first call on providing our armed forces equipment.
- UKIP is committed to maintaining the Trident nuclear deterrent.

11. Veterans' Issues

Whenever HM Government calls on our brave armed forces to go into action on our behalf they never let us down. UKIP will not let them down, we will honour the military covenant.

- UKIP will establish a **Veterans' Administration Department**, headed by a government minister, organisationally independent and financially separate from the Ministry of Defence. This Ministry will promote and protect the interests of veterans in a variety of fields: for example, housing, health care, education and training.
- We will bring forward legislation to prevent veterans from being pursued by police and prosecutors many years after the event, for actions they undertook in good faith whilst they were in the service of the Crown.
- We would seek to guarantee a job offer with the police, prison service or the UK Border Force, or emergency services, for anyone who has successfully served in the Armed Forces for a minimum of twelve years. Veterans would be prime candidates for jobs in the new **Migration Control Department** designed to control immigration (see section 5).

- Skills gained in the Armed Forces can be useful when running a small business. We will create a 'Boots to Business' scheme to channel loans, grants and access to free professional advice and mentors, to veterans who wish to set up and run their own businesses after leaving the forces.

12. Police and Criminal Justice

The last Royal Commission into policing took place in 1962. Now is the time to conduct a root and branch review of policing, with a Royal Commission, which will establish what is required to ensure that the police deliver a service to the public that is fit for purpose, both now and in the future.

- The police should be adequately funded and paid. The entire police budget for 2018/19 at £7.3bn is half the Overseas Aid budget. The first priority of HM Government should be the protection of its own citizens.
- In 2013, David Cameron's Coalition Government introduced direct entry to the senior ranks of policing, thus ending 180 years of tradition which holds that all recruits to the police start their careers as constables. UKIP will reverse this decision.
- The Crown Prosecution Service has consistently shown itself to be unfit for purpose. UKIP will abolish the CPS and return prosecutorial powers to police forces and their own prosecution lawyers.
- UKIP will scrap the Crown Prosecution Service's guidelines on 'hate crime', which are purely subjective. Victims of crime should all be treated equally, irrespective of the motives of the criminal.
- UKIP will repeal all of the EU-inspired legislation that binds us to EU legal institutions and EU legal instruments, e.g. the **European Arrest Warrant**, and replace them with the pre-existing agreements on mutual co-operation, or new treaties that protect the fundamental rights of UK citizens under our laws. Likewise, UKIP would **repeal the USA Extradition Treaty** and negotiate a new treaty that protects the rights of our citizens under our laws.
- Police forces must be required to investigate real crimes against the person and property as a priority and not social media 'hate speech' accusations. London's Metropolitan Police reportedly has **900** plus officers dedicated to investigating 'hate-crime' while the city endures a stabbing and acid attack epidemic.
- We will ensure that the police and relevant bodies take a zero-tolerance approach to unacceptable 'cultural' practices such as female genital mutilation (FGM).

13. The Prison Service

Our prison service is in disarray and close to meltdown. It is under-funded, under-resourced, privatised to make profits for private companies, and in some instances the prisoners are taking control of the prisons. Around **11%** of the prison population are foreign nationals – over 9,000. [6]

- Currently, most prisoners usually serve only half of their sentence. Prison sentences should mean what they say, with **10%** off for good behaviour subject to the discretion of prison governors and independent review.

6 House of Common Library, UK Prison Population Statistics, Ref CBP-04334. July 2018.

- The prison service should be adequately funded and prison officers adequately paid. UKIP opposes the privatisation of the prison system and will reverse the process. All prisoners should be in the custody of officers of the Crown answerable to Ministers and not private companies.

- UKIP would seek to deport foreign criminals, and where possible to have agreements with foreign states whereby we pay them so that their citizens can serve their sentences in their own countries. It would be cheaper, and might also act as something of a deterrent. Such criminals would be have a life-time ban on re-entry to the UK.

- UKIP would build new prisons as necessary to accommodate the number of persons convicted of imprisonable crimes.

14. Agriculture

Post Brexit, the UK will be free of the costs and impositions of the Common Agricultural Policy. We will move from a system which subsidises large landowners to one that supports food producers, environmental protection and food safety.

- Leaving the EU will enable UK to design a tailor-made agricultural policy, rather than a one-size fits all scheme, designed to benefit continental farmers.

- Offer a wide range of grants with tackling anti-microbial resistance as a major priority.

- UKIP would introduce a Modern Food Act to ensure traceability and origins of raw materials.

- Create a National Agricultural Council to ensure 'joined-up thinking' between different Government Departments for food, farming and environmental matters.

- We will re-establish the Agricultural Wages Board for England, which would protect the incomes and conditions of farm workers.

- Legislate for food labelling to show country of origin, method of production, transport and slaughter.

15. Fisheries

UKIP wants total withdrawal from the EU's Common Fisheries Policy without the need for a transition period when we leave the EU.

- Post Brexit UKIP will take control of the UK's full 200-mile Exclusive Economic Zone (EEZ), as is our entitlement under international law; allowing us to rebuild our fishing industry, its ancillary industries, and our coastal towns.

- UKIP wants a complete overhaul of our fisheries systems for a fairer allocation of post-Brexit fishing opportunities, with priority given to the low-impact, small-scale fishers.

- UKIP will end the discard system, with no fish going to waste.

- UKIP wants investment in British ports and fishing infrastructure, and to amend the Maritime Shipping Act with a view to limiting the exploitation of UK fishing waters by foreign vessels. These changes will provide opportunities for British business and career opportunities for British citizens.

16. Economy and Trade

Britain's trade policy has been under the control of the European Union since we joined in 1973. Our businesses have been obliged to obey EU legislation, even when they do not export to the EU. Leaving the EU will free Britain to pursue its own trade and commercial policies, which offer enormous opportunity for increased trade and employment.

- Post Brexit, Britain will regain its independent seat on the World Trade Organisation and we will be free to decide our own trade policy and negotiate trade agreements, where appropriate, with other countries.
- Approximately **10%** to **12%** of the UK economy is concerned with exporting to the countries of the European Union, whereas **100%** of businesses have to abide by EU laws. Outside the EU, a British government can reduce regulation to an appropriate level, which will aid economic growth, prosperity and employment.
- Brexit will allow the UK to strengthen its economic ties with our historical friends and allies in the Commonwealth. This could include a **Commonwealth Free Trade Agreement**.
- UKIP would seek to minimise the use of Zero Hour Contracts except where they are to the mutual benefit of employee and employer, and to ensure that everyone can earn a living wage.

17. Industry

Britain's manufacturing has been in steady decline for many years. We now have a massive and growing trade deficit in goods with the EU. In the 25 years of membership of the EU Single Market the UK's deficit **in goods** with the EU has grown remorselessly from £5 billion in **1992** to £96 billion p.a. in **2016**. The deficit with the whole world totalled £134 billion (2016) or **6.5%** of GDP. [7]

- Halving this deficit should be a 10-year priority in a 20-year programme of manufacturing expansion worth £90 billion of increased added value, costing around £50 billion of repayable public loans, paid for by cancelling HS2.
- On average UK manufacturing supplies only **12%** of the UK market. This level of manufacturing capacity is dangerous for both economic stability and national security.
- Our national strategy has therefore to be to increase the range of UK products, with particular emphasis on Sustainable Design principles, namely the three Rs: reuse, repair, recycle.
- There are also pressing needs for new capital goods industries including: ship-building for a **post-Brexit fishing fleet and coastal protection vessels**, and for a new generation of factory-built modular homes.
- Two new forms of manufacturing organisation will be needed to achieve these goals for virtually all product sectors with both public and private investment: (1) Existing companies prepared to expand and collaborate in consortia with specially recruited design and marketing staff; (2) New grant-aided companies set up on the co-ownership principle.

7 This section is provided courtesy of Professor Stephen Bush, as published in his paper 'Produce & Prosper'. Stephen is Emeritus Professor of Process Manufacture and Polymer Engineering at Manchester University.

18. Energy

The UK needs a mix of energy sources comprising nuclear, conventional and renewable. Brexit will allow the UK to set its own future energy policy, with lower prices and more secure supplies.

- Outside the European Union UKIP will remove the **5% VAT** levy on domestic fuel.
- UKIP will scrap the **Climate Change Act** (2008), which requires the UK to achieve annual decarbonisation rates of more than **5%** - a figure no other country in the world has ever, or is ever likely, to attain. The total cost of this wildly unrealistic legislation has been calculated at an eye-watering £720 billion, over a period of 40 years.
- UKIP will end subsidies for wind turbines and solar voltaic arrays. We will support renewable energy where it can deliver electricity at competitive prices.
- UKIP would seek to rejuvenate the UK's coal industry, wherever that is possible.

19. Environment

We should separate the dogma of anthropogenic (man-made) climate change from environmentalism - care for and protection of the environment.

- Post Brexit, UKIP would re-establish the successful local drainage supervisory boards run by those most affected by flooding. Farmers and riparian[8] landowners must be allowed to undertake the necessary work on their land to prevent flooding without penalties.
- The Green Belt must be protected in order to preserve our quality of life. The most significant threat to the Green Belt, and the UK environment in general, especially in England, is unsustainable population growth, which is predominantly fuelled by mass uncontrolled immigration.
- UKIP seeks to develop policies that address excessive packaging and the use of plastics where they are detrimental to the environment. For example, the 5p cost of plastic bags is just another money-making racket. UKIP would legislate to bring about the use of biodegradable carrier bags and packaging.

20. Small Businesses

Britain's **5.7 million** small and medium sized businesses make up around **50%** of the jobs in the UK. They are the lifeblood and the backbone of the British economy. Many a young person's first job is with a small or medium sized business.

- It is vital that they have a trading environment that makes it easier for entrepreneurs to start businesses, to recruit staff, to attract investment, and to have fair access to UK Government markets.
- UKIP will ensure that HMRC thoroughly investigates big business or public-sector bodies that repeatedly make late payment to smaller customers, and we would create an anonymous reporting system. Fines proportionate to the amount of delayed payments will be levied. And will escalate for repeat offenders.

8 Land next to riverbanks.

- UKIP will improve access to trade credit insurance especially as it relates to exports, to remove the drag on growth for businesses struggling to secure loans and give small traders the confidence to expand their businesses.
- We will encourage local trade by pushing local authorities in the country to offer at least 30 minutes free parking in town centres and shopping parades.
- We will also freeze **Insurance Premium Tax**. Previous governments have raised this tax as an easy way to generate extra revenue, yet it cannot be claimed back by businesses, so increases have been especially tough on smaller traders.

21. Taxation

UKIP believes in allowing people to keep as much of their own income and wealth to spend according to their own needs and priorities.

- UKIP will raise the personal tax allowance to £13,000. This will help those on low earnings.
- UKIP will legislate to change the **BBC TV licence** from a tax to a voluntary subscription. The licence fee currently costs the holders £3.7 billion per annum. The licence fee is an outdated, regressive tax, which unjustly criminalises those who don't wish to watch the BBC, particularly the poor. The **BBC World Service** could be retained under Government control.
- **Channel 4** is a publicly owned entity under the control of the Department of Digital, Culture, Media & Sport. Although funded by advertising, any potential liabilities fall to the taxpayer. **UKIP would sell it off on the commercial market.**
- **UKIP will abolish inheritance tax** (currently £5.2bn per annum).[9] Assets purchased out of taxed income should not be taxed again when their owners die. UKIP will kill this 'death tax'. It hits the middle classes hardest, those who have worked to provide for their dependants, because the wealthiest can often manage to avoid paying it.
- UKIP will abolish **Stamp Duty**. This is a tax on people moving house, which very often affects people struggling to accommodate a growing family, and currently costs house buyers £16.2bn per annum.[10]
- We will ensure that all businesses and multi-national corporations pay the appropriate taxes to HM Treasury. Post Brexit, these companies will not be able to take advantage of EU tax avoidance schemes.
- Once outside the EU, the UK will have control over VAT. UKIP will take the opportunity to zero-rate certain goods, such as domestic fuel, sanitary products and repairs to commercial, residential buildings and historic and listed buildings.
- Council tax as it currently stands is outdated and needs to undergo a full and thorough review.

9 Office for National Statistics figures for 2017-2018. Published July 2018.
10 Office for National Statistics April 2018

22. Children and Families

Stable, active and intact two-parent families are the bedrock of a robust society, whereas broken families are much more likely to be dependent on the state, have poorer physical and mental health and contribute less to wider society.

- Family breakdowns may occur for a variety of reasons, but whatever the reasons the cost to the taxpayer of family breakdown is estimated to cost some £50 billion a year. UKIP policy is to use the taxation and benefits system to help families without disadvantaging others.
- UKIP opposes the disempowerment of parents by the state, whereby its institutions are increasingly dictating the norms and values children learn and supplanting the role of parents. For example, the education system is being used more as a means of indoctrination than education.
- We will introduce further safeguards into the operation of the Family Courts to ensure that injustices are not perpetrated on parents.

23. Sexual Exploitation & Paedophile Gangs

The systematic and industrialised sexual abuse of under-age and vulnerable young people is one of the greatest social scandals in English history. A scandal not just because it happened but because the responsible authorities swept it under the carpet for decades.

- It is now accepted that one of the key factors that drove the cover up of this phenomenon was adherence by the authorities to political correctness and the fear of identifying the vast majority of the perpetrators as Muslims.
- An independent national enquiry into local authorities and police forces' historical failure to protect children from rape gangs should be set up in order to bring them to account. Where found to be in dereliction of duty those responsible should be prosecuted and or sacked, as applicable.
- UK laws to protect children must be implemented fully and impartially, irrespective of the culture, ethnicity or religious beliefs of the perpetrators. There are issues to be addressed, such as the failure to prosecute cases of female genital mutilation and forced marriages.

24. Animal Welfare

Animal welfare standards in the UK are some of the highest in the world. Much of the current EU legislation relating to welfare for pets, farm animals, wild animals, and animals used in research, has been drawn from the UK. When we leave the EU, we will be able to take back control of animal health and welfare legislation, and to update and improve our laws to ensure that animals in the UK have the most robust protections.

- When we have left the EU, we will be able to end the export of live animals for slaughter – an inhumane practice made possible by EU legislation.[11] **UKIP would end the export of live animals for slaughter.**

11 Exemptions would be the export of live animals from Northern Ireland across the border to the Republic of Ireland, or for racehorses internationally, or rare animals for breeding etc.

- The general population is already consuming ritually slaughtered, non-stunned meat unknowingly and by default because its use is now commonplace in schools, restaurants, works canteens etc. Killing animals without first rendering them unconscious causes unnecessary suffering. The percentage of non-stunned meat is at least **25%** of the total, if not more.[12]
- Current UK law states all animals must be stunned prior to slaughter – unless it is for a religious purpose. **UKIP will repeal the law allowing exemptions for ritual non-stun slaughter**. This is an animal welfare issue and we should all abide by the same laws. Legislation banning non-stunned slaughter already exists in some European countries, for example, Germany, Norway, Sweden and Switzerland.[13]
- Those wishing to eat non-stunned slaughtered meat can continue to do so as World Trade Organisation rules allow the importation of such meat; but UKIP would require this meat to be clearly labelled, so that consumers may make an informed choice.

25. Islamic Extremism

The worst excesses of a literalist interpretation of Islamic doctrine has seen unprecedented acts of terrorism in Britain and across the world. This can only be countered with practical measures.

- UKIP will legislate to ban the overseas funding of mosques and imams. A large proportion of UK mosques are funded from countries such as Qatar, Saudi Arabia and Pakistan, who export their extremist ideology to the UK.
- UKIP will end mass uncontrolled immigration, and under a security-based screening policy we restrict any limited migration from Islamic countries to those people we can be sure, as far as possible, do not follow a literalist and extremist interpretation of Islam.
- Islamic extremism is actively fostered in HM Prisons at state expense. Islamic gangs hold sway in some prisons and non-Islamic prisoners are converting for their own protection. UKIP would introduce the separation of prisoners or prisons exclusively for Islamic prisoners who promote extremism or try to convert non-Islamic prisoners.
- UKIP would repeal the legislation that gives legal recognition for Sharia law courts.
- Islamic extremism is an on-going problem that will take generations to resolve, and effective policy ideas will have to be developed whoever is in power.

26. Constitutional and Political Reform

Constitutional and political reform is a pressing issue if we are to restore faith in our democratic system. Under the first-past-the-post voting system MPs are usually elected on a minority of the votes cast. Most votes don't elect anyone. In the General Election of 2015 UKIP achieved **3.8 million** or **12.6%** of the vote. This was exactly the same percentage as the combined vote of the Liberal Democrat and the Scottish

12 The Barbarity of Ritual Slaughter of Animals in the European Union. Gerard Batten MEP. Page 7. Jan 2018

13 Such a ban is supported by such animal welfare bodies as the RSPCA and the Royal College of Veterinary Surgeons, as well as Governments Farm Animal Welfare Committee.

Nationalists, and yet they won **62** seats compared to UKIP's **single** seat.[14] The Electoral Reform Society calculated that under one of the proportional voting systems available UKIP would have won between **54** to **80** seats in the 2015 election.[15] Meanwhile, the unelected and appointed members of the House of Lords represent no one but themselves.

- UKIP would convene an all-party constitutional convention, charged with addressing the many anomalies in our political system that need to be corrected if we are to be a modern democracy. The convention will report and table legislation within the life of a parliament.
- The first-past-the-post local and parliamentary voting system is not fair and does not deliver what the voters vote for. Many local authorities are effectively 'one-party states', e.g. the **London Borough of Newham** which currently has **100%** Labour councillors. Most Members of Parliament are elected on a minority of the vote in their constituencies.
- Mrs Thatcher in 1979 achieved only **44%** of the vote, and likewise, Tony Blair introduced the most far-reaching legislation on **43%** or less of the vote.
- UKIP wants to see a **Proportional Voting** system introduced for local and parliamentary elections that would deliver results in accordance with how the voters voted. A number of options for how this could be done are available for discussion.
- The **House of Lords** is now an affront to democracy. It consists largely of political appointees who represent no-one but themselves. UKIP favour a Second Chamber elected on some form of proportional representation.
- We will end postal voting fraud by restricting postal votes to those with a valid reason for needing one. We will reinstate the system that operated prior to the Labour government's changes.

27. English Identity and Issues

The UK population in 2017 was estimated by the Office for National Statistics at **66m.** England makes up the vast majority of the population at **55.6m** (84.2%), with Scotland at **5.4m** (8.2%), Wales at **3.1m** (4.7%), and Northern Ireland at **1.8m** (2.8%). Although England is the largest constituent part of the UK, with the largest population, English identity has been all but airbrushed out of our national life.

- In a recent lecture for the BBC former Labour MP **Professor John Denham** referred to a survey on British and English identity and to the emergence of a minority who are antipathetic to the English. This segment amounted to only **7%** of the sample, but this anti-English minority is over represented in the institutions of government, politics, the leadership of the public sector, the media, corporate capitalism and academia. Exactly the kind of people prominent in the Remain campaign.
- The English taxpayer meanwhile subsidises the other constituent parts of the United Kingdom, with a higher per head tax spend in Scotland, Wales and Northern Ireland than in England.
- While the Scots, Welsh and Northern Irish are rightly proud of their national identities the English are deemed not to exist. UKIP asserts that English identity is something to be proud of, and anyone who

14 In the 2015 General Election UKIP received 3,881,129 votes compared to the combined Scot Nat and Lib-Dem vote of 3,870,324. UKIP received the same percentage vote but 10,805 more votes.

15 The Electoral Reform Society. The 2015 General Election, A Voting System in Crisis.

wishes to embrace that identity should do so, whatever their ethnic origins may be. English identity resides in the heart and mind not on the skin.

- **To redress this democratic imbalance UKIP would reform the Westminster Parliament to adopt a system whereby only MPs representing English constituencies would vote on laws exclusively affecting England.**
- The funding of the other constituent parts of the United Kingdom needs to be reviewed so that it is fair for all taxpayers, particularly with regard to the Barnett Formula for Scotland.

28. Free Speech and Political Correctness

UKIP believes in allowing our people their traditional rights of freedom of conscience, liberty and speech. These rights have been eroded over recent decades by the burgeoning concepts of so-called 'hate speech', driven by the political doctrine of Cultural Marxism, which seeks to close down discussion and alternative views, so that only one extreme left-wing 'politically correct' viewpoint is allowed.

- UKIP will repeal hate speech guidelines because pre-existing laws are more than adequate to deal with 'insulting or threatening behaviour' or 'behaviour likely to cause a breach of the peace', etc.
- UKIP will repeal the **Public Space Protection Orders** (PSPOs) introduced in 2014 which have been abused by local authorities to curtail lawful protest and criminalise speech.
- UKIP will repeal the **Equality Act 2010** which gives special rights and privileges to certain groups with 'protected characteristics' and revert to pre-existing equality laws. For example, it allowed the BBC to advertise BAME (Black Asian Minority Ethnic) only internships and training schemes – thereby discriminating against white youngsters. Our people should be treated equally under the same laws.
- UKIP will shut down the **Equalities and Human Rights Commission** (£20 million pa)[16] and the **Government Equalities Office (£47 million pa)**[17] and end their politically correct social engineering of society - with the added benefit of saving about £67 million per annum.

29. Cost Savings

The national debt currently stands at **£1.78 trillion** or 86.58% of GDP. The annual cost of servicing this debt (paying interest) is currently around **£39.4 billion** per annum, approx. **£108m** per day.[18] Every area of spending should be scrutinised. UKIP believes in small government and low taxation, and unnecessary spending must be cut to help pay for those services we need.

Some of the policies itemised above will save money, some will cost money. UKIP does not intend to raise taxes but wants to reduce taxation wherever possible. Therefore, where expenditure is indicated above we would look to save money in other areas to pay for it.

16 https://www.equalityhumanrights.com/sites/default/files/annual-report-and-accounts-2017-2018.pdf
17 https://en.wikipedia.org/wiki/Government_Equalities_Office
18 Office for National Statistics, Public Sector Finances.

- Leaving the European Union will save about **£13.9 billion** per annum (if we stay in the EU the cost of membership will rise)**.** The ONS figures for 2016 show that we paid **£18.9 billion** gross, less the £5 billion rebate which equals **£13.9 billion** – this however includes **Public Sector Receipts** (our money spent in the UK by the EU) of **£4.4 billion**. Less the PSR, and rounded down, this leaves an absolute minimum saving of **£9.4 billion** per annum.

- Abolishing the Department for International Development (DfID) and the Overseas Aid Budget would save the taxpayer in the region of **£14 billion** per annum.

- The **Tax Payers' Alliance** think tank calculated in 2017 that there are **1,148 Quangos** (Quasi Autonomous Non-Governmental Organisations) costing the taxpayer **£90 billion** per year. The Tory/ Lib-Dem Coalition Government of 2010-2015 promised a 'bonfire of the quangos' but only managed to abolish 192 and merge another 118. UKIP will conduct a comprehensive audit of quangos leading to abolition wherever possible. An estimated 400 of these (35% of the total) could be disbanded. If this achieved only a **25%** reduction in overall expenditure this would save **£22.5 billion**.

- On the basis of the previous three bullet points alone a minimum potential saving of **£46 billion** could be made.

- In addition to the savings above there is enormous scope for cutting government expenditure (and therefore borrowing). For example, abolishing HS2 would save an estimated cost of **£100 billion** - £2.3 billion has already been spent without a yard of track being laid.

- Scrapping the **Department for Digital, Culture, Media & Sport** offers potential savings of **£6 billion**.

- Abolishing the Foreign Office quango, the **British Council** would save **£182 million** per annum.

- Scrapping the Equalities and Human Rights Commission and the Government Equalities Office we can save **£67 million** p.a. (see Section 28 last bullet point).

These are just a few examples, and there are a host of other areas where cost savings can be made in order to pay for public services in health, education, defence, policing etc. When the full UKIP Manifesto is published before the next General Election we will give more details of cost savings that can be made.

30. Northern Ireland, Scotland and Wales.

Many of the above are national policies that would apply to the whole of the UK. However, UKIP in Northern Ireland, Scotland and Wales will publish their own Manifestos at the appropriate times.

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Ref: v7 22/9/2018

Aircraft engine exhaust emissions and other airport-related contributions to ambient air pollution

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DOI:
10.1016/j.atmosenv.2014.05.070

AIRCRAFT ENGINE EXHAUST EMISSIONS AND OTHER AIRPORT-RELATED CONTRIBUTIONS TO AMBIENT AIR POLLUTION: A REVIEW

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Highlights

- Aviation is globally growing (+5% y^{-1}) mainly driven by developing countries
- Airport operations cause an increase in ground-level pollution
- Chemical and physical properties of the emitted gases and particles are reviewed
- An overview of other additional sources within airports is provided
- Future research needs on aircraft emissions are highlighted

ABSTRACT

Civil aviation is fast-growing (about +5% every year), mainly driven by the developing economies and globalization. Its impact on the environment is heavily debated, particularly in relation to climate forcing attributed to emissions at cruising altitudes and the noise and the deterioration of air quality at ground-level due to airport operations. This latter environmental issue is of particular interest to the scientific community and policymakers, especially in relation to the breach of limit and target values for many air pollutants, mainly nitrogen oxides and particulate matter, near the busiest airports and the resulting consequences for public health. Despite the increased attention given to aircraft emissions at ground-level and air pollution in the vicinity of airports, many research gaps remain. Sources relevant to air quality include not only engine exhaust and non-exhaust emissions from aircraft, but also emissions from the units providing power to the aircraft on the ground, the traffic due to the airport ground service, maintenance work, heating facilities, fugitive vapours from refuelling operations, kitchens and restaurants for passengers and operators, intermodal transportation systems, and road traffic for transporting people and goods in and out to the airport. Many of these sources have received inadequate attention, despite their high potential for impact on air quality. This review aims to summarise the state-of-the-art research on aircraft and airport emissions and attempts to synthesise the results of studies that have addressed this issue. It also aims to describe the key characteristics of pollution, the impacts upon global and local air quality and to address the future potential of research by highlighting research needs.

Keywords: Aviation; atmospheric pollution; emissions; LTO cycles; particulate matter; oxides of nitrogen

List of abbreviations

AAFEX	Alternative Aviation Fuel Experiment
AEs	Airport emissions
APEX	Aircraft Particle Emissions eXperiment
APU	Auxliary power unit
BC	Black carbon
C^*	Effective saturation concentration
CIs	Chemi-ions
CIMS	Chemical ionisation mass spectrometry
EC	Elemental carbon
EI	Emission index
EXCAVATE	EXperiment to Characterise Aircraft Volatile Aerosol and Trace-species Emissions
F_{00}	Engine thrust expressed as a percentage of maximum rated power
FGEP	Fixed ground electrical power
FSC	Fuel sulfur content
FT	Fischer-Tropsch fuel
GMD	Geometric number mean diameter
GPUs	Ground power units
GRPs	Ground running procedures
GSEs	Ground service equipments
ICAO	International Civil Aviation Organization
LTO	Landing and take-off cycle
OC	Organic carbon
NMHC	Non-methane hydrocarbon
NO_x	Nitrogen oxides (NO+NO_2)
NO_y	Reactive odd nitrogen (NO_x and their oxidation products)

OA	Organic aerosol
PAHs	Polycyclic aromatic hydrocarbons
PM	Particulate matter
PM_1	Particulate matter (aerodynamic diameter less than 1 μm)
$PM_{2.5}$	Particulate matter (aerodynamic diameter less than 2.5 μm)
PM_{10}	Particulate matter (aerodynamic diameter less than 10 μm)
RF	Radiative forcing
RPK	Revenue passenger kilometres
RTK	Revenue tonne kilometres
SARS	Severe acute respiratory syndrome
SIA	Secondary inorganic aerosol
SN	Smoke number
SOA	Secondary organic aerosol
SVOCs	Semi-volatile organic compounds
TC	Total carbon
TF	Turbofan engine
TIM	Time-in-mode
TJ	Turbojet engine
TP	Turboprop engine
TS	Turboshaft engine
UFP	Ultrafine particles (diameter <100 nm)
UHC	Unburned hydrocarbons
VOCs	Volatile organic compounds
ε	Abundance ratio ((SO_3+H_2SO_4) /total sulfur)
ξ	Partitioning coefficient

1. INTRODUCTION

Among pollution issues, poor air quality attracts a high level of interest within the scientific community and engages public opinion because of the known relationship between exposure to many air pollutants and increased adverse short- and long-term effects on human health (e.g., Schwartz, 1997; Ayres, 1998; Brunekreef and Holgate, 2002; Kampa and Castanas, 2008; Maynard, 2009; Yang and Omaye, 2009; Rückerl et al., 2011). In addition, air pollution can seriously impair visibility (Hyslop, 2009), may damage materials in buildings and cultural heritage (Watt et al., 2009; Screpanti and De Marco, 2009) and has direct and indirect effects upon climate (Ramanathan and Feng, 2009). While air pollution remains a major concern for developing countries (Fenger, 2009; Liaquat et al., 2010) as a result of the rapid growth of population, energy demand and economic growth, developed countries have experienced a significant decline in the concentrations of many air pollutants over the past decade.

Airport emissions (AEs) have received increasing attention in recent years because of the rapid growth of air transport volumes and the expected expansion to meet capacity needs for future years (Amato et al., 2010; Kurniawan and Khardi, 2011; Kinsey et al., 2011). Most studies highlight knowledge gaps (e.g., Webb et al., 2008; Wood et al., 2008a; Lee et al., 2010) which are a matter of concern as the literature indicates that aircraft emissions can significantly affect air quality near airports (Unal et al., 2005; Carslaw et al., 2006; Herndon et al., 2008; Carslaw et al., 2008; Mazaheri et al., 2009; Dodson et al., 2009) and in their surroundings (Farias and ApSimon, 2006; Peace et al., 2006; Hu et al., 2009; Amato et al., 2010; Jung et al., 2011; Hsu et al., 2012). Emission standards for new types of aircraft engines have been implemented since the late 1970s by the International Civil Aviation Organization (ICAO) through the Committee on Aircraft Engine Emissions (CAEE) and the subsequent Committee on Aviation Environmental Protection (CAEP). One of the key actions of the ICAO committees was the provision on engine emissions in Volume II of Annex 16 to the Convention on International Civil Aviation, the so-called “Chicago

Convention", which recommended protocols for the measurement of carbon monoxide (CO), nitrogen oxides ($NO+NO_2=NO_x$), unburned hydrocarbons (UHC) and smoke number (SN) for new engines (ICAO, 2008). Standards were listed on a certification databank (EASA, 2013), which represents a benchmark for engine emissions performance and is used in many regulatory evaluations (ICAO, 2011). This regulation has produced significant improvements in engine and fuel efficiency and technical progress to reduce emissions. However, although these efforts have led to a substantial reduction in direct aircraft emissions over the past two decades, these gains may be offset by the forecast growth of the aviation industry and the resulting increase in airport traffic (ICAO, 2011). Furthermore, the ICAO regulation address only four main generic pollutants and a more detailed chemical and physical characterization of exhausts is required to quantitatively and qualitatively assess aircraft emissions. An increasing number of studies provide a detailed chemical speciation for many exhaust compounds, including gases and airborne particulate matter (e.g., Anderson et al., 2006; Herndon et al., 2008; Agrawal et al., 2008; Mazaheri et al., 2009; Onash et al., 2009; Herndon et al., 2009; Kinsey et al., 2011; Mazaheri et al., 2011; Santoni et al., 2011). However, the literature remains very sparse and many questions remain unresolved because of the large differences in measurement strategies, technologies and methods, compounds analysed and environments studied.

Aircraft exhausts are only one of several sources of emission at an airport (ICAO, 2011). Although exhaust plumes from aircraft engines were conventionally considered to account for most of the emissions, other sources are present within modern airports and contribute to air pollution at the local scale. Among these, tyre, brake and asphalt wear and the re-suspension of particles due to the turbulence created by the aircraft movements can account for large fractions of total particulate matter mass (e.g., British Airports Authority, 2006), but their chemical and physical characteristics have been investigated in only a few studies (Bennett and Christie, 2011; Bennett et al., 2011). Moreover, the emissions of the units providing power to the aircraft on the ground have received relatively little consideration despite their potentially high impact on the local air quality (Schäfer et al., 2003; Ratliff et al., 2009; Mazaheri et al., 2011). These units include the auxiliary power units (APUs), which are small on-board gas-turbine engines, and the ground power units (GPUs) provided by airports. In addition, airport ground service equipment (GSEs) further impact the air quality (e.g., Nambisan et al., 2000; Amin, 2001; Schäfer et al., 2003). GSEs include most of the equipment that an airport offers as a service for flights and passengers and includes a large number of vehicles, such as passenger buses, baggage and food carriers, container loader, refilling trucks, cleaning, lavatory services and de/anti-icing vehicles, and tugs, which are used to move any equipment or to push the aircraft between gates and taxiways. Only few studies are available on the air traffic-related emissions produced by ground services such as GSEs, GPUs or APUs (e.g., Webb et al., 2008; Ratliff et al., 2009; Mazaheri et al., 2011; Presto et al., 2011).

Additional sources may also be present at airports, including maintenance work, heating facilities, fugitive vapours from refuelling operations, kitchens and restaurants for passengers and operators, etc. Moreover, as many airports are located far from cities, their emission inventories should also include sources not directly present within a terminal, but on which the airport has an influence. These sources may include intermodal transportation systems or road traffic including private cars, taxis, shuttle buses and trucks for transporting people and goods in and out of the airport.

As most large airports are located near heavily populated urban settlements, in combination they have a potentially significant impact on the environment and health of people living in their vicinity. For example, 150 airports in the USA are located in areas designated to be in non-attainment for one or more criteria air pollutants (Ratliff et al., 2009). In undertaking air quality assessments and the development of successful mitigation strategies, it is therefore fundamental to consider all the aspects associated with the entire “airport system”. However, current information on many aspects of this polluting source is inadequate, including a detailed speciation of hydrocarbons, physicochemical characteristics of particles, volatile and semi-volatile emissions and especially the secondary transformations from the aging of aircraft exhausts and other airport-related emissions. Some of these gaps are well summarised in a US Transportation Research Board report (Webb et al., 2008).

1.1 Aims and Outline of the Review

Since the scientific literature on AEs remains very sparse and many questions are still open, this review aims to summarise the state-of-the-art of airport emissions research and attempts to synthesise and analyse the published studies. An overview of current information on airport-related emissions is presented and the key characteristics of the pollution and the impacts on the local and global air quality are discussed. This review further summarises the various methodologies used for measurements and attempts to critically interpret the data available in the literature. Finally, this review will highlight priority areas for research.

The next section traces the main stages of the development of civil aviation, by focusing especially on the changes and development strategies of modern airport systems. Recent traffic data and statistics are presented and the trends are also discussed in order to understand the potential future growth of air transport, which is fundamental to forecasting the impacts of aviation in future years. The third section gives an overview of the operation of aircraft engines, briefly discusses the most widely used technologies, describes some fuel characteristics, such as the sulfur content, and analyses the current use and future jet fuel consumption scenarios. The fourth section reviews the current information on aircraft engine exhaust: the landing and take-off cycles are described since they are commonly used to assess aircraft emissions during the operational conditions within an airport and within the atmospheric surface boundary layer; the main gaseous and particulate-phase compounds emitted by aircraft are listed and their key chemical and physical characteristics are described in separate subsections. A summary of data on the emission indices for many pollutants is also provided. The fifth section describes the non-exhaust emissions related to aircraft operations, such as the tyre and brake wear and the re-suspension of runway material, which have been little investigated even though they may have serious impacts on local air quality. The sixth section reviews data on the non-aircraft emissions potentially present within an airport, including the ground service equipment emissions, the auxiliary/ground power units and others. The seventh section presents the results of studies conducted indoors and outdoors at airports to directly assess the impacts of AEs upon human health. Finally, this paper reviews the results of the recent literature on aircraft emissions and other airport-related contributions to highlight the potential role of AEs upon local air quality.

2. PRESENT SCENARIOS AND FUTURE PERSPECTIVES OF CIVIL AVIATION AND AIRPORTS

The Airport Council International (ACI, 2013) has reported recent statistics on the air traffic volumes for 2012: more than 79 million aircraft movements carried annually 5.7 billion passengers between 1,598 airports located in 159 countries, and reported that the total cargo volume handled by airports was 93 million tonnes. However, these numbers are expected to further increase in the forthcoming decades: in the past half century, the aviation industry has experienced a strong and rapid expansion as the world economy has grown and the technology of air transport has developed (Baughcum et al., 1999). Generally, air traffic has been expressed as revenue passenger kilometres (RPKs) by multiplying the number of revenue-paying passengers aboard the vehicle by the travelled distance, or occasionally in revenue tonne kilometres (RTK). Figure 1 shows the absolute growth of aviation recorded by ICAO in terms of RPK, RTK and aircraft kilometres from the 1930s to today (ICAO, 2013; Airlines for America, 2013). Despite some global-scale events, such as the Gulf crisis (1991), the terrorist attack of 11th September 2011, the outbreak of severe acute respiratory syndrome (SARS) in 2002–2003 and the recent global economic crisis (2008–2009), an average annual growth rate of 5% was observed and this trend is expected to continue over the next decades mainly driven by the economic growth of emerging regions (ACI, 2007; 2008; Airbus, 2012; Boeing, 2013). It is anticipated that there will be more than 9 billion passengers globally by 2025 and more than 214 million tonnes of total world freight traffic are forecast over almost 120 million air traffic movements (ACI, 2007). The future growth of air transport will inevitably lead to the growth of airline fleets and route networks and will therefore lead to an associated increase in airport capacity in terms of both passengers and cargo. This poses questions as to the consequent impact on air quality.

3. AIRCRAFT: CHARACTERISTICS AND IN-USE TECHNOLOGIES

Emissions from aircraft engines are recognised as a major source of pollutants at airports and have been extensively investigated over the past 40 years. Initially, the main historical concern for supersonic aircraft was over stratospheric ozone depletion (Johnston, 1971) and secondarily about the formation of contrails at cruising heights (Murcray, 1970; Schumann, 2005) and indirect effect on the Earth's radiative budgets (Kuhn, 1970). Apart the development of the Concorde and the Tupolev Tu-144, a supersonic fleet flying in the stratosphere was never developed and today all commercial airliners are subsonic equipped with turbofan or turboprop engines. Therefore, the main present issue arising from civil aviation has today shifted to the increased levels of ozone in the upper troposphere and lower stratosphere resulting from the atmospheric chemistry of emitted NO_x (Lee et al., 2010 and reference therein). Furthermore, the development of increasingly restrictive legislation on ambient air quality and the implementation of enhanced monitoring networks in many developed countries has highlighted the effects of aircraft emissions at ground-level and the deterioration of air quality near airports.

3.1 Engines

Engines for civil and general aviation are generally classified as gas turbine engines (turbofan and turboprop) fuelled with aviation kerosene (also named jet fuel) and internal combustion piston engines fuelled with aviation gasoline, often referred as avgas (ICAO, 2011). The majority of modern airliners are equipped with turbofan engines. These engines are derived from predecessor turbojet engines developed during World War II. A turbojet is composed of an inlet compressor, a combustion section adding and igniting fuel, one or more turbines extracting energy from the exhaust gas in expansion and driving the compressor. A final exhaust nozzle accelerates the exhaust gas from the back of the engine to generate thrust. Turbofan engines use a turbojet as a core to produce energy for thrust and for driving a large fan placed in front of the compressor. In modern airliners, the fan provides most of the thrust. The "bypass ratio" refers to the ratio of mass flux bypassing the combustor and turbine to the mass flux through the core: high-bypass ratios are preferred for civil aviation for good fuel efficiency and low noise. Some small and regional airliners are instead equipped with turboprop engines, which use a turbine engine core fitted with a reduction gear to power propellers. A simplified diagram of a turbofan engine is provided in Figure 2. In August 2013 the ICAO (EASA, 2013) listed a total of 487 in-use turbofan engines (including packages): Table 1 provides a summary of the current engine families mounted in the most popular airliners (75% of total in-use turbofan engines).

Reciprocating piston engines are predominately fitted in small-sized aircraft typically related to private use, flying clubs, flight training, crop spraying and tourism. Internal piston engines run under the same basic principles as spark ignition engines for cars, but generally require higher performance. Four-stroke-cycle engines are commonly used, more rarely these can be two-stroke and occasionally diesel. The principal difference between jet and piston engines is that combustion is continuous in jet engines and intermittent in piston engines. Other flying vehicles may be present within an airport, such as helicopters. These vehicles are usually less numerous than the airliners in most terminals, but in some circumstances their contribution to the air quality cannot be disregarded. Today, most modern helicopters are equipped with turboshaft engines, whose functioning is similar to a turbojet but are optimised to generate shaft power instead of jet thrust. This review abbreviates turbojet (TJ), turbofan (TF), turboprop (TP) and turboshaft (TS).

3.2 Fuel Characteristics

At the current time, almost all aviation fuel (jet fuel) is extracted from the middle distillates of crude oil (kerosene fraction), which distils between the gasoline and the diesel fractions. The kerosene-type fuels most used worldwide in civil aviation are of Jet A and Jet A-1 grades: Jet A is used in most of the world, except North America where Jet A-1 is used. An exhaustive review of jet fuel production processes is given elsewhere (Liu et al., 2013). The specifications of such fuels are addressed by two organizations, the American Society for Testing and Materials (ASTM) and the United Kingdom Ministry of Defence (MOD). Jet A is used for almost all commercial aviation flying within or from the USA and is supplied against the ASTM D1655 specification. It has a flash point minimum of 38°C and a freeze point maximum of −40°C. Jet A-1 is widely used outside the USA and follows the UK DEF STAN 91-91 (Jet A-1) and ASTM D 1655 (Jet A-1) specifications. It has same flash point as Jet A but a lower freeze point (maximum of –47°C) and a mean C/H ratio of $C_{12}H_{23}$ (Lewis et al., 1999; Chevron Corporation, 2006; Lee et al., 2010). Other fuels can be used as an alternative to Jet A-1. Jet B is a wide-cut type fuel covering both the naphtha and kerosene fractions of crude oil and is used in very cold climates, e.g. in northern Canada where its thermodynamic characteristics (mainly lower freeze point and higher volatility) are suitable for handling and cold starting. ASTM publishes a specification for Jet B, but in Canada it is supplied against the Canadian specification CAN/CGSB 3.23. Other specifications also exist such as DCSEA (France) and GHOST (Russia). TS-1 is the main jet fuel grade available in Russian and CIS states, along with T-1, T-2 and RT; it is a kerosene-type fuel with slightly higher volatility (flash point is 28°C minimum) and lower freeze point (<−50°C) compared to Jet A and A-1 fuels. Various types of jet fuels are instead regulated by Chinese specifications: RP-1 and RP-2 are kerosene-type fuels similar to Russian TS-1, while RP-4 to Jet B. Nowadays, virtually all jet fuel in

China is RP-3, which is quite comparable to Jet A-1 (Shell, 2013). Fuels for military purposes are formulated for high-performances and are regulated separately by many governments; some of these (JP grades for USA and NATO forces) were used in several studies (e.g., Anderson et al., 2006; Chen et al., 2006; Cowen et al., 2009; Cheng et al., 2009; Cheng and Corporan, 2010; Santoni et al., 2011). The kerosene-based JP-8 grade is currently the primary fuel for NATO aircraft. Corporan et al. (2011) reported some JP-8 characteristics.

Jet fuels are a mixture of thousands of different hydrocarbons. The range of their molecular weights is restricted by the distillation: in kerosene-type fuels (e.g., Jet A and Jet A-1) the carbon number ranges between about 8 and 16, while in wide-cut jet fuels (Jet B), between about 5 and 15. Spicer et al. (1994) reported that jet fuel is primarily composed of species with five or more carbons and 70% of the compounds by weight contain 11–14 carbon atoms. Most of the hydrocarbons in jet fuel are members of the normal parafins, iso-paraffin, cycloparaffin, aromatic and alkene classes: 20% *n*-paraffins, 40% iso-paraffin, 20% naphthenes and 20% aromatics are typical (Lindstedt and Maurice, 2000; Liu et al., 2013 and reference therein). Moreover, a series of different additives are required or approved for use by ASTM and DEF STAN specifications to enhance or maintain some fuel properties, improve performance or handling. Among those approved for Jet A and Jet A-1 fuels, some hindered phenols serve as antioxidants, the di-ethylene glycol monomethyl ether acts as icing inhibitor, the N,N´-disalicylidene-1,2-propane diamine is added as chelating agent for many metal ions. Other additives act as electrical conductivity/static dissipaters, corrosion inhibitor and biocides: a summary is listed in Chevron Corporation (2006).

The aviation industry is nowadays investing significant effort towards the use of alternative fuels (Blakey et al., 2011; Williams et al., 2012). Since aircraft emissions are recognised to be closely linked to the fuel composition (Beyersdorf et al., 2013 and reference therein), recently the introduction of synthetic fuels and bio-fuels instead of common oil-derivate jet fuels has been much discussed in terms of beneficial effects upon exhaust emissions (e.g., Corporan et al., 2005; 2007; DeWitt et al., 2008; Timko et al., 2010a; Corporan et al., 2011; Lobo et al., 2011; Williams et al., 2012; Cain et al., 2013). Among others, the Fischer-Tropsch (FT) fuel seems to be a potential candidate for replacing, or mixing with, oil-derived conventional jet fuels. The FT reaction was developed in the first half of twentieth century and uses a mixture of carbon monoxide and hydrogen to produce a complex product stream of paraffins, olefins, and oxygenated compounds such as alcohols and aldehydes via product upgrading (e.g., cracking, fractionation, and isomerisation). The mechanism is explained in Liu et al. (2013). The FT process leads to a fuel with low aromatic content and no sulfur, which are reported to be beneficial in reduction of emissions of particulate matter and its precursors from aircraft engines (Corporan et al., 2007; Timko et al., 2010a; Lobo et al., 2011). Corporan et al. (2011) report gas chromatograms and hydrocarbon content of JP-8 and various alternative jet fuels. To study the effects of FT fuel usage on aircraft gaseous and particulate emissions the Alternative Aviation Fuel Experiment (AAFEX) was carried out in 2009: results are spread across various papers (e.g., Lee et al., 2011; Santoni et al., 2011; Anderson et al., 2011; Kinsey et al., 2012a,b; Beyersdorf et al., 2013).

Avgas for general aviation is distilled separately from the most common motor gasoline and is formulated for stability, safety, and predictable performance under a wide range of environments. Nowadays there are two main grades (100 and 100LL low lead) regulated by the ASTM D 910 and UK DEF STAN 91-90 specifications. Tetraethyl Pb is added to avgas for increasing fuel octane and avgas 100LL has a lead content up to 0.56 g Pb L^{-1}. The impact of general aviation is under discussion, since it was reported as one of the largest remaining source of lead emissions to the air in the USA (e.g., Carr et al., 2011). Avgas is principally composed of isoparaffinic and aromatic hydrocarbons and their carbon numbers vary from about 4 (butane) to 10, with the most prevalent carbon number being 8 (Chevron Corporation, 2006). It may include tetraethyl lead as antiknock additive, icing inhibitors, antioxidants and others.

3.3 Sulfur Content in Fuels

Over the past decades there has been a worldwide trend to decrease sulfur content in fuels and many jurisdictions, including the USA and the European Union, have recently required very low sulfur levels in road and marine fuels to reduce the SO_x and particulate matter emissions from the transport sector. A similar reduction has not occurred for jet fuel although at the beginning of the 2000s the IPCC indicated that reducing the sulfur content of kerosene will reduce SO_x emissions and sulphate particle formation (IPCC, 1999). The maximum sulfur content of aviation fuel has remained at 3 g S kg fuel^{-1}, or 3000 ppm by mass (Lewis et al., 1999; Ebbinghaus and Wiesen, 2001; Anderson et al., 2005; Barrett et al., 2012). However, lower values of fuel sulfur content (FSC) have commonly been reported: Fahey et al.(1999) stated that in the world market at the beginnings of the 2000s the FSC was near 400 ppm; Hileman et al. (2010) reported that average FSC in commercial Jet A, Jet A-1 and military JP-8 fuel grades varied between 550 to 750 ppm; Agrawal et al. (2008) reported that FSC in the fuel was 300 ppm. Popovicheva et al. (2004) and Demirdjian et al. (2007) reported that the aviation kerosene TS-1 has a FSC of 1100 ppm and less than 10^{-4} wt.% of metals.

FSC in jet fuels is directly related to the SO_2 emissions in aircraft exhaust (e.g., Arnold et al., 1998a; Schumann et al., 1998; Hunton et al., 2000). Some research projects, such as APEX-1, were designed to study the effects of FSC on aircraft engine emissions (e.g., Wey et al., 2006; 2007; Kinsey, 2009; Onash et al., 2009). Generally the studies reported that the emissions of both SO_2 and sulphates are proportional to S levels in fuels, but no systematic difference between the low and high sulfur fuels in terms of other emitted organic sulfur species (OCS and CS_2) were reported (Anderson et al., 2006). The conversion of S(IV) to S(VI) is amply discussed later in this review.

Recently, the impact of ultra-low sulfur jet fuel (15 ppm) upon public health, climate, and economics was examined by Barrett et al. (2012). They reported that the use of ultra-low sulfur fuels on a global-scale will cost 1−4 billion US $ per year, but may prevent 900−4000 air quality-related premature mortalities per year. Moreover, Barrett and co-authors also stated that the radiative forcing (RF) associated with reductions in atmospheric sulphate, nitrate, and ammonium loading can be estimated as +3.4 mW m^{-2}, i.e. equivalent to about 1/10th of the warming due to CO_2 emissions from aviation.

3.4 Current Use and Future Jet Fuel Consumption Scenarios

The availability of reliable information on fuel consumption is essential to make robust estimates of aviation emissions at both global and regional scales. Various estimates of aviation fuel consumption are available in the literature and generally refer only to jet fuel, since piston-powered flights were estimated to account for approximately 2% of propeller (piston plus turboprops) and ~ 0.05% of total (propeller plus jet) fuel burn (Kim et al., 2007). Gauss et al. (2006) estimated a total of 169 Tg fuel globally burned in 2000, of which 152 Tg is due to civil flights. The AERO2k global aviation emissions inventories reported a total of 176 Tg of kerosene used in 2002 for both civil (156 Tg) and military (19.5 Tg) aviation (Eyers et al., 2004); other studies of the 2000-2005 period estimated that the global aviation industry consumed approximately 170-203 Tg of kerosene per year with an evident decrease in 2001-2002 following the drop of aviation traffic due to the 11th September 2001 and SARS events (Kim et al., 2007); Wilkerson et al. (2010), Whitt et al. (2011) and Olsen et al. (2013) reported that the global commercial aircraft fleet burned 188 Tg of fuel in 2006; Chèze et al. (2011) reported a world consumption of 229 Mt of jet fuel in 2008. These estimates accounted for approximately 3% of current annual fossil fuel energy usage (Barrett et al., 2010, and reference therein). Data from OPEC (Mazraati, 2010) stated that the aviation sector in 2006 was the second major consumer of total oil demand in the transportation sector (11.2%) and accounted for 5.8% of total oil consumed in the world. Given the past and future growth of the aviation industry, this consumption may rise further: AERO2k emission inventories estimated a forecast scenario for 2025 in which the fuel demand for aviation will be 327 Tg y^{-1} (Eyers et al., 2004); Chèze et al. (2011) reported that the world jet fuel demand is projected to grow by 38% between 2008 and 2025, rising to more than 316 Mt in 2025 at a mean growth rate of 1.9% per year. Owen et al. (2010) estimated the future global aviation emissions under four of the IPCC/SRES (Intergovernmental Panel on Climate Change/Special Report on Emissions Scenarios) marker scenarios and reported a fuel use of 336 Tg in 2020 and varying from 426 and 766 Tg for 2050. This study also reported an estimate of 325 Tg for 2050 if the ambitious technology targets of the Advisory Council for Aeronautical Research in Europe (ACARE, 2002) were to be achieved. Table 2 summarises the yearly global fuel consumption reported in recent studies. However, aviation traffic growth and jet fuel demand have been shown not to be strictly correlated, since the efficiencies of aircraft engines and air traffic management are improving and modern airliners are 75% quieter with consequent fuel consumption reduced by 70% with respect to the 1960s (Baughum et al., 1999; Nygren et al., 2009, and references therein). In particular, the current average fuel consumption of in-use fleets was estimated to be less than 5 L fuel every 100 RPK, while in most modern aircraft it drops to approximately 3.5 L / 100 RPK: Nygren et al. (2009) reported the historical world fleet of aircraft average fuel consumption and found an exponential trend in fuel consumption reduction from 1987 to the present day. Oil prices have driven investment in more efficient aircraft models. Fuel costs exceed those of labour costs for airlines. Fuel costs accounted for ~13% of total costs in 2002, but today they are closer to 34% (Boeing, 2013).

4. AIRCRAFT EXHAUST EMISSIONS

Emissions from aircraft engines are generally considered to be the dominant source at airports and the large majority of studies available in the literature focus on aircraft emissions. Common airliners burning kerosene-type fuels primarily produce carbon dioxide and water (Wahner et al., 1995; Lewis et al.,1999; Anderson et al., 2006; Lee et al., 2010), which are directly related to the burned fuel, with minor variations due to the carbon-hydrogen ratio of the fuel. In this context, it is reported that the fuel flow of common airliner engines is approximately linearly proportional to engine thrust setting (e.g., Anderson et al., 2005; Wey et al., 2006).

The oxidation of atmospheric nitrogen at the very high temperatures in engine combustors drives the formation of nitrogen oxides, while the presence of trace amounts of sulfur, nitrogen and some metals (e.g., Fe, Cu, Zn) in fuels (Lewis et al., 1999) and non-ideal combustion conditions within engines may lead to the production of by-products, including sulfur oxides, additional nitrogen oxides, unburned hydrocarbons and particulate soot. Furthermore, exhausts can also contain species from the combustion and release of lubricant oils (Dakhel et al., 2007; Timko et al., 2010b; Yu et al., 2010; Kinsey et al., 2011; Yu et al., 2012) and from mechanical component wear (Petzold et al., 1998; Demirdjian et al., 2007). Therefore a more realistic, but simplified, combustion scheme in aircraft engines can be summarised as (Lee et al., 2009):

$$C_nH_m+N_2+O_2+S \rightarrow CO_2+N_2+H_2O+O_2+CO+SO_x+NO_x+HC+soot$$

IPCC reported that approximately 99.5-99.9% of the molar content of typical commercial engine exhaust consists of N_2, O_2, CO_2, and H_2O (Lewis et al., 1999). Figure 3 reports a more detailed breakdown of combustion products for a core engine mass flow: the combustion products in aircraft exhausts are mainly made up of CO_2 (~72%), H_2O (~27.6%), while residual products account for less than 1%. Figure 2 summarises the main exhaust components of aircraft engines and their potential effects on the environment and human health. It is estimated that roughly 90% of aircraft emissions, except hydrocarbons and CO (~70%), are produced while cruising at altitude, while the remainder is emitted during landing, take-off, and ground level operations (e.g., FAA, 2005).

Aircraft emissions have been studied extensively since the late-1960s and initially the interest was mainly driven by their direct and indirect effects on climate and the generation of contrails. For this reason, many early studies focused on emissions at high cruise altitudes (e.g., Reinking, 1968; Kuhn, 1970; Arnold et al., 1992; Fahey et al., 1995a,b; Wahner et al., 1995; Brasseur et al., 1996;

Schumann, 1996;1997; Anderson et al., 1998a,b). The interest in aviation emissions at airports also dates back many years (e.g., Daley and Naugle, 1979; Naugle and Fox, 1981), but only recently was there an increasing awareness of the effects of aircraft emissions at ground level, or at least within the planetary boundary layer. The recent interest in aircraft emissions at ground-level was initially motivated by public concern, given that more and more often airports are held responsible for air pollution and noise in nearby residential areas (e.g., Mahashabde et al., 2011). Since aircraft emissions are related to engine thrust (e.g., Anderson et al., 2006; Lobo et al., 2007; Whitefield et al., 2008; Timko et al., 2010b; Kinsey et al., 2010; Kinsey et al., 2011) and engines are designed for high performance while cruising at high altitudes, some aircraft operations within airports require that engines operate outside of their optimal regimes, ranging from maximum thrust during take-off to low power settings during operations on the ground. This fact was clearly highlighted during the APEX-1 campaign by Onash et al. (2009), who reported that a CFM56 engine is less efficient at the low thrust levels usually used at airports. This may result in potentially higher emissions on the ground than that during cruising for those pollutants mainly emitted at low power, such as CO and hydrocarbons.

Early reports of nitrogen oxides, carbon monoxide, hydrocarbons and particulate matter from jet aircraft turbine engines were made by Spicer et al. (1984). Subsequent studies (Spicer et al., 1992; 1994) added further information and provided detailed information on the organic component of turbine engine emissions. Following from these pioneering studies, the scientific literature now comprises a large number of studies and most have concluded that aircraft exhausts are responsible for significant emissions of a series of gaseous, semi-volatile and non-volatile species. Non-volatile emissions are produced in the combustor and are made up of refractory material such as soot (e.g., Agrawal et al., 2008; Kinsey, 2009; Dodson et al., 2009; Lee et al., 2010; Presto et al., 2011), which is emitted into the atmosphere as particulate matter even at the high engine exit temperatures, but also contains many organic compounds (e.g., Herndon et al., 2006; Anderson et al., 2006; Webb et al., 2008; Wood et al., 2008a; Agrawal et al., 2008; Herndon et al., 2009; Lee et al., 2010; Mazaheri et al., 2011; Presto et al., 2011; Kinsey et al, 2011; Mazaheri et al., 2013).

Volatile emissions include compounds that exists as vapour at engine exit temperature and pressure (Presto et al., 2011) and are made up of gaseous and vapour-phase pollutants, such as CO_2, CO, NO_x, SO_2, O_3 and many organic compounds, including alkanes, alkenes, carbonyls, aromatic compounds and a number of other volatile organic species. The least volatile fraction has been shown to range from 10 to 20% of the total organic emissions (Presto et al., 2011) and its presence is particularly challenging, because it can react in the atmosphere and may undergo condensation in the exhaust plumes leading to aerosol particles or volatile coating of pre-existing particles (Lee et al., 2010; Miracolo et al., 2011). This latter component is named volatile PM, however there is today a considerable controversy about its definition (Kinsey, 2009). Such particles may act as condensation nuclei or may interact with soot to form condensation nuclei and thus may have effects on cloud formation, precipitation and climate. In addition, additional compounds may subsequently originate from the aging of exhausts following a chain of oxidation with atmospheric oxidants and gases.

The relative amount of exhaust emissions depends upon combustor temperature and pressure, fuel to air ratio and the extent to which fuel is atomised and mixed with inlet air (Anderson et al., 2006). It is well recognised that the amounts of many pollutants may vary considerably with the engine technology, model and especially with the thrust. For example Slemr et al. (1998, 2001) and Spicer et al. (1992; 1994) reported that hydrocarbon emissions can be dependent upon engine type, use and maintenance history as well as fuel composition.

4.1 Geographical and Vertical Distributions of Flights

Based upon the main air traffic routes, a series of studies have discussed the geographical and vertical distributions of fuel consumption, which can be used to further assess the relative emissions from aviation (e.g., Kim et al., 2007; Wilkerson et al., 2010; DeWitt et al., 2011; Olsen et al., 2013; Simone et al., 2013). Due to the geographical distribution of civil aviation in the 2000s, the global fuel burn by domestic flights is dominated by the North America and Caribbean regions, while fuel consumed by international flights is dominated by Asia, North America and the Caribbean, and Western Europe and North Atlantic (Kim et al., 2007). Using the Aviation Emissions Inventory Code (AEIC, Stettler et al., 2011) Simone et al. (2013) estimated the fuel burn by country of origin/destination in 2005 and reported that the USA was the most important (59.1 Tg), followed by Japan (9.7 Tg), UK (9.4 Tg), China (8.5 Tg, excluding Hong Kong), Germany (6.7 Tg) and France (5.4 Tg). A map showing the column sum of global fuel burn from scheduled civil aviation in 2005 is provided in Figure 4a. Other studies have been carried out to estimate annual fuel consumption and pollutant emissions more locally: for example Fan et al. (2012) assessed the fuel consumption and emissions for each airline in China in 2010.

Kim et al. (2007) and Lee et al. (2007) used the System for assessing Aviation's Global Emissions (SAGE) model to estimate the vertical profiles of commercial aviation and pointed out that the highest fuel burn and emissions are between 9 and 12 km, which corresponds to typical cruise altitude. Generally, most studies also reported that about 5−7% of total jet fuel is consumed within 1 km above ground level during airport operations (Kim et al., 2007; Simone et al., 2013), and Olsen et al. (2013) reported a comparison of the annual global vertical distribution of fuel burn by the commercial aviation deriving from different estimates (Figure 4b). Although most studies have concluded that 5-10% of fuel is burned below 1000 m, aircraft operations within airports may further increase fuel consumption due to the acceleration and deceleration of the engines following airport congestion (Anderson et al., 2005; Nikoleris et al., 2011) or due the unaccounted use of fuel for APUs (Ratliff et al., 2009).

4.2 Emissions at Ground

4.2.1 *Landing and take-off (LTO) cycles*

The emissions of all aircraft engine must comply with applicable standards promulgated by the International Civil Aviation Organization (ICAO, 2008) and measured upon the landing and take-off (LTO) cycles. A LTO cycle refers to all the operations the aircraft carry out below 3000 ft above field elevation (equivalent to 914 m) over a specific range of certifiable operating conditions and includes four stages in terms of both engine thrust settings (expressed as a percentage of maximum rated thrust, or F_{00}) and typical time in each specific mode of operation (time-in-mode, TIM). The 3000 ft height roughly corresponds to the atmospheric mixing height, i.e. the lower part of the troposphere within which pollutants emitted at ground-level mix rapidly (e.g., Schäfer et al., 2006). The LTO cycles are designed for aircraft engines manufactured after 1985 whose rated output is greater than 26.7 kN and aim to guarantee they not exceed certain regulatory environmental limits for a series of pollutants, namely unburned total hydrocarbons, carbon monoxide, nitrogen oxides and smoke number (SN). This latter parameter is roughly representative of the amount of soot an engine generates (e.g., Wayson et al., 2009; Stettler et al., 2013a,b). In the first LTO phase the aircraft descends from cruising altitude toward the runway and lands at the airport. This phase is named "approach" and is estimated as lasting for 4 min with engines at 30% F_{00}. After landing, the aircraft enters in the "idle" phase which include all the ground-based operations: it proceeds at a low speed to the gate (taxi-in), remains on stand-by for the loading and unloading operations and again prepares for take-off proceeding towards the runway (taxi-out). Idle lasts 26 min and the engines are required to be at 7% F_{00}. The subsequent operating modes include the "take-off" with engines stressed to the full thrust (100% F_{00}) for 0.7 min, and the "climb" (85% F_{00} for 2.2 min) up to 3000 ft height. A standardised LTO cycle is shown in Figure 5.

4.2.2 *Engine ground running procedures*

In addition to the operations falling within LTO cycles, the ground running procedures (GRPs) may lead to further emission loads from aircraft engines at airports. GRPs refer to the operation of some or all engines carried out on the ground for the purpose of functionally checking the operation of either engines or aircraft systems. GRPs are therefore an essential part of the operation of any airliner prior to the release to service of an aircraft from maintenance. The main reasons for running the engines on the ground are (Buttress and Morris, 2005): (i) check starts after minor maintenance actions; (ii) runs at no more than ground idle to ensure that the engine operates correctly after maintenance action, these include thrust reverser function checks, etc.; (iii) runs at powers greater than ground idle to check the correct operation of certain valves, leak checks, etc. To date, only few studies take into account the emissions from GRPs, but their importance for the atmospheric loads of some pollutants cannot be neglected. For example, Buttress and Morris (2005) showed that GRPs at London Heathrow airport release approximately 15.6 Mg y^{-1} NO_x. Mazaheri et al. (2011) investigated the annual emissions of particle number, particle mass and NO_x throughout the LTO cycles and GRP at the Brisbane Airport and showed that annual emissions account for less than 3%. Despite the evidence that GRPs may have a substantial impact on local air quality at airports, up to now they have received only minor consideration. GRPs are not yet regulated internationally and must comply only with local regulatory requirements imposing limitations on the locations, times and engine thrust levels employed during ground running which may differ from one airport to another.

4.2.3 *Limitations in the use of standard LTO cycles*

The use of standard LTO cycles as a surrogate for typical aircraft operations close to the ground represents an approximation and is not always representative of operations at airports. One limitation is that the ICAO engine emissions standards are applied through national and multi-national certification processes to turbojet and turbofan engines, but not turboprop, turboshaft and piston engines (ICAO, 2011). This limitation may be negligible at large airports, where most traffic is due to common airliners equipped with TF engines, but may represent a major approximation for small and medium-sized airports where small, private, business and regional aircraft account for a large portion of flight traffic. In addition, despite LTO cycles having been designed to model optimally all the operational procedures of aircraft in the vicinity of airports, sometimes they are not well adapted to engine settings and actual TIM, which depend upon pilot' technique, fleets, airport layouts and flight traffic. In fact, default ICAO TIM are not representative of real operations and are for certification purposes. Consequently, although some inventories account for the deviations from the ICAO default TIMs and thrust settings, some deviations from the standardised LTO procedures may occur during actual LTO cycles. This inevitably leads to some differences between actual airport operations and emission inventories used in modelling studies. The main deviations/limitations are:

- reduced thrust during take-off. This practice is often carried out for performance and cost-efficiency reasons (ICAO, 2011) and has been widely observed on operational runways (Carslaw et al., 2008; Herndon et al., 2008); it may depend on aircraft weight and weather factors (Morris, 2002) and is often largely unknown (Carslaw et al., 2008). Since the emissions of some pollutants increase monotonically with the thrust (e.g., NO_x), this could lead to an overestimation of emissions from airports;
- lower thrust at idle/taxi mode. It has been reported that most aircraft use a thrust of 3%–4% F_{00} instead of 7% (Morris, 2005a,b; Nikoleris et al., 2011 and reference therein) during idle operations. Since most pollutants emitted in exhaust plumes are strongly increased at decreased power settings (CO and generally all hydrocarbons), this may lead to underestimation of emissions at airports. In this context, Wood et al. (2008b) suggested that the thrust used in taxi operations can be split in two modes, i.e. 'ground idle' carried out at

4% F_{00} and 'taxiway acceleration' with thrust settings up to 17%. Moreover, higher thrust levels are sometimes used for turning;

- acceleration and deceleration of the engines or stop-and-go situations. This is mainly the result of congestion on taxiways and is known to be responsible for significant increases in fuel consumption and increased emissions (Anderson et al., 2005; Nikoleris et al., 2011). For example Morris (2005a) reported that instant accelerations up to 10% F_{00} and lasting ~10 s may occur at London Heathrow airport when aircraft cross an active runway or make a sharp turn. Due to this, the entire taxiway phase of operation using a uniform engine thrust level have been also recognised as problematic for emission inventory estimates because of the nonlinear emission rate of many compounds at low power (Herndon et al., 2009);
- use of a reverse thrust phase during landing. Reverse thrust is applied to assist mechanical brakes in slowing down the landing aircraft and is not generally required for normal operations onto a dry runway (ICAO, 2011). However, it generally occurs with idle thrust power as a prudent safety precaution, and under some circumstances it may also occur at power higher than 10% F_{00} (Morris and Easey, 2005; Stettler et al., 2011). Generally, reverse thrust is applied for 10–20 s (Fanning et al., 2007; Stettler et al., 2011), but may vary as a function of the landing velocity, runway length and aircraft weight;
- the evident differences between the standard TIM, which is used as part of the ICAO engine emissions certification processes, and the actual TIM used at airports (e.g., Unique, 2004; Watterson et al., 2004; Patterson et al., 2009; Stettler et al., 2011; Mazaheri et al., 2011; Khadilkar and Balakrishnan, 2012). For example, Patterson et al. (2009) and Khadilkar and Balakrishnan (2012) observed that total fuel burn during departures and arrivals at airports is generally overestimated by the ICAO method with respect to emissions computed from real-time aircraft flight data. Other studies have also reported measured TIM at airports: Unique (2004) reported TIM in Zurich airport and detected differences in all the LTO phases: idle (-43%), approach (+10%), climb (-77%) and take-off (+129%) which have been estimated to

have a strong impact on the calculation of emissions, resulting in reduced fuel flow (–38%) and NO_x emissions (–31%);

- the composition of the fleet that serves an airport and the weight of the aircraft. Since the ICAO certifies the engines and not the full aircraft, some airplane characteristics, mainly the aircraft weight, may have a key role in determining the emissions. Furthermore, in addition to the mass of the aircraft, its load of fuel, passengers and goods affect the overall weight: it is reported that passengers, crew and luggage usually add 6-15% to aircraft weight (Hu et al., 2009). Most of those factors vary from flight to flight, are largely unknown and may have direct implications for reduced thrust during take-off. In fact, it should be inferred that the increase of the aircraft weight has direct effects upon the thrust levels needed for carrying out usual LTO operations. For example, Carslaw et al. (2008) studied the NO_x emissions at London Heathrow and found evidence for statistically significant differences in the emissions from the same engine type used on the same aircraft frame. Among other factors, they speculated that the aircraft weight could be a cause. In a study conducted in eight major busy airports, Turgut and Rosen (2010) detected significant differences in the emissions of some pollutants and concluded that every airport has LTO cycles carried out by aircraft with different characteristics and, consequently, emissions. Another recent study by Turgut et al. (2013) showed a good relationship between aircraft mass and the NO_x emission during take-off and climb, which supports the concept of an explicit relationship between the aircraft weight and emissions. There is a general lack of knowledge about the relationships between aircraft mass and emissions, although some recent studies have indicated that heavier aircraft also emit more particles (Zhu et al., 2011).

Recent studies assessing airport emissions have proposed and used LTO cycles which are much more complex than those standardised by the ICAO. For example, in a study of the air quality and public health impacts of UK airports, Stettler et al. (2011) used specific TIMs derived from

Watterson et al. (2004) and Underwood et al. (2004) composed of 12 phases, namely approach, landing roll, reverse thrust, taxi-in, taxiway acceleration, APU, taxi-out, taxiway acceleration, hold, take-off, initial climb and climb-out. Proposed TIMs were developed by analysing the common procedures of an A320 aircraft at London Heathrow, but may vary by aircraft size category. Other studies (e.g., Ratliff et al., 2009), used models, such as the Emissions and Dispersion Modelling System (EDMS), which also requires jet fuel quality data, main engine and APU specifications, aircraft weight and ground operating time to generate more reliable emission estimates.

4.2.4 *The emission indices (EIs)*

The emissions during standardised LTO cycles are then reported as emission indices (EIs) expressed as mass of pollutant emitted per unit mass of fuel burned. Fuel-based emission indices for the compound X are calculated according to:

$$EI(X)=Fc\cdot(M_X/M_{CO2})\cdot(\Delta X/\Delta CO_2)$$

where Fc represents the stoichiometric calculation of CO_2 produced per kilogram of fuel consumed (with units g CO_2 kg $Fuel^{-1}$) assuming complete combustion and given a particular hydrogen to carbon ratio (e.g., Herndon et al., 2004). M_X and M_{CO2} are the molecular weights of the compound X and CO_2, respectively, and ΔX and ΔCO_2 are the enhancements of compound X and CO_2 within the plume, respectively (e.g., Anderson et al., 2006). Unless specified differently, by convention $EI(NO_x)$ is defined in terms of NO_2 and therefore the mass of NO_x emissions is:

$$NO_x \text{ as } NO_2 = NO_2 \text{ emissions} + NO \text{ emissions} \cdot M(NO_2)/M(NO)$$

where $M(NO_2)$ and M(NO) are the molecular weights of NO_2 and NO, respectively. In a similar way it should be specified that EI(hydrocarbons) is often referenced to methane (Wahner et al., 1995). ICAO maintains a databank of engine certification data for commercial aviation reporting EIs for the four selected pollutants (EASA, 2013). Emissions of a pollutant X from an engine can be therefore calculated using three parameters: the first two are provided by the ICAO databank and are the main engine EI(X) and the engine fuel flow, i.e., the burned fuel at a defined power setting (expressed as kg s^{-1}); the third parameter is the time-in-mode (TIM), i.e. the time the engines spend at an identified power setting (ICAO, 2011):

$$\text{Emission(X)=EI(X)·TIM·fuel flow}$$

Analogous to the EI for the emitted pollutant, emission indices for the number of particles have been commonly reported in the literature. For convention, they are here reported as EI(#).

Using ICAO EIs and standardised LTO TIMs, Figure 6, 7 and 8 report a reprocessing of the data included in the ICAO databank. In particular, Figure 6 shows the total burned fuel and the mass of emitted pollutants (CO, NO_x and hydrocarbons) during a complete LTO cycle, i.e. the sum of standardised time in each mode per fuel flow per average EI at each of the four power settings (ICAO, 2013); data are organised to show the changes in the ICAO emission data for in-use engines certified from 1973 to present (five year steps). Since different engines have different characteristics, including the thrust force, Figure 6 also shows the ratios between the fuel burned during complete LTO cycles and the engine maximum rated thrust (in kN) to normalise the fuel consumption of the engine power. Figure 7 summarises the ICAO EI data (all in-use engines certified from 1976 to today) per each LTO stage, expressed as g pollutant emitted per kg fuel burned. Figure 8 shows the total burned fuel and emissions per each LTO phase, i.e. the product of EIs per standardised time in each phase per fuel flow. The reprocessing of ICAO data does not take into account the number of units produced for each engine model, but only the different models produced and still in service in April 2013 (and included in the ICAO databank), regardless of manufacturer, type and technology. Moreover, data refer to single engines, and generally conventional aircraft are equipped with 1 to 4 engines. Therefore the sole purpose of the reprocessing of ICAO data is to report qualitatively the trends in fuel consumption and emissions for in-use TF engines.

Currently, the scientific literature includes several studies aiming to give EIs for comparison with reported ICAO databank certification data and for many other components, including particulate matter, elements, ions and speciated hydrocarbons. However, such data are often sparse and results poorly comparable. Most studies were carried out using single or a few engine types, under certain environmental conditions, without a standardised thrust and/or often using different measurement techniques and instrumental set-up. Table 3 lists the most recent studies available in the literature reporting EIs for various engines in aircraft and helicopters. The table also shows some information (if available) about tested aircraft, engine models, selected thrust, type of fuel, sampling methodologies and analytical techniques. Table 4 provides a list of recent studies which measured EIs during real aircraft operations at airports. Most of the data in such studies (both engine tests and real world operations) are summarised in the Supplemental Information Tables SI1, SI2, SI3 and SI4, which provide detailed information about the EIs for many gaseous pollutants, speciated hydrocarbons, particle number, particle mass (including soot) and species/ions in particulate matter, respectively. Note that specific thrust levels provided in the tables are derived from the literature and are categorised in five groups, named idle, approach, cruise, climb and take-off, on the basis of the engine type. The thrust, expressed as F_{00}, is always provided along with the EIs. Additional tested thrust levels (if available) are also reported, along with fuel and analytical methodologies.

4.2.5 *Considerations about the EIs*

As indicated by the large number of studies in Tables 3 and 4, most of the literature provides results through the calculation of EIs. When applied to the specific testing studies on engines or airplanes, such methodology has the advantage of giving data easily comparable with EIs reported in the ICAO databank. This may allow a better evaluation of the differences amongst tested engines and technologies or, in case of the use of innovative analytical devices, allows a check the agreement between data obtained and certified values. In contrast, expressing the results as EIs from studies conducted during real-world operations at airports has both advantages and limitations. An advantage of the specific studies may be comparison of the results with the ICAO data to detect changes due to evolution of the exhaust plume, e.g. aging and gas-to-particle partitioning. Carslaw et al. (2008) noticed that EIs do not give a clear indication of the absolute contribution of aircraft emissions to ground-level concentrations, which is important for assessing air quality at airports. Furthermore, they commented that the value of EIs may be substantially affected by limited knowledge of some important aircraft operational factors, such as the aircraft weight and thrust setting at take-off. A list of remaining studies conducted at airports and in their surroundings, which do not report data expressed as EIs, is provided in Table 5. In summary, Tables 3, 4 and 5 provide an overview of the most important studies reported in this review for the characterisation of aircraft emissions in both tests and real operations.

4.3 Emissions at Cruise Altitudes

Although injected at high altitudes, aircraft cruise emissions have been found to impact surface air quality through the mean meridional streamlines due to the polar, Ferrel, and Hadley cells (Barrett et al., 2010; 2012) and they are not currently regulated. Consequently, although this review focuses on airport emissions, a brief statement upon the aircraft emissions during cruise (8-12 km) is presented, as the majority of exhaust from aircraft is emitted at high altitudes (e.g., Gardner et al., 1997; FAA, 2005; Wilkerson et al. 2010; Whitt et al., 2011). A more exhaustive summary of the effects of both civil (subsonic) aviation in the upper troposphere and supersonic aircraft in the stratosphere is reported in two reviews by Lee and co-authors (Lee et al., 2009; 2010).

Impacts of aviation during cruising first focused the interest of the scientific community in the late 1960s in relation to contrail generation at high altitudes and the relative effect on climate (Reinking, 1968; Kuhn, 1970). Contrails are formed whenever the requisite conditions of either ice or water supersaturation exist within aircraft exhaust plumes (DeWitt and Hwang, 2005). Subsequently, in the early 1970s, concern grew over a possible role in stratospheric ozone depletion while interest in the impact of nitrogen oxide emissions on the formation of tropospheric ozone began in the late 1980s (Lee et al., 2009, and references therein). Subsequent studies (e.g., Wahner et al., 1995;

Brasseur et al., 1996; Schumann, 1997) investigated a number of emissions other than CO_2, and effects from aviation with potential effects on climate. To date there are a large number of studies characterising aircraft emissions during cruising (e.g., Fahey et al., 1995a,b; Busen and Schumann, 1995; Schumann et al., 1996; Schlager et al., 1997; Paladino et al., 1998; Anderson et al., 1998a; Curtius et al., 1998; Brock et al., 2000; Schröder et al., 2000; Schumann et al., 2000; 2002; Curtius et al., 2002; Jurkat et al., 2011).

The RF of civil aviation emissions has been extensively studied (e.g., Prather et al., 1999; Wuebbles et al., 2007; Lee et al., 2009) and can be summarised in the following emitted compounds and processes, each having positive (+) or negative (–) forcing: H_2O (+); CO_2 (+); the atmospheric chemistry of NO_x causes the formation of tropospheric O_3 (+) but also the destruction of methane (–);oxidation of SO_2 results in sulphate particles (–); contrails (+); aviation-induced cloudiness (potentially +); soot, mainly composed of black carbon (+). Lee et al. (2009) estimated that aviation-induced RF in 2005 was ~55 mW m^{-2}, which accounted for 3.5% of global anthropogenic RF. In addition, black carbon emissions generated by aircraft at altitude have been shown to have a role in the formation of contrails (Schumann, 1996) and contrail-induced cirrus clouds, which affect the Earth's radiation balance by reflecting incoming solar radiation and by absorbing and re-emitting long wave radiation. The result is an additional positive RF of a magnitude similar to that of CO_2 (IPCC, 1999; Sausen et al. 2005; Lee et al., 2010). Recently, Azar and Johansson (2012) also assessed the non-CO_2 climate impact of aviation, including NO_x and contrails, and calculated the emissions weighting factors, i.e. the factor by which aviation CO_2 emissions should be multiplied to get the CO_2-equivalent emissions for annual fleet average conditions. Recently, Gettelman and Chen (2013) reported the climate impact of aviation aerosol. Although such studies highlighted the climate impact of aviation, it should be borne in mind that the magnitude of the total emissions of pollutants from aviation in terms of mass with direct and/or indirect effects on climate are one to two orders of magnitude smaller than from road transport or shipping (Balkanski et al., 2010; Eyring et al., 2010). The study of aircraft emissions at cruise altitudes is very challenging mainly due to the obvious difficulty of sampling. Thus, measurements are commonly performed indirectly or extrapolated from data collected on the ground or in the laboratory. For this reason, the assessment of cruise emissions at altitude offers unique challenges to understanding the impacts of atmospheric emissions and their processing (Herndon et al., 2008, and reference therein). Computational models are available to extrapolate the test stand EI data to cruise altitude conditions (Baughcum et al., 1996b; Sutkus et al., 2001).

4.4 Military Aircraft Emissions

Despite most attention being given to civil aviation, a number of studies have also addressed emissions from military aircraft (e.g., Spicer et al., 1984; 1992; 1994; Heland and Schäfer, 1997;1998; Gerstle et al., 1999; 2002; Miller et al., 2003; Anderson et al., 2005; Brundish et al., 2007; Corporan et al., 2008; Cheng, 2009; Cowen et al., 2009; Spicer et al., 2009; Cheng et al., 2009; Cheng and Corporan, 2010). Despite the relatively high potential impact of military aircraft emissions under particular circumstances, the task of studying military emissions is very difficult. Unlike civil aviation, military operations generally do not work to set flight profiles and do not follow fixed plans (Wahner et al., 1995). In addition, national and military authorities are reluctant to disclose sensitive information either about operations or in-use technologies. The lack of comprehensive data about military operations makes realistic assessments of the contribution of military aircraft in terms of fuel consumption extremely difficult. In addition, some aircraft may have a dual function, such as the C-130 Hercules, which can be engaged in both military and civilian operations. Henderson et al. (1999) reported a historical breakdown of aviation fuel burn for civil and military aviation: in 1976 fuel burned by civil aviation was 64%, while military was 36%. In 1992 the percentages were 82% and 18%, respectively. Subsequent studies stated that military aviation fleets used 11% (19.5 Tg) of fuel in 2002 and estimated that the military contribution is in the range of 10-13% of total aviation emissions (Eyers et al., 2004; Waitz et al., 2005). Table 2 provides estimates of fuel consumption and exhaust emissions from military aviation by the AERO2k model (Eyers et al., 2004). Among the large number of military aircraft, Cheng and Corporan (2010) stated that the three classes of military engines T56, TF33, and T700/ T701C fitted in the C130 Hercules, B-52 bomber and Apache/Blackhawk helicopters, respectively, consume 70%–80% of the USA military aviation fuel each year.

4.5 Water Vapour

Water is a key product of all hydrocarbon combustion and aircraft engines release H_2O as vapour (Lewis et al., 1999). Water vapour is a greenhouse gas and its increase in the stratosphere (Solomon et al., 2010) and the free troposphere (Sherwood et al., 2010) tend to warm the Earth's surface (Prather et al., 1999). Water vapour, via latent heat released or absorbed during condensation and evaporation cycles also play an active role in dynamic processes that shape the global circulation of the atmosphere (Schneider et al., 2010). Moreover its effect on the formation of contrails and on the enhanced cirrus generation in the upper troposphere can be relevant for additional global RF with an indirect consequent potential increase of positive effects on global warming (Lee et al., 2009). The annual and global-mean RF due to present-day aviation water vapour emissions has been found to be 0.9 (range 0.3–1.4) mW m^{-2} (Wilcox et al., 2012). The increased water vapour in the lower troposphere may have secondary effects on precipitation, fog, visibility and some microphysical processes.

An emission index of 1230±20 g H_2O kg $Fuel^{-1}$ is commonly reported for completely burnt fuel (Lewis et al., 1999; Lee et al., 2010): this represents a little less than 30% of all combustion products in aircraft exhaust (Figure 3). No differences in emission indices during idle, take-off and cruise power settings are reported (Lewis et al., 1999), as emissions of H_2O are a simple function of fuel consumption. The AERO2k inventories (Eyers et al., 2004) estimate a global emission of 217 Tg H_2O for 2002, 193 Tg from civil aviation and 24 Tg from military operations. Other more recent estimates report 251 Tg H_2O in 2005 (Kim et al., 2007) and 233 Tg H_2O in 2006 (Wilkerson et al., 2010). However, the emissions of water by the global aircraft fleet into the troposphere are small if compared with fluxes within the natural hydrological cycle (IPCC, 1999) and thus water vapour from aircraft exhausts is not considered relevant for local air pollution and human health. An estimation of H_2O produced by aircraft below 1000 m can be assessed by considering the global use of fuel reported in the literature for LTO cycles: considering the total consumption of 13.9 Tg fuel in 2005 (Kim et al., 2007), a total emission of ~17 Tg H_2O can be estimated (Table 2). Considering the fuel burn breakdown provided by Simone et al. (2013) for the EU (3.1 Tg in 2005), a total of 3.8 Tg y^{-1} H_2O are emitted within European countries.

4.6 Carbon Dioxide

Carbon dioxide is recognised as the main greenhouse gas, has a primary role in the Earth's climate warming and its behaviour within the atmosphere is simple and well understood (IPCC, 1999). Its main anthropogenic source is the combustion of fossil fuels: CO_2 emissions from fossil fuel combustion, including small contributions from cement production and gas flaring, were estimated to be 8.7±0.5 Pg C yr^{-1} in 2008 an increase of 2% from 2007, 29% from 2000 and 41% from 1990 (Le Quéré et al., 2009). More recently, Peters et al. (2011) indicated that global CO_2 emissions from fossil-fuel combustion and cement production further grew by 5.9% in 2010, surpassing 9 Pg C yr^{-1} principally due to the strong emissions growth in emerging economies. Once emitted, there are no important processes involving CO_2 formation or destruction and sinks occur principally at the Earth surface by exchange with the biosphere and the oceans (Solomon et al., 2007).

Carbon dioxide is the most abundant carbon-based effluent from aircraft engines (e.g., IPCC, 1999; Anderson et al., 2006; Lee et al., 2010) and Lewis et al. (1999) report that it accounts for ~72% of total combustion products (Figure 3). Typically, the EI(CO_2) from modern aircraft engines is 3160±60 g kg $Fuel^{-1}$ for complete combustion (Lewis et al., 1999; Lee et al., 2010) and emissions of CO_2 are a simple function of fuel consumption (e.g., Owen et al., 2010). However, some studies reported that EI(CO_2) decreases slightly at low thrust because incomplete combustion may result in a relative increase of CO and hydrocarbons in the exhaust (e.g., Wey et al., 2006; Stettler et al., 2011). The role of aviation in the rise of CO_2 emissions on a global scale may not be neglected and a list of estimates of CO_2 emissions is provided in Table 2. In 1992, global aviation emissions of CO_2 were about 2% of total anthropogenic sources and equivalent to about 13% of emissions from all transportation sources (IPCC, 1999). The AERO2k inventories (Eyers et al., 2004) estimated a global emission of 553 Tg CO_2 for 2002, 492 Tg from civil aviation and 61 Tg from military operations, while a higher global emission of 733 Tg y^{-1} was reported for 2005 (Lee et al., 2009), accounting for approximately 3% of the total CO_2 emissions from the combustion of fossil fuels (Howitt et al., 2011). Other estimates reported are 641 Tg CO_2 in 2005 (Kim et al., 2007) and 595 Tg CO_2 in 2006 (Wilkerson et al., 2010). As for H_2O, an estimate of CO_2 produced by aircraft below 1000 m was derived by assuming a constant EI(CO_2) of 3160 g kg $Fuel^{-1}$ and by considering the global use of fuel reported in the literature during LTO cycles in 2005 (Table 2). Results show a global emission of 44 Tg CO_2 of which about 9.8 Tg y^{-1} are emitted within Europe.

4.7 Carbon Monoxide

Carbon monoxide (CO) in the atmosphere is mainly generated by photochemical oxidation of methane and nonmethane hydrocarbons as well as direct emissions from anthropogenic combustion processes, such as vehicular exhaust, domestic heating, industrial emissions and biomass burning. In the troposphere, CO has a chemical lifetime varying from 30 to 90 days and its major sink is oxidation by hydroxyl radicals (Novelli et al., 1998; Seinfeld and Pandis, 2006). Its ability to form a strong bond with haemoglobin to form carboxyhaemoglobin can cause adverse effects on human health due to the reduction of blood oxygen-carrying capacity. At high exposure levels, CO can lead to asphyxia, whereas at low doses it may cause impaired neuropsychological performance and risk for myocardial ischemia and rhythm disturbances in persons with cardiovascular diseases (Samoli et al., 2007; Bell et al., 2009).

Carbon monoxide is generally emitted in aircraft exhaust as result of incomplete combustion of jet fuel. Emissions of CO are regulated by ICAO international standards and engine manufacturers must provide emission indices for this pollutant during an LTO cycle (ICAO, 2008). In the last 40 years, the improvement of engine technology has led to a significant reduction in CO emissions during the LTO cycle. Figure 6 shows a decrease in CO emissions at the end of the 1970s and nowadays most newly certified engines emit less than 10 kg CO per complete LTO cycle.

Carbon monoxide emissions indices are highest at low power settings where combustor temperatures and pressures are low and combustion is less efficient (Sutkus et al., 2001). Table SI1 summarises values of EI(CO) certified by ICAO for specific in-use aircraft engines and also lists EI(CO) for various military engines. Figure 7 reports the ICAO data (all in-use engines certified from 1976 to today) as a function of LTO stages and shows that CO emission indices are generally greater at lower thrusts. Generally, average EI(CO) for in-use commercial engines included in the ICAO databank vary from 0.6 g kg $Fuel^{-1}$ at take-off power to 31 g kg $Fuel^{-1}$ at idle. Anderson et al. (2006) observed large decreases in CO emissions with increasing engine power for various FSCs (by a factor of ~8 from idle to 61% F_{00}) and reported that CO was observed to account for ~1% of the total carbon emissions at engine idle, but emissions drop off at cruise thrust (61% F_{00}) contributing $<0.1\%$. Cain et al. (2013) measured emissions from a turbo-shaft engine burning different types of fuel and observed a decrease of CO with increasing engine power mainly due to improved combustion efficiency at higher power settings. Because of their predominant emission at lower power settings, CO emissions from aircraft are of high relevance to air quality in the vicinity of airports because of idle and taxi phases conducted at low thrust and which take up most of the time aircraft spend at an airport. Figure 8 reports the total CO emissions for in-use engines during the four LTO phases and shows that CO emissions during idle are generally two orders of magnitude higher than climb and take-off phases.

After emission, CO may undergo to a series of chemical reactions in the troposphere involving hydroxyl radical, O_2 and NO to form carbon dioxide, nitrogen dioxide, and ozone.

Some studies have derived EI(CO) directly from measurements during normal operation of idle and taxi at airports and have revealed some considerable differences compared to ICAO data, with results generally higher than those certified. For example, Heland and Schäfer (1998) reported an EI(CO) of 51.8 ± 4.6 g kg $Fuel^{-1}$ at idle for a CFM56-3 engine, which was about 27-48% higher than the ICAO data. Herndon et al. (2008) reported that EI(CO) observed in ground idle plumes was greater (up to 100%) than predicted by engine certification data for the 7% thrust condition. Since CO emissions increase with decreasing thrust, these studies seem to confirm that normal idle and taxi operations at airports occur at lower thrust than the standardised ICAO LTO cycle, resulting in more CO emitted than certified values (e.g., Schäfer et al., 2003).

Some studies have measured the carbon monoxide in ambient air at airports (e.g., Schürmann et al., 2007; Heland and Schäfer, 1998; Yu et al., 2004; Herndon et al., 2008). In a study carried out at two different airports, Yu et al. (2004) observed that aircraft are an important contributor to CO in Hong Kong airport, whereas emissions from ground vehicles going in and out of the airport dominated emissions at Los Angeles. A study carried out at Zurich airport (Schürmann et al., 2007) demonstrated that CO concentrations in the vicinity of the terminals are highly dependent on aircraft movements.

4.8 Nitrogen Oxides and Nitrogen Acids

Nitrogen oxides (NO_x=NO+NO_2) in urban environments are principally emitted from fossil fuel combustion as NO, as described by the extended Zeldovich mechanism (Lavoi et al., 1970):

$$N_2+O \rightarrow NO+N$$

$$N+O_2 \rightarrow NO+O$$

$$N+ HO\cdot \rightarrow NO+H$$

NO plays an important role in atmospheric chemistry by rapidly reacting with ambient ozone or radicals to form NO_2 on a timescale of minutes (Finlayson Pitts and Pitts, 2000; Seinfeld and Pandis, 2006):

$$NO+O_3 \rightarrow NO_2+O_2$$

Other primary sources of NO_x in the troposphere are biomass burning, soil emissions, lightning, transport from the stratosphere and ammonia oxidation (IPCC, 1999). NO_2 is a strong respiratory irritant gas and its effects on human health have been extensively reviewed (Samoli et al., 2006; Weinmayr et al., 2010; Chiusolo et al., 2011) indicating a relationship with cardiovascular and respiratory diseases and mortality.

Nitrogen oxides are produced in the high temperature regions of the combustor primarily through the thermal oxidation of atmospheric N_2 and therefore NO_x formation is sensitive to combustor pressure, temperature, flow rate, and geometry (Sutkus et al., 2001). Additional NO_x may derive from the combustion of the fuel-bound nitrogen: nitrogen in the fuel is not controlled or typically measured, but it can range from near zero to perhaps 20 ppm (Chevron Corporation, 2006). Gardner et al. (1997) estimated that 93% of NO_x from aircraft is emitted in the Northern Hemisphere and ~60% at cruise altitudes. More recent estimates indicated that in 2005 the NO_x emitted during LTO was 0.23 Tg (Kim et al., 2007), accounting for ~8% of global emissions from aviation.

NO_x is included in the parameters certified by ICAO. There is a difference in the molecular mass of NO and NO_2, and in the ICAO methodology data are reported as NO_2 equivalent (unless otherwise specified). Being sensitive to combustor pressure, NO_x emissions increase monotonically with engine thrust (Table SI1, Figure 7). Generally, EI(NO_x) for in-use engines included in the ICAO databank vary from 4±1 g NO_x kg^{-1} burned $Fuel^{-1}$ at idle to 29±12 g NO_x kg^{-1} burned $Fuel^{-1}$ at take-off power. However, despite the strong relationships to power settings, NO_x total emissions per each standardised LTO phase are pretty constant during idle, approach and take-off operations (Figure 8). Carslaw et al. (2008) measured individual plumes from aircraft departing Heathrow Airport and found that engines with higher reported NO_x emissions result in proportionately lower concentrations than engines with lower emissions. This result was hypothesised to be linked to aircraft operational factors, such as take-off weight and aircraft thrust setting, which therefore may have an important influence on concentrations of NO_x. Furthermore, Carslaw and co-authors reported that NO_x concentrations can differ by up to 41% for aircraft using the same airframe and engine type, while those due to the same engine type in different airframes can differ by 28%.

In recent years there has been a growing concern over emissions of primary NO_2 as a fraction of NO_x from road traffic mainly because of the failure of NO_x emission reductions to deliver an improvement in urban NO_2 concentrations (e.g., Jenkin, 2004; Carslaw and Beevers, 2004; Carslaw, 2005; Hueglin et al., 2006; Grice et al., 2009; Mavroidis and Chaloulakou, 2011; Cyrys et al., 2012). The ratio of NO_2 to NO_x in aircraft emissions is diagnostic of combustor efficiency and several studies reported that, unlike many other forms of combustion, the majority of the NO_x emitted from modern high bypass TF engines at idle is in the form of NO_2. On the contrary, NO is dominant at high power regimes. For example, Wormhoudt et al. (2007) performed ground measurements and observed that emitted NO_2 may represent up to 80% of the total NO_x emissions for a modern engine at low thrust and 7% at the highest power setting. Other studies (Timko et al., 2010b,c; Wood et al., 2008b) reported that the NO_2/NO_x ratio may vary between 75% and 98% at low thrust, while for approach, thrust may range from 12% to 20%. Presto et al. (2011) observed that the NO/NO_x ratio increases from 0.2-0.3 at 4% F_{00} to 1 at 30% and 85% F_{00}. Other measurements carried out within 350 m of a taxiway and 550 m of a runway during common airport operations indicated that 28–35% of NO_x exists in the form of NO_2 (Herndon et al., 2004). However it was reported that the relative abundance of NO and NO_2 are subject to large uncertainties due to conversion in the plumes and the contribution of other sources. The results of a study performed by Schäfer et al. (2003) using remote sensing methodologies suggested that NO was rapidly converted to NO_2 in the exhaust plume. The NO_2 formation and destruction processes of aircraft exhausts were investigated by Wood et al. (2008b), who observed that the NO_2/NO_x fraction is significantly higher in advected measurements than in engine tests. The results suggested that a significant portion of the NO in the exhaust can be converted into NO_2 by mechanisms that do not involve ozone.

Nitrogen oxides may also be oxidised to other reactive nitrogen species and the complete family of reactive nitrogen species is denoted as reactive odd nitrogen (NO_y), which includes the sum of NO_x and its oxidation products (HNO_3, HONO, $NO_3\cdot$, N_2O_5, HNO_4, peroxyacyl nitrates, alkyl nitrates and others). Nitric acid is the major oxidation product and increasing atmospheric concentrations of NO_x favour nitric acid formation as a result of the daytime gas phase recombination reaction of hydroxyl radical with NO_2. NO_x plays a key role in secondary inorganic aerosol formation (Finlayson-Pitts and Pitts, 2000; Seinfeld and Pandis, 2006).

High levels of NO_x, particularly NO_2, are a matter of concern for air quality near major airports. For example, current NO_2 concentrations breach the UK annual mean air quality objective (40 µg m^{-3}) at some locations around Heathrow, London (UK) (UK Department of Transport, 2006; UK Statutory Instrument, 2007; HAL, 2011), while some exceedences of the Swiss annual mean NO_2 limit value (30 µg m^{-3}) have been observed near Zürich airport (Fleuti and Hofmann, 2005).

However, as most airports are located in the vicinity of large cities, the contribution of airport-related emissions to those exceedences is hard to quantify due to the major influence of other sources, such as traffic and industry. For example, Yu et al. (2004) observed that ground vehicles were the dominant source of NO_x emissions at Los Angeles airport.

Although various studies have attempted to estimate the contribution of airport operations to ambient NO_x levels, the results are often conflicting. For example, Carslaw et al. (2006) estimated that Heathrow operations accounted for ~27% of the annual mean NO_x and NO_2 at the airfield boundary and less than 15% (<10 μg m^{-3}) at background locations 2-3 km downwind of the airport, while Fleuti and Hofmann (2005) estimated the Zürich airport influence upon NO_2 to be below 1 μg m^{-3} at a distance of three or more kilometers. In both case studies concentrations of NO_x close to the airport were dominated by road traffic sources. A detailed emission inventory of UK airports was computed by Stettler et al. (2011), who pointed out that LTO emissions at London Heathrow in 2005 accounted for about 8.19×10^6 kg NO_x, of which more than 80% is in the form of NO. An emission inventory study of NO_x emissions at Zurich airport in 2003 (Unique, 2004) reported that most nitrogen oxides were released from LTO operations, while minor contributions were calculated for landside traffic, handling/airside traffic and airport infrastructure.

4.8.1 *Nitrous oxide*

Apart from NO_x, other nitrogen species have been detected and analysed in aircraft exhaust plumes and at airports. Few data are available for the emissions of nitrous oxide (N_2O) and some are contradictory. Wiesen et al.(1994) examined nitrous oxide emissions from different commercial jet engines using different fuels and reported average EI(N_2O) ranging from 97 to 122 mg kg $Fuel^{-1}$. Heland and Schäfer (1998) further analysed N_2O using FTIR techniques and observed that N_2O emitted by a CFM56-family engine was under the detection limits at idle thrust and detectable at higher power settings, with a related EI(N_2O) of 1300 mg kg $Fuel^{-1}$. Conversely, Santoni et al.

(2011) measured N_2O emissions from a CFM56-2C1 engine and concluded that at low thrust EI N_2O were 110±50 mg kg $Fuel^{-1}$ (mean±standard deviation), while a drop of emissions was observed at higher thrust levels (32±18 mg kg $Fuel^{-1}$).

4.8.2 *Nitrous acid*

HONO is generated in the gas turbines via reaction of hydroxyl radical with NO (Wormhoudt et al., 2007; Brundish et al., 2007) and ~1.1% of the total NO_y is in the form of HONO by the engine exit (Lukachko et al., 1998). Anderson et al. (2005) measured nitrous acid (HONO) in the exhaust of a B757 and observed a clear power dependence, increasing with increasing power; at high power, over 2 ppmv of HONO was detected. The same authors (Wormhoudt et al., 2007) further reported an increasing EI(HONO) at increasing thrust, but also reported that the EI(HONO)/EI(NO_2) ratio decreases with increasing engine regimes. They found that HONO is a minor constituent (up to 7%) compared with NO_x. Herndon et al. (2006) measured NO_y at Logan airport in Boston (USA) and reported that the emission index for a B737 increased from idle (2±1.9 g(NO_y) kg $Fuel^{-1}$) to take-off (19.5±3.9 g(NO_y) kg $Fuel^{-1}$). Wood et al. (2008b) reported that HONO accounts for 0.5% to 7% of NO_y emissions from aircraft exhaust depending on thrust and engine type: 2–7% for low thrust and 0.5–1% for high thrust (65–100% F_{00}). In conclusion, using data available in the literature, Lee et al. (2010) proposed that EI(HONO) should range between 0.08 and 0.8 g kg $Fuel^{-1}$. More recently, Lee et al. (2011) performed measurements of HONO from a DC-8 aircraft equipped with CFM56-series engines using both traditional and synthetic fuels and observed that the EI(HONO) increases approximately 6-fold from idle to take-off conditions, but plateaus between 65 and 100% of maximum rated engine thrust. This study also discussed the kinetics behind the HONO formation/destruction.

Jurkat et al. (2011) measured the gaseous nitrogen emissions in young aircraft exhaust plumes emitted by 8 different types of modern jet airliners in flight and calculated molar ratios of

HONO/NO and HONO/NO_y of 0.038±0.010 and 0.027 ± 0.005, respectively. The relative EI(HONO) at cruise thrust was reported to be 0.31±0.12 g NO_2 kg $Fuel^{-1}$.

4.8.3 *Nitric acid*

Most studies of HNO_3 emissions were performed using experimental measurements with chemical ionisation mass spectrometry (CIMS) in both exhaust plumes at cruising altitudes (e.g., Arnold et al., 1992;1998a; Tremmel et al., 1998; Miller et al., 2003) and simulated gas turbines (Katragkou et al., 2004) or using plume models (e.g., Garnier et al., 1997; Kraabøl et al., 2002). Generation of HNO_3 is generally lower than HONO: Lukachko et al. (1998) reported that only ~0.07% of the total NO_y is oxidised to HNO_3 by the engine exit, while Lee et al. (2010, and references therein) reported EI(HNO_3) of 0.003–0.3 g kg $Fuel^{-1}$. Because of the very low levels expected in aircraft exhaust, few studies have been carried out on the ground. There is consequently a lack of data about nitric acid measured in engine exhaust plumes during real working conditions.

4.9 Sulfur Oxides and Sulfuric Acid

4.9.1 *Sulfur oxides*

Sulfur dioxide (SO_2) is emitted into the atmosphere from both natural (volcanic activity, grassland and forest fires) and anthropogenic sources, including crude oil and coal transformation processes, fossil fuel combustion, metal smelting and various industrial processes (e.g., Seinfeld and Pandis, 2006; Smith et al., 2011). Exposure is associated with increased mortality and morbidity (Katsouyanni et al., 1997; Sunyer et al., 2003a) including cardiovascular admissions, particularly for ischemic heart disease (Sunyer et al., 2003b). Oxidation of SO_2 (S(IV)) is recognised as the major channel for the formation of atmospheric sulfuric acid (S(VI)), and sulfur trioxide (SO_3) is an important intermediate in the oxidation processes (Vahedpour et al., 2011). Consequently, SO_2 has an indirect effect on acid deposition and a key role in the aerosol system by acting as sulphate precursor. Since sulphate aerosol is known to modify the direct and indirect RF, SO_2 also has an indirect influence on climate.

Sulfur dioxide is the overwhelmingly predominant S-containing species in aircraft exhaust (Anderson et al., 2005; Lee et al., 2010) and originates mainly from the oxidation of fuel sulfur in the engines (Brown et al., 1996a: Schumann et al., 2002). Therefore, SO_2 emissions may vary greatly as a function of FSC. In the past, studies were carried out to analyse and model the sulfur emissions of aircraft and to estimate their role in the formation of visible contrails (e.g., Busen and Schumann, 1995; Schumann et al., 1996; Brown et al., 1996b; 1997; Arnold et al., 1998a). Generally an emission index of 0.8–1.3 g of SO_x (as SO_2) per kg Fuel was reported for complete combustion (e.g., Lewis et al., 1999; Kim et al., 2007; Lee et al., 2010; Presto et al., 2011), however measurements at flight altitudes have showed that sulfur dioxide varies with the average FSC (e.g., Arnold et al., 1998a; Schumann et al., 1998). For example, Hunton et al. (2000) reported that the EI(SO_2) varied from 2.49 g SO_2 kg fuel^{-1} for a high-sulfur fuel (~1150 ppmm S) in a test chamber to less than 0.01 g SO_2 kg fuel^{-1} for a low-sulfur fuel (~10 ppmm S). They also reported that there is no dependence of emission indices upon engine power.

In this context, it is very important to stress that no S is created or destroyed from the fuel to the exhausts, therefore for every fuel S atom there is a molecule of SO_2 or SO_3 at the exhaust plane (the SO_3 quickly converts to H_2SO_4). In this way the emission indices of total emitted S may vary according to the FSC, whereas the only uncertainties are in the speciation between S(IV) to S(VI) species, i.e. in the conversion efficiency, which is discussed fully later.

The importance of SO_2 emissions at local scale, i.e. near the airports, was highlighted by Yu et al. (2004), who found that sulfur dioxide was a good tracer of aircraft emissions at both Los Angeles and Hong Kong airports. However, on a global scale the aviation source is considered to be secondary with respect to other major sources of SO_2: Kjellström et al. (1999) used a atmospheric general circulation model including the atmospheric sulfur cycle to investigate the impact of aircraft sulfur emissions on the global sulfur budget of the atmosphere and concluded that aviation accounted for about 1% of the total sulphate mass north of 40°N, where aircraft emissions are largest. In 2004, about 0.18 Tg of SO_2 was estimated to be emitted from aviation (Lee et al., 2010) using an EI(SO_2) of 0.8 g Fuel^{-1}. An estimation of SO_2 produced by aircraft below 1000 m can be computed by applying a constant EI(SO_2) of 0.8 g kg Fuel^{-1} and by considering the global use of fuel reported by the literature during LTO cycles in 2005 (Table 2). Results show a global emission of 11 Mg SO_2 of which about 2.5 Mg y^{-1} are emitted within Europe.

4.9.2 *Conversion of S(IV) to S(VI)*

Despite SO_2 being the dominant S-species in aircraft exhaust emissions, a fraction can be further oxidised to form S(VI) as SO_3 and H_2SO_4 (Lee et al., 2010). The presence of SO_3 has been established in gas turbine engine exhaust and as attributed mainly to the oxidation of SO_2 by O atoms (Arnold et al., 1998a) or by hydroxyl radicals in exhaust plumes (Tremmel and Schumann, 1999). The further reaction with water vapour rapidly converts SO_3 to sulfuric acid, according to Stockwell and Calvert (1983); Stockwell (1994); Brown et al., (1996a) and Seinfeld and Pandis, (2006):

$$SO_2 + HO\cdot + M \rightarrow HOSO_2\cdot + M$$

$$HOSO_2\cdot + O_2 \rightarrow SO_3 + HO_2\cdot$$

$$SO_3 + H_2O + M \rightarrow H_2SO_4 + M$$

Starik et al. (2002) computed that ~1% of the sulfur is converted into SO_3 within the combustor and about 10% into SO_3 and H_2SO_4 before the engine exit. Past numerical simulations of H_2SO_4 formation from atomic oxygen and hydroxyl radical in aircraft engines indicated that between 2% and 10% of the fuel sulfur is emitted as S(VI) (Brown et al., 1996a; Lukachko et al., 1998). However, current understanding indicates a more realistic value of 2% (or possibly less). These studies also indicate that S(VI) conversion in the turbine is kinetically limited by the level of atomic oxygen, resulting in a higher oxidation efficiency at lower FSCs. Katragkou et al. (2004) report that the limiting factor of this series of reactions is the oxidation of SO_2 by the hydroxyl radical, which is somewhat uncertain at the high temperatures in gas turbine engines. The knowledge of the mechanisms involving sulfur species and their interactions with H, O atoms and radicals occurring within a combustor is far from complete and are the subject of discussion (e.g., Blitz et al., 2003; Somnitz et al., 2005; DeWitt and Hwang, 2005; Yilmaz et al., 2006; Hindiyarti et al., 2007; Rasmussen et al., 2007; Wheeler and Schaefer, 2009; Hwang et al., 2010).

Once emitted, the gaseous sulfuric acid may act as an important precursor for aerosol because of its low vapour pressure. An understanding of the processes controlling sulphate aerosols is therefore essential to the study of the mechanisms of formation of particles generated by aircraft (e.g., Starik et al., 2004). For example, Arnold et al (1998a) reported no detectable levels of sulfuric acid in the gas phase behind an in-flight commercial aircraft, leading to the inference that initially formed H_2SO_4 experiences a rapid gas-to-particle conversion at plume ages <1.6 s. Sulfuric acid was measured in several other studies at cruising altitudes and for different FSCs (e.g., Fahey et al., 1995b; Busen and Schumann, 1995; Schumann et al., 1996; Curtius et al., 1998; Arnold et al., 1998a; Schröder et al., 2000; Schumann et al., 2000; Curtius et al., 2002) as well as in fuel combustion experiments at ground-level (Frenzel and Arnold, 1994; Curtius et al., 1998; 2002; Kiendler and Arnold, 2002; Sorokin et al., 2004) and during combustor testing (Katragkou et al., 2004). Curtius et al. (2002) reported H_2SO_4 concentrations measured in the plume were up to 600 pptv for a 56 ppmm FSC, while the average concentration of H_2SO_4 measured in the ambient atmosphere outside the aircraft plume was 88 pptv and the maximum ambient atmospheric concentration 300 pptv.

The abundance ratio, sometime named conversion factor (ε=(SO_3+H_2SO_4) /total sulfur) has been widely used to assess the ratio of S(VI) to total sulfur at the exit of engines. The literature offers numerous estimates or measures of ε. However, the results are often difficult to compare as they are derived by different methods, ranging from direct measurements, indirect computations and models. In addition, most studies take in account only particulate sulphate, while only a few studies have measured both particulate and gaseous phases. Anyway, Timko et al. (2010b) demonstrated that the conversion of S(IV) to S(VI) is independent of engine technology for most modern in-use engines. Earlier values of ε are well summarised in DeWitt and Hwang (2005), while most recent measurements and modelling studies of aircraft plume chemistry reported other direct, indirect and inferred values of ε. Generally, ε values between 1 and 3% are commonly reported. For example, ε values between 6 and 31% have been calculated for a B757 aircraft (Miake-Lye et al., 1998), while Schumann et al. (2002) observed ε between 0.34 and 4.5% for an old engine (Mk501) and 3.3±1.8% for a modern engine (CFM56-3B1). For low FSC, they also reported that ε was considerably smaller than implied by the volume of volatile particles in the exhaust, while for FSC≥100 ppm, sulfuric acid is the most important precursor of volatile aerosols formed in aircraft exhaust plumes of modern engines. Kiendler and Arnold (2002) inferred an ε value of 2±0.8% for a M45H engine on the ground, while Curtius et al. (1998; 2002) reported 3.3±1.8% in the plume of a B737-300 aircraft in flight by measuring the total H_2SO_4 content in both gaseous and aerosol phases. The sulfur conversion fraction of an RB211 engine was computed by Starik et al. (2002) using a model and results showed that increases in FSC cause a minor reduction in ε, reporting values ≈9%, and ≈8.4% for FSC of 0.04% and 0.3%, respectively. Wilson et al. (2004) and Sorokin et al. (2004) observed ε of 2.3±1.2% in an A310 equipped with a CF6-series engine at an exhaust age of about 5 ms from the combustor exit, while Jurkat et al (2011) derived ε for various in-flight aircraft and reported an average value of 2.2 ± 0.5%, varying from a minimum of 1.2% for a Trent-series and a maximum of 2.8% for a CMF56-series engines. Wong et al. (2008) modelled the microphysical processes involved and suggested conversion efficiency of 1–2%. Timko et al. (2010b) reported ε ranging from 0.08% to 0.01%, while Kinsey et al. (2011) suggest a median value of 2.4%. Petzold et al. (2005b) reported that sulfur partitioning at 150°C was 97 % $SO_2 \leq$ 2.7% gaseous $H_2SO_4 <$ 0.3% chemisorbed H_2SO_4 at soot particle surface. Regarding the relative abundance of the two S(VI) species, during the COMS experiments Sorokin et al. (2004) reported that SO_3 represented the major fraction of S(VI) in the exhaust behind the combustor and that SO_3 conversion to H_2SO_4 takes place in the sampling line where the exhaust gases spend a sufficiently long time and where the temperature is markedly lower than in the hot exhaust. Other experimental measurements made during the EXCAVATE experiment by Anderson et al. (2005) led to the conclusion that the fraction of total sulfur that existed as SO_3 would have to be less than 0.005%.

According to the conversion factors for sulfur species and taking in account the mass conservation of S in the exhaust plumes (no S is created or destroyed from the fuel to the exhausts), the computation of the EIs can be assessed by applying:

$$EI(SO_2) = (M(SO_2)/M(S)) \cdot FSC \cdot (1-\varepsilon)$$

and

$$EI(SO_4^{2-}) = (M(SO_4^{2-})/M(S)) \cdot FSC \cdot \varepsilon$$

where M( ) represents the molecular weights of sulfur species, FSC is the fuel sulfur content and ε is the S(IV) to S(VI) conversion efficiency as a fraction, e.g. 0.02 and a unit conversion may be necessary (e.g. if FSC is in expressed ppmm, etc).

Another important consideration concerning the sulphate derived from aircraft engines was pointed out during the APEX-1 project, which was primarily developed to investigate the effects of fuel composition on emissions at various power settings (e.g., Wey et al., 2006; Knighton et al., 2007; Yelvington et al., 2007; Onash et al., 2009). General results from the testing of a CFM56-series engine showed a strong linear relationship (r^2=0.93) between FSC and emission indices for sulphate, which can be approximately described by the linear equation EI(sulfur in mg kg Fuel^{-1})=0.0136·FSC(in ppm)+4.4952 (Kinsey, 2009).

4.10 Ozone

Ozone (O_3) is a reactive oxidant gas playing a key role in photochemical air pollution and in atmospheric oxidation processes. Ozone is associated with decrements in respiratory function and death from respiratory causes (Jerrett et al., 2009; Yang and Omaye, 2009). Although in the upper atmosphere it acts as a barrier for ultraviolet radiation, in the lower troposphere is a secondary air pollutant generated through a series of complex photochemical reactions involving reactive hydrocarbons, solar radiation and NO_2 (Finlayson-Pitts and Pitts, 2000; Seinfeld and Pandis, 2006).

Ozone is not primarily produced by aircraft engines, however some ozone precursor such as CO, NO_x and VOCs are emitted from the exhaust and may subsequently increase the boundary layer O_3 pollution. Note that, amongst the ozone precursors, both CO and many VOCs are mainly emitted at low power settings during airport taxi and idle operations, while NO_x is mainly released during take-off and climb phases, when engines reach higher thrusts. It is reported that NO emissions, which are dominant at highest thrusts, initially cause local ozone reductions in aircraft plumes (Kraabøl et al., 2000a,b) following:

$$O_3+NO \rightarrow NO_2+O_2$$

but subsequently the photolysis of NO_2 may form atomic oxygen which reacts with molecular O_2 to form O_3:

$$NO_2+h\nu \rightarrow NO+O$$

$$O+O_2+M \rightarrow O_3+M$$

where M is N_2, O_2 or another molecule absorbing the excess energy to stabilise the ozone formed (Seinfeld and Pandis, 2006). A contrary effect, i.e. a decrease in O_3 concentrations, may also occur due to the reaction of ozone with other compounds emitted from aircraft. For example, it is recognised that alkenes, which are emitted in the exhaust plumes, are susceptible to reaction with ozone forming primary carbonyls and bi-radicals (e.g., Grosjean et al., 1994; Seinfeld and Pandis, 2006) and consuming O_3.

Although the effects of aircraft emissions on ozone depletion in the upper troposphere and stratosphere have been addressed by IPCC (1999) and the European 6th Framework 'ATTICA' (Assessment of Transport Impacts on Climate Change and Ozone Depletion) project (Lee et al., 2010), less attention has been given to the effects within the boundary layer due to emissions during LTO operations.

4.11 Hydrocarbons

Unburned hydrocarbons (UHC) are emitted as a result of the inefficiency of jet turbine engines to completely convert fuel to CO_2 and H_2O (Knighton et al., 2009). Although the levels of UHC emitted by aviation are considered negligible relative to emissions from surface transportation systems such road traffic, they may cause adverse health effects on exposed people, including workers and travellers at airports, and residents who live near large hubs. Therefore, UHC are included as parameter to be monitored during the LTO cycles by ICAO (ICAO, 2008). Analyzing the data provided by the ICAO databank (EASA, 2013), a large range in the magnitude of UHC emissions between different engine models can be observed. Moreover, ICAO data clearly show that the emission of UHC during complete LTO cycles have fallen considerably since the 1970s (Figure 6), mainly due to the development of more efficient technologies.

Unfortunately, the UHC parameter used by ICAO only refers to the lump sum of all hydrocarbons, including contributions from methane, and no corrections are made for background levels within the engine intake air (Anderson et al., 2006; Lee et al., 2010). Consequently, UHC data give no information on the large number of specific non-methane hydrocarbons (NMHCs) nowadays identified, and in some cases quantified, in aircraft exhaust plumes (Wilson et al., 2004; Anderson et al., 2006; Lobo et al., 2007; Agrawal et al., 2008; Herndon et al., 2009). This fact clearly represents a significant gap in the knowledge of impacts of aircraft on both environmental and human health endpoints, because of the very different physicochemical and toxicological properties of each class of organic compounds. Most emitted VOC are known ozone precursors, many are particle precursors and can impact visibility after particle formation. Some compounds are known or are suspected to have adverse effects on human health and the environment. Among the hydrocarbons emitted in aircraft exhaust, 14 species (12 compounds and two groups of complex organic compounds) are present in the Hazardous Air Pollutants (HAP) list compiled by the USEPA (Federal Aviation Administration, 2003). These compounds are 1,3-butadiene, *n*-hexane, acetaldehyde, xylene, acrolein, propionaldehyde, benzene, styrene, ethylbenzene, toluene, formaldehyde, lead compounds and polycyclic organic matter as 7 and 16 PAH groups.

In the last 20 years, various research programmes and experiments have been carried out to give more detailed data on the speciated hydrocarbon emissions of aircraft engines. Among others, some milestones are listed hereafter. Spicer et al. (1984;1994) measured detailed organic emissions for the CFM56- class engines burning various JP-grade fuels; Gerstle et al. (1999; 2002) reported UHC emission rates for several military engines not included in the ICAO databank; the EXCAVATE campaign (Anderson et al., 2005; 2006) investigated the speciated-hydrocarbon emissions from an RB211-535-E4 engine at two different fuel sulfur levels; Herndon et al. (2006) investigated a set of hydrocarbons from in-use aircraft at Boston Logan International Airport; the APEX-1 campaign (Wey et al., 2006) reported the hydrocarbon speciation for a CFM56-2C1 engine using fuels with differing FSC (Knighton et al., 2007; Yelvington et al., 2007); Schürmann et al. (2007) sampled volatile organic compounds in diluted exhausts; the JETS/APEX-2 and APEX-3 campaigns (Lobo et al., 2007; Kinsey, 2009) reported data for speciated hydrocarbons in both a staged aircraft test (Yelvington et al., 2007; Wey et al., 2007; Agrawal et al., 2008; Timko et al., 2010c) and at airports (Wood et al., 2008b; Herndon et al., 2009); Knighton et al. (2009) consolidated earlier data from

Spicer et al. (1984;1994), EXCAVATE and APEX studies; Cain et al. (2013) measured speciated hydrocarbon emissions from a TS engine burning various (conventional, alternative and surrogate) fuels.

Although those studies have yielded much useful information for characterizing the emissions of hydrocarbons, to date there is still a great deal of work to be done, many chemical and physical characteristics remain unclear, and some conflicting results need to the further investigated. Firstly, Spicer et al. (1984) reported that a significant percentage (30%–40%) of the total hydrocarbon emissions at idle are made up of a large number of exhaust compounds with aliphatic, cycloaliphatic and aromatic structures, predominantly ethylene, propylene, acetylene, 1-butene, methane, and formaldehyde. This latter carbonyl was found to be the predominant aldehyde present in the exhaust. In addition to byproducts of combustion, some studies (Spicer et al., 1992;1994; Slemr et al., 2001) also observed that unburned/unreacted fuel compounds are emitted in the engine exhaust from fuel cracking and incomplete combustion. Spicer et al. (1984) reported that compounds from unburned fuel may represent a major component of exhausts and that they are mainly composed of normal C_{10} -C_{16} paraffins with smaller amounts of alkyl substituted aromatics, cycloparaffins, and branched alkanes. The unburned fuel component was also observed to be virtually eliminated at the 30% and 80% F_{00} conditions, when concentrations of all of the individual hydrocarbons are very low. Similar results were reported by Slemr et al. (2001) in both modern commercial high bypass TF engines (CFM56-2C1) and older technology engines (Rolls Royce M45H Mk501) with emissions dominated by alkenes and alkynes due to fuel cracking and aromatic compounds arising from unburned fuel.

These pioneering results were largely confirmed by more recent studies, which generally reported that emitted hydrocarbons are composed of relatively light weight (C_2–C_6) species, including alkanes and alkenes, formaldehyde, methanol, ethylene, acetaldehyde, acetic acid, benzene, toluene, phenol, styrene, naphthalene and methylnaphthalenes (Slemr et al., 2001; Anderson et al., 2006; Knighton et al., 2007; Yelvington et al., 2007; Schürmann et al., 2007; Kinsey, 2009). The results of the whole APEX study (Kinsey, 2009) partially confirmed previous data, indicating that generally the gaseous hydrocarbon emissions of various engines primarily consist of formaldehyde (16-28% of total gaseous emissions), ethylene (8-23%), acetaldehyde (5-13%), acetylene (5-15%), propene (2-8%) and glyoxal (3-8%), with significant quantities of acrolein (<4%), benzene (<3%), 1,3-butadiene (<3%), and toluene (<1%), while 16-42% of total non-methane volatile compounds remained unresolved. The sum of HCHO, ethylene, acetaldehyde, and propene may account for roughly 75% of the volatile organic compounds, while benzene, toluene, xylenes, and other substituted benzene compounds, oxygenates (acetone, glyoxal, and propanal), olefins (butene, pentene, hexane), and naphthalenes constitute the remaining 20% (Timko et al., 2010c). In addition to the numerous papers published, US Environmental Protection Agency (US EPA, 2009) also created a companion spreadsheet including data on speciated hydrocarbon from APEX projects. Figure 9 summarises the data from APEX campaigns in terms of profile (mass fraction) of the emitted hydrocarbons.

The total hydrocarbon EIs are highest at low power settings, where combustor temperatures and pressures are low and combustion is less efficient (Sutkus et al., 2001; Yelvington et al., 2007). UHC data provided by ICAO also confirm this behaviour for in-use TF engines (Figure 7). Similarly, many studies have reported the same behaviour for individual hydrocarbon species. Spicer et al. (1992; 1994) and Slemr et al. (2001) first reported that the emissions of many hydrocarbon species dropped at higher engine power by a factor of 20–50 and unburned fuel components disappeared. The EXCAVATE campaign (Anderson et al., 2006) also highlighted that most hydrocarbon species are strongly power dependent, with EIs at high thrusts dramatically lower than at idle. During APEX-1,2,3 campaigns, Knighton et al. (2007) observed that at engine power conditions significantly higher than 15% F_{00}, the engine combustion efficiency is close to 100%, resulting in hydrocarbon emissions often below the detection levels for many individual compounds. The inverse dependence of UHC upon thrust has a high relevance for air quality at airports, where idle and taxi phases are conducted at low thrusts and take up most of the time. Figure 8 shows that the cumulative UHC emission spans over two order of magnitude for in-use engines passing from idle to take-off during standardised LTO cycles.

Despite these interesting studies, the scientific literature still offers poor information on the hydrocarbon speciation and the few available data are often conflicting. For example, the potential changes in the hydrocarbon profiles at varying power are still unclear and deserve further investigation. Despite the large dependence of the magnitude of total UHC emitted from different engines, Knighton et al. (2009) observed that the ratios between the formaldehyde versus other hydrocarbon species were constant and independent of power settings. Although this result indicates constant hydrocarbon profiles with varying thrust, these results are inconsistent with other studies showing clear shifts of the hydrocarbon speciation with power. For example, during the EXCAVATE campaign, Anderson et al. (2006) observed that alkenes (mainly ethene) constituted more than 70% of the observed total NMHC emissions at idle, while at 61% F_{00} aromatic species (mostly toluene) accounted for over 50% of the total. There is currently a lack of information about the emitted hydrocarbons and this gap is mainly evident for emissions at power settings below the ICAO 7% idle. The behaviour and data for the most important classes of organics are discussed hereafter in separate sub-subsections.

4.11.1 ***Methane***

Methane (CH_4) is a radiatively active gas and is estimated to be 25 times more effective on a per-molecule level than CO_2 in terms of greenhouse effect at hundred-year time scales (Lelieveld et al, 1998). Moreover, its roles in atmospheric chemistry to produce tropospheric ozone and stratospheric water vapour indirectly enhance its climate forcing effects. Although natural emissions from wetlands are largely recognised as dominant sources of methane at global scales, anthropogenic sources, such as energy, agriculture, waste and biomass burning can further contribute to its load in the atmosphere (Dlugokencky et al., 2011 and references therein). Most studies report that that turbine engines are not a significant source of CH_4 and have concluded that most engines tend to produce minor amounts of methane at idle and may consume it at higher engine power (Spicer et al., 1992, 1994; Vay et al., 1998; Slemr et al., 2001; Anderson et al., 2006; Santoni et al., 2011). Wiesen et al.(1994) examined methane emissions from different commercial jet engines (PW 305 and RB 211) under various flight conditions using different fuels and concluded that air traffic does not contribute significantly to the global budget of methane. Santoni et al. (2011) measured methane emissions from a CFM56-2C1 engine aboard a NASA DC-8 aircraft and reported that the EI for CH_4 was (mean±standard deviation) 170±160 mg kg $Fuel^{-1}$ at 4% and 7% F_{00}, while negative values (54±33 mg kg $Fuel^{-1}$) were reported for higher thrust settings, indicating consumption of methane by the engine.

4.11.2 *Alkanes, alkenes and alkynes*

During the EXCAVATE campaign, Anderson et al. (2006) reported that the alkene species constituted over 90% of the observed total NMHC at idle but less than 20% at higher engine power settings. They also observed large decreases in alkane and alkene emissions with increasing engine power for various FSCs. In particular, EXCAVATE results showed that propylene underwent the most dramatic decrease, exhibiting a drop of mixing ratios by a factor ~280 from 7 to 61% F_{00}. In the same manner, isoprene dropped from ~2.5 ppbv to less than ~5 pptv (i.e., below the detection limit). On the other hand, these results reported decreases in alkane compounds which were much more modest, typically under a factor of 10. Schürmann et al. (2007) revealed that though isoprene was not directly found in emissions from kerosene refuelling, it was detected in considerable amounts in the aircraft exhaust which indicates that isoprene is most likely formed in the combustion process of a jet engine.

4.11.3 *Carbonyls*

Due to their known adverse effects on human health, some carbonyls (formaldehyde, acetaldehyde, propionaldehyde and acrolein) have been included in the HAP list (Federal Aviation Administration, 2003). However, nowadays there is a gap in the current state of knowledge regarding the toxicity of many other aldehydes (including glyoxal, methylglyoxal and crotonaldehyde) which are detected in sizeable quantities in aircraft exhaust plumes and have potential toxic effects (Wood et al., 2008). APEX results (Kinsey, 2009) clearly showed that carbonyls generally account for most of the gaseous hydrocarbons emitted by common aircraft engines. Agrawal et al. (2008) reported that the major three contributors to carbonyl emissions are formaldehyde, acetaldehyde and acetone, and showed that carbonyl emissions are significantly higher during the idle mode than at higher thrusts. However, measurements of carbonyl EIs were also found to be very variable since they are sensitive to changes in ambient temperature (Yelvington et al., 2007; Knighton et al., 2007; Agrawal et al., 2008). Similar results were obtained for TS engines: Cain et al. (2013) observed that the EIs for the most prevalent aldehydes emitted at various engine power combinations were formaldehyde, acetaldehyde, and propionaldehyde and also reported a decrease with increasing engine power. The results of such engine tests seem to be confirmed by ambient measurements. For example, Fanning et al. (2007) and Zhu et al. (2011) reported that the time averaged concentrations of formaldehyde and acrolein were elevated at the Los Angeles International airport relative to a background reference site.

4.11.4 *Aromatic compounds*

Benzene, toluene, ethylbenzene, and *ortho*-, *meta*-, and *para*-xylenes are an important group of VOCs collectively known as BTEX. In urban environments BTEX are principally emitted by vehicle exhaust gases because of their presence in fuels, lubricating and heating oil, while minor sources include gasoline evaporation, use of solvents and paint, leakage from natural gas and liquefied petroleum gas. The adverse health effects of benzene are well known (e.g., WHO, 2000;

Saillenfait et al., 2003; Pariselli et al., 2009, and reference therein) and it is included as a known human carcinogen by the IARC classification system. BTEX are highly reactive in the troposphere playing a key role in atmospheric chemistry as important photochemical precursors for tropospheric ozone and secondary organic aerosol generation (Atkinson, 2000; Atkinson and Arey, 2003).

Aromatic compounds are present in jet fuels, and can therefore be emitted as both unburned material and byproducts of incomplete hydrocarbon combustion, but also from fuel evaporation and refueling (Anderson et al., 2005; 2006). In this context, the benzene to toluene ratio (B/T) was often proposed to identify the fuel vs combustion origin of hydrocarbon mixtures. For example, Schürmann et al. (2007) observed that the B/T ratio at an airport is well below 1 for refuelling emissions and engine ignition while in the exhaust this value reaches up to 1.7. The US EPA (2009) mass fraction profiles (Figure 9) clearly show that BTEX account for ~4% of identified compounds, while other relevant aromatics (in order of decreasing mass fraction) are phenol, 1,2,4-trimethylbenzene, styrene, m-ethyltoluene and 1,2,3-trimethylbenzene. Generally, the literature shows large decreases in benzene and toluene emissions with increasing engine power, both for TF (Anderson et al., 2006) and TS engines (Cain et al., 2013). In particular, by studying the hydrocarbon emissions from a TS engine operating with conventional (JP-8), alternative and surrogate fuels, Cain et al. (2013) hypothesised that fuel composition and structure may play a significant role in the aromatic emissions of aircraft. They speculated that the propensity of the molecular structure of paraffins in fuels to produce benzene or toluene was observed to follow cycloparaffin > iso-paraffin > *n*-paraffin. This study also attempted to depict the chemical processes at the basis of their observations and hypothesised that iso- and *n*-paraffins must first undergo either ring closure or decomposition to combustion/pyrolytic intermediates prone to ring formation (e.g., propargyl radicals and propylene) to ultimately form cyclic and aromatic compounds. In addition, Cain et al. (2013) reported that an increased branching ratio of iso-paraffins resulted in higher production rates of the C_3-intermediates, which further contribute to ring/aromatic formation and growth.

4.11.5 *Polycyclic aromatic hydrocarbons*

Among the large number of hydrocarbon species emitted by aircraft engines, the polycyclic aromatic hydrocarbons (PAHs) deserve particular attention because most congeners are known, probable or possible human carcinogens (WHO, 2000; Armstrong et al., 2004; IARC, 2010) and because of their ubiquitous presence in the urban atmosphere (Ravindra et al., 2008; Zhang and Tao, 2009). PAH are semi-volatile and partition between the gaseous and particulate phases; lighter PAHs (2 to 3 aromatic rings) are present almost exclusively in the vapour-phase, whereas PAHs with higher molecular weights (>4 rings) are almost totally adsorbed on particles. Although PAHs may undergo oxidation by several atmospheric oxidants, their potential for long range transport cannot be disregarded (e.g., Keyte et al., 2013).

Agrawal et al. (2008) showed that lighter congeners such naphthalene and its 1-methyl and 2-methyl derivatives contribute strongly to the total PAH mass in various aircraft (TF) emissions at differing thrust modes. Moreover, they also reported that the EI(naphthalene) increased as power increased from idle mode falling off as the engine operated at the highest power. Chen et al. (2006) characterised the PAH emissions of the TS engine of a helicopter at five power settings and reported a mean total PAH concentration in the exhaust of 843 μg m^{-3}, with a maximum of 1653 μg m^{-3} emitted during ground idle. The emission level of total PAHs during a complete LTO cycle was estimated to be 1.15 g PAHs LTO^{-1}. Even if the results provide evidence for high mass concentrations of total emitted PAH, the speciation revealed that lighter congeners, which have generally lower carcinogenic potencies, were dominant: 59.7% of total PAHs emissions were made up of naphthalene, 37.8% of three-ring congeners, while the remaining 2.5% of PAHs had four- to seven-rings. The emission factor revealed U-shaped behaviour: maximum at idle (50%), minimum at fly idle (67%) and increasing until max thrust (100% F_{00}).

Although the PAH pollution at airports can be overwhelmed by external sources, such as vehicular traffic and industrial emissions, a number of studies have indicated airport emissions cannot be neglected. Cavallo et al. (2006) measured the concentrations of 23 PAH in three areas (airport apron, building and terminal/office) of a major Italian airport (Fiumicino, Rome). The airport apron was found to be suffering the highest levels of total PAHs (27.7 μg m^{-3}) with a prevalence of 2–3 ring PAH such as methylnaphthalenes and acenaphthene presumably associated with jet fuel combustion. However, they also showed that PAH levels were lower than the threshold limit value proposed for occupational exposure by ACGIH (0.2 mg m^{-3}). Similar results were obtained by Zhu et al. (2011), who observed that the semi-volatile PAHs (from phenanthrene to chrysene) were consistently higher at both blast fence and downwind sites from the take-off runway of Los Angeles airport than at a background site. This study also indicated naphthalene as the most abundant gas-phase PAH (80-85% of the total PAHs).

4.11.6 *Organic sulfur, nitrogen and chlorinated species*

Since jet fuels contain variable FSC, some organic sulfur species may form during combustion. Anderson et al. (2006) measured the emissions of OCS, CS_2 and dimethyl sulphide (DMS) from a RB211-series TF engine at varying engine power and burning two different FSC fuels. Results showed no consistent trends for OCS and CS_2 with varying thrust settings and suggested that the sources of those gases are insensitive to the FSC. In contrast, this study revealed that levels of DMS are dramatically reduced from approximately ambient levels at idle to near the instrument detection limit as engine power is increased and speculated that ambient DMS is essentially burned (oxidised) out of the exhaust stream at combustor temperatures associated with high engine power.

The presence of organic nitrogen species in aircraft exhaust may derive from the presence of nitrogen in fuels and from the potential reaction between alkanes and NO_x within the exhaust plume. During the EXCAVATE campaign, alkylnitrate species were observed in exhaust plumes with methyl nitrate, iso-propyl nitrate, and 2-butyl nitrate accounting for 80–90% of the total N-containing organic species (Anderson et al., 2006). In particular, methyl nitrate was observed to follow U-shaped curves of EI vs. fuel flow, with minimum emissions at mid-range thrust, slightly increased emissions at low thrust and strongly increased at higher powers.

Chlorinated organic compounds can form in aircraft exhaust as by-products of fossil fuel combustion in the presence of chlorine. Chlorine can be present in fuels because refineries can use salt driers to remove water from fuels (Anderson et al., 2006), and in certain circumstances may be present in ambient air as sea salt, such as in coastal environments. Despite the lack of available data in the literature, there is no evidence to date that chlorinated compounds are produced by aircraft engines. For example, Agrawal et al. (2008) observed that the emissions of dioxins from various aircraft engines are below the detection limit.

4.12 Chemi-ions

Aircraft exhausts also contain gaseous ions, the so called chemi-ions (CIs), have been measured in several studies (e.g., Reiner and Arnold, 1993;1994; Arnold et al., 1998b; Yu and Turco, 1997; Kiendler and Arnold, 2002; Eichkorn et al., 2002; Haverkamp et al., 2004; Sorokin et al., 2004; Miller et al., 2005; Anderson et al., 2005). Their formation was also found in various mobile sources (e.g., Seigneur, 2009) and is attributed to the radical–radical reactions during combustion processes. Once emitted, CIs may evolve chemically via ion-ion recombination and ion-molecule reactions involving trace gas molecules present in the exhaust (Kiendler and Arnold, 2002) and may act as aerosol precursors (Sorokin and Mirabel, 2001; Eichkorn et al., 2002). Starik (2008) provides a scheme of ion formation in hydrocarbon flames and inside the combustor.

Relatively high number concentrations of CIs have been measured: in the SULFUR experiments (Schumann et al., 2002 and reference therein) 10^9 ions cm^{-3} were reported at ground level, i.e., of the order of 10^{17} CIs kg $Fuel^{-1}$, but it was also reported that CIs decrease rapidly with increasing plume age (Arnold et al., 2000; Sorokin and Mirabel, 2001). Haverkamp et al. (2004) measured EI for the total (positive and negative) ions of $1.2x10^{16}$ - $2x10^{16}$ CIs kg $Fuel^{-1}$ and observed number concentrations of the same order of magnitude for both negative and positive ions: negative CIs varied from $6x10^7$ and $2.1x10^8$ molecules cm^{-3}, while positive ions ranged from $4x10^7$ to $1.7x10^8$ molecules cm^{-3}. About 50% of the measured ions have masses heavier than 100 amu and the most massive ions show masses up to 1500-3000 amu, depending on the fuel flow (thrust) and FSC (Haverkamp et al., 2004). Schumann et al. (2002) reported masses also exceeding 8500 amu. Identified negative CIs include many organic ions and cluster ions containing sulfuric acid, e.g., $HSO_4^-(H_2SO_4)_n$, $HSO_4^-(H_2SO_4)_n(SO_3)_m$ ($n<3$, m =0,1), NO_3^- $(HNO_3)_m$ and $HSO_4^-(HNO_3)_m$ (m=1,2). Kiendler and Arnold (2002) further reported a low stability of $HSO_4^-(H_2SO_4)_n$ ($n \geq 3$) against thermal detachment of H_2SO_4 at high temperatures, indicating the presence of gaseous H_2SO_4 in exhaust plumes. Positive CIs are mostly oxygen-containing organic compounds (Schumann et al., 2002) and considering the heavy masses of most CI, Haverkamp et al. (2004) also hypothesized the presence of large organic molecules, such as PAHs.

The generation of CIs in the combustor, their physico-chemical characteristics and the changes occurring along with plume aging are not yet well understood and merit further investigation as these ions may play a key role in the formation of numerous volatile aerosol particles (e.g., Yu and Turco, 1997; Arnold et al., 2000; Sorokin and Mirabel, 2001; Haverkamp et al., 2004; Miller et al., 2005).

4.13 Particulate Matter

Particulate matter (PM) is emitted by a great variety of both natural and anthropogenic sources. The latter include a large variety of anthropogenic processes, which emit particles with very different chemical composition and physical properties. Nowadays, PM composition and sources have been extensively investigated in a large number of different environments (e.g., Viana et al., 2008; Harrison et al., 2012; Amato et al., 2013). However, few data on PM emissions are historically available for aircraft engines (Wayson et al., 2009, Kinsey et al., 2011). In addition, ICAO has not yet defined any emission standard for PM to be applied during LTO cycles and is therefore interested in setting a certification limit for this pollutant to address related air quality and climate issues (Kinsey, 2009). In this context, there are some current programmes aiming to describe the PM emissions from aircraft engines, e.g., the Society of Automotive Engineers (SAE) E-31 Committee is developing a standard PM test method for aircraft engine certification (SAE, 2009).

Despite a number of studies which have been published recently on PM emissions from gas turbine engines from both a physical and a chemical point of view (e.g., Corporan et al., 2008; Whitefield et al., 2008; Herndon et al., 2008; Agrawal et al., 2008; Westerdahl et al., 2008; Kinsey et al., 2010; 2011), current data on aircraft-generated PM are still wholly inadequate and many open questions wait to be addressed. This gap appears to be a pressing issue because many epidemiological studies have found a strong correlation between the exposure to PM and some significant adverse human health effects (e.g., Pope and Dockery, 2006; Valavanidis et al., 2008; Polichetti et al., 2009; Karakatsani et al., 2012; Anderson et al., 2012; Heal et al., 2012; Martinelli et al., 2013). PM inhalation can affect morbidity and can lead to an increase in hospital admissions, and is significantly associated with mortality and to a substantial reduction in life expectancy (Pope et al., 2009; Hoek et al., 2010; Sapkota et al., 2012; Raaschou-Nielsen et al., 2013).

4.13.1 *Volatile and non-volatile PM*

PM generated from aircraft engines can be classified into two major fractions: non-volatile and volatile PM (e.g., Kinsey et al., 2009; Presto et al., 2011), while the combination of both volatile and non-volatile PM is commonly referred as total PM. Non-volatile PM is directly emitted by engines and is mainly composed of graphitic/elemental/black carbon with traces of metals, which are stable at the high temperatures and pressures normally reached in the exhaust plumes. Volatile PM is instead formed through the gas-to-particle partitioning and conversion processes of sulfur and various organic gases (Robinson et al., 2010; Timko et al., 2010b), which occur after the emission in the near-field plume downstream of the engine (Kinsey et al., 2011). Since the most volatile PM components are partitioned into the gas- and particulate-phases, their behaviour is sensitive on the changes in the environmental conditions with respect to the near-plume and in any case many compounds can remain in equilibrium between the two phases. This component is therefore very sensitive to the sampling conditions (Wey et al., 2006; Wong et al., 2011; Presto et al., 2011). In particular, the organic component of the volatile PM undergoing partitioning between the two phases is named organic aerosol (OA) and can be composed of a large number of different hydrocarbon classes. Moreover, as the reactive compounds can be affected by oxidation by a number of atmospheric oxidant species (mainly hydroxyl, nitrate radicals and ozone), it can be expected that the composition and the quantity of volatile PM changes progressively away from the plume, after natural cooling, dilution and chemical processes occur in the atmosphere. Many hydrocarbons of high volatility, such as BTEX, low molecular weight PAHs, alkanes and many others, may be easily oxidised to species with substantially lower volatilities (Kroll and Seinfeld, 2008) and, thus, may act as precursors for the formation of the secondary organic aerosol (SOA). The formation and the properties of the SOA, including their gas/particle partitioning, are an intense area of research (e.g., Pandis et al., 1992; Pankov, 1994; Odum et al., 1996; Kroll and Seinfeld, 2008; Hallquist et al., 2009) and the common way to describe the partitioning of a constituent *i* between the gas- and the condensed- phases with mass concentration C_{OA} can be described by a partitioning coefficient, ξ_i:

$$\xi_i=1/[1+(C^*_i/C_{OA})]$$

where C^*_i is the effective saturation concentration of the compound, i.e. a semi-empirical property describing the partitioning of complex mixtures. Donahue et al. (2009) proposed three different classes of compounds on the basis of their C^* values: (i) the low volatility organic compounds, showing C^* from 10^{-2} to 10^{-1} μg m^{-3} and mostly remaining in the condensed phase under common atmospheric conditions; (ii) the SVOCs, exhibiting C^* between 10^0 and 10^2 μg m^{-3} and undergoing significant partitioning and (iii) the intermediate volatility organic compounds (IVOCs), having C^* in the order of magnitude of 10^3—10^6 μg m^{-3}, which are almost entirely in the gas-phase. Recently, some studies have pointed out that most hydrocarbons emitted by aircraft engines are thought to be important SOA precursors (Miracolo et al., 2011; Presto et al., 2011), being in the IVOC and SVOC classes. However, the potential of hydrocarbons emitted by aircraft exhaust to form secondary components is currently poorly understood.

4.13.2 *Particulate mass*

Generally, the emission indices of PM mass range from approximately 10 to 550 mg PM kg $Fuel^{-1}$ (Kinsey, 2009). U-shaped curves of PM emissions versus thrust are commonly reported in the literature, showing elevated emissions at low power settings, a decrease to a minimum at midrange power, and then an increase at high or full power (Whitefield et al., 2008; Kinsey, 2009; Kinsey et al., 2010; 2011). Agrawal et al. (2008) noted a 10 to 40-fold increase in the EI(PM) as the engine power increased from idle to climb thrust. However, there are deviations from this behaviour: the PM mass emission indices at varying thrusts have been shown to depend on various factors, including engine families, technology, FSC, operating power, cold and warm engine conditions and environmental conditions (e.g., Kinsey, 2009) and real-time emission rates for PM for a typical TF engine have revealed significant PM spikes during changes in power settings (Agrawal et al., 2008).

The measurements of PM from aircraft exhaust are heavily dependent on the adopted methodology (e.g., Presto et al., 2011). Since the volatile PM may undergo rapid changes in time and space, the sampling protocol, such as the distance from the engine exit, and other parameters having implications on the aging of plumes play a key role in the mass of sampled particles. In addition, the environmental conditions (e.g., temperature, humidity, sunlight, wind, etc.) can also affect PM mass, particularly through the potential for particle formation, coagulation, and growth (e.g., Herndon et al., 2005). Timko et al. (2010b) reported that soot is the only type of particle detected at the engine exit plane, while volatile particles are only detected downwind (15–50 m) due to the nucleation of sulphate and organic materials in the cooling exhaust plume. Kinsey et al. (2010) indicated that a variable amount (40% to 80%) of the total PM can be composed of volatile matter, mainly in the form of sulfur and organics. Lobo et al. (2012) measured the specific PM emissions during normal LTO operations at a distance of 100-300 m downwind of an active taxi-/runway at the Oakland International Airport and reported EI(PM) between 100 and 700 mg PM kg Fuel^{-1} under both the idle/taxi and take-off conditions for various aircraft/engine combinations.

4.13.3 *Particle number concentration*

During the APEX campaigns, the observed EI(#) varied from approximately $1\cdot10^{15}$ to $1\cdot10^{17}$ particles kg Fuel^{-1} (Kinsey, 2009; Kinsey et al., 2010) and are therefore comparable on a per unit fuel burn basis to the number of particles generated from other combustion sources, such as ship emissions, biomass burning and forest fires (Kumar et al., 2013). Generally most TF engines tested during APEX projects exhibited EI(#) strongly correlated with fuel flow (Kinsey et al., 2010), with higher EI at low power settings following a logarithmic relationship of EI(#) to thrust:

$$\mathrm{EI}(\#)=m\cdot[\ln(\text{fuel flow})]+b$$

where m represents the slope of the regression line with values ranging from $-2\cdot10^{15}$ to $-3\cdot10^{16}$ and b is the intercept of the regression line varying from $2\cdot10^{16}$ to $2\cdot10^{17}$ (Kinsey, 2009). Similarly to EI(PM) the particle number indices were however observed to be sensitive to engine technology, FSC, operating power and environmental conditions: Kinsey (2009) also reported a completely different behaviour for a TJ engine (CJ610-8ATJ), with EI(#) lower at idle and relatively constant at higher F_{00}.

It was shown that EI(#) tends to increase moving away from the engine exit plane. EXCAVATE results (Anderson et al., 2005) reported increases by a factor of 10 at 25 to 35 m than at 1 m downstream of the exhaust plane. Timko et al. (2010b) further observed differences in particle number emissions sampled at engine exit plane and downwind (15-50 m) of the engine. They reported that soot is the main species detected at the engine exit plane, while the nucleation of volatile particles in the cooling exhaust gases measured downwind further led to increases in the particle number of 1-2 orders of magnitude.

Cheng and Corporan (2010) reported particle number emissions from military engines operated with JP-8 fuel in various thrust settings. They observed that a common TF engine emits increasing number of particles at increasing thrust with particle number emission indices of $5.5 \cdot 10^{15}$, $5.3 \cdot 10^{15}$, $9.6 \cdot 10^{15}$, and $8.9 \cdot 10^{15}$ particles kg Fuel^{-1} for the idle, 80%, 90% and 95% power setting, respectively. A inverse pattern with decreasing emissions at increased power settings was instead reported for a common TP engine equipping the widespread used military cargo C-130 Hercules: averaged EI were $1.8 \cdot 10^{16}$,$1.4 \cdot 10^{16}$,$1.4 \cdot 10^{16}$,$1.0 \cdot 10^{16}$, and $1.2 \cdot 10^{16}$ particles kg-fuel^{-1} for 4%, 7%, 20%, 41% and max thrusts, respectively. This study also examined two common TS engines used in most helicopters and aircraft and reported increasing emissions of particles with increasing thrust: $3.1 \cdot 10^{15}$ (idle), $3.3 \cdot 10^{15}$ (75%) and $5.5 \cdot 10^{15}$ (max thrust) particles kg-fuel^{-1} and $1.1 \cdot 10^{14}$ (idle) $1.8 \cdot 10^{15}$ (75%) and $3.0 \cdot 10^{15}$ (max thrust), respectively. Similar results were observed by Cain et al. (2013) in a TS engine burning various types of fuel: JP-8 fuel emissions were between 10^{15} and 10^{16} particles kg-fuel^{-1}, while emissions from other alternative and surrogate fuels were 1 to 2 order of magnitude lower.

Measurements of EI(#) at airports indicated similar results. Lobo et al. (2012) measured the specific PM emissions during normal LTO operations at a distance 100-300 m downwind of an active taxi-/runway at the Oakland International Airport and associated the data with various aircraft/engine combinations. They observed similar EI(#) for both idle/taxi ($7 \cdot 10^{15}$-$3 \cdot 10^{17}$ particles kg Fuel^{-1}) and take-off ($4 \cdot 10^{15}$-$2 \cdot 10^{17}$ particles kg Fuel^{-1}) phases. Klapmeyer and Marr (2012) reported that the EI(#) for in-use aircraft at a regional airport varied from $1.4 \cdot 10^{16}$ to $7.1 \cdot 10^{16}$ particles kg Fuel^{-1} and observed slightly higher concentrations during taxi phases than during take-offs.

The beneficial effects of alternative fuels upon particle emissions are nowadays under discussion. Although this review does not focus on such effects, it is interesting to note that some studies have highlighted potential positive effects on the EI(#) and EI(PM). For example, Lobo et al. (2011) reported reduced emissions of PM number emissions of about one third using 50% FT/50% Jet-A1 blend instead of Jet-A1.

4.13.4 *Size distributions*

Size distributions of airborne particles influence their residence time and dispersion (Allen et al., 2001). In addition, the dimensions of particles are directly related to their emission sources, as mechanically generated particles (e.g., wind-blown dust, sea spray) are generally largest than 1 µm, while combustion-generated (high-temperature processes, traffic, many industrial activities) are typically smaller than 1 µm (e.g., Lewis and Schwartz, 2004; Seinfeld and Pandis, 2006; Ning and Sioutas, 2010). Ultrafine particles (UFPs, diameter <100 nm) typically constitute ∼90% or more of particle number count in areas influenced by vehicle emissions (Morawska et al., 2008). UFPs have larger surface area per unit mass with respect to larger particles and can potentially contain high proportions of organic material such as polycyclic aromatic hydrocarbons. Moreover, UFPs can penetrate deeper into the respiratory tract and into cells possibly posing an elevated risk for human health (Oberdorster et al., 2004; Delfino et al., 2005; Bräuner et al., 2007; Belleudi et al., 2010; Knibbs et al., 2011).

A large number of studies (e.g., Herndon et al., 2005; Wey et al., 2007; Westerdahl et al., 2008; Cheng et al., 2008; Mazaheri et al., 2009; Dodson et al., 2009; Kinsey, 2009; Kinsey et al., 2011; Zhu et al., 2011; Presto et al., 2011; Hsu et al., 2013) have provided evidence that AEs may lead to increased concentrations of UFPs. However, the nature of semi-volatile compounds emitted by aircraft, the possible mechanisms of secondary aerosol formation and the dilution effect, make it difficult to associate a measured size distribution with a specific source. Studies performed at the exhaust exit-plane or directly downstream of the engine cannot usefully be compared with data obtained in ambient air sampled at airports. However, even if differences and limitations exist, some trends and recurring modes have been identified in most studies.

A study by Schumway (2002) used scanning electron microscopy to analyse individual particles emitted from military engines and reported predominant particles with dimensions ranging from 22 to 120 nm. It was observed that emitted particles were discrete at low thrust (approach and idle), while they tended to agglomerate at higher power (intermediate and military modes). Similar results have recently been reported by Mazaheri et al. (2013), who analyzed the aircraft emissions during normal takeoff and landing operations at an international airport by using the transmission electron microscopy technique. They reported particles in the range of 5−100 nm in diameter with a dominant nucleation mode (18−20 nm) and semisolid spherical shapes. Nowadays most studies measure particle size distributions using automatic instruments, such as scanning mobility particle sizers (SMPS), electrical low pressure impactors (ELPI), and differential mobility spectrometers (DMS). A comprehensive review of these devices is provided elsewhere (Kumar et al., 2010). Anderson et al. (2005) reported that exhaust exit-plane measurements on engines mounted in test cells and B757 aircraft in run-up facilities produce of the order of 10^{15} soot particles per kg of fuel burned with a mean mass diameter of 40 to 60 nm. Using an improved version of the nanometre aerosol size analyser (nASA), they also reported that the aerosol size distribution at 1 m from a B757 engine is a combination of volatile and non-volatile particles with a bimodal distribution. The first (non-volatile) mode was measured by heating the aerosol to 300°C before analysis with the nASA and was found to be around 20 nm; this mode was thought to be primarily composed of soot and other components including zinc, aluminium, and titanium which are from the abrasion of engine components or the trace metal impurities in the fuel. The second (volatile) mode was observed at 7 nm and comprised particles that vaporise below 300°C.

During the APEX campaigns (e.g., Wey et al., 2007; Kinsey, 2009; Kinsey et al., 2010), the particle size distributions of the emissions were generally found to be unimodal and log-normally distributed, with electrical mobility diameters ranging from ~3 nm to >100 nm and a geometric number mean diameter (GMD) of ~10–35 nm. A slightly dependence of GMD on thrust was detected, with GMD of 10–20 nm at low fuel flow rates, a decrease at mid-power and then an increase at higher thrust. These studies also reported the presence of a prominent nucleation mode mainly on samples collected farther from the engine exit (30 m) with respect to gases sampled at 1 or 10 m. This second mode was attributed to the secondary aerosol generation caused by the expansion and cooling of the exhaust plume and is composed of sulfuric acid and low-volatility hydrocarbons (Wey et al., 2007). APEX results detected changes in both the GMD and related geometric standard deviation (GSD) of the particle size distributions at varying engine and fuel type, thrust, and environmental conditions.

While APEX reported size distributions for commercial in-use airliner engines, we report data from other studies on differing engine types and technologies. Rogers et al. (2005) showed that the particles measured in the exhaust of two military engines (a FT with afterburner and a TS) were unimodally distributed with peaks at 20–40 nm. Cheng et al. (2008) observed that the particle number size distributions downstream of a C-130 Hercules showed peaks between 50 and 80 nm for engine power settings ranging from idle to maximum thrust. They also observed a clear trend of increasing particle diameter with increasing engine power setting and distance from the engine exit. Cheng et al. (2008) detected the presence of another peak corresponding to the lower instrumental limit, presumed to be an additional mode below 20 nm. Cheng and Corporan (2010) reported unimodal size distributions for military turbofan, turboprop and turboshaft emissions sampled at the engine exhaust plane. They observed that both the total particle number concentration and GMD increased as the engine power increased for all tested engines. In particular, the observed GMD ranged from 55 nm (at idle) to 85 nm (at 95% F_{00}) in turbofan, from 51 nm (at idle) to 67 nm (at max thrust) in turboprop and from 20 nm (at idle) to 42 nm (at max thrust) in a turboshaft engine.

4.13.5 *Changes of particle number and size after the dilution of plumes*

The effects of the aircraft-related emissions of UFP at airports have received increasing attention in recent years and some studies have demonstrated a clear dependence of UFP concentrations and size distributions upon aircraft operations. In addition, UFP measurements upwind and downwind of airports are of particular importance because they are performed under ambient conditions, i.e. after the plume has been diluted by air and the particle coagulation and gas-to-particle condensation processes have occurred.

Hu et al. (2009) studied the effect of aircraft movements in a neighbourhood adjacent to the regional airport of Santa Monica and observed that spikes in the particle number concentration related to the take-off phase were 440 times elevated above background and reached 2.2×10^6 particles cm^{-3}. At a site located at the blast fence of Los Angeles International Airport, Zhu et al. (2011) reported that total UFPs counts exceeded 10^7 particles cm^{-3} during take-offs. This study further investigated temporal profiles in particle concentration of 30 nm mobility diameter (corresponding to the mean geometric mode of emitted particles) due to isolated aircraft take-off events: dramatic increases of particle concentrations (from $1.6 \cdot 10^3$ to $1.7 \cdot 10^4$ particles cm^{-3}) were reported when aircraft engines are accelerated to the 100% thrust power for take-off, followed by decreases of number concentrations showing an exponential decay. Similar findings have been reported by Hsu et al. (2012), who observed that departures of jet engine aircraft on a runway may contribute to $1 \cdot 10^3$ to $7 \cdot 10^4$ particles cm^{-3}. The same authors further revealed significant higher increases of UFP at Los Angeles International airport (Hsu et al., 2013) due to the LTO activity: $2 \cdot 10^6$–$7 \cdot 10^6$ particles cm^{-3} increase at a monitor at the end of the departure runway, $8 \cdot 10^4$–$1.4 \cdot 10^5$ particles cm^{-3} at a site 250 m downwind from the runway.

Changes in the particle size distributions can also occur after plumes are diluted in ambient air due to coagulation. However, most studies have shown that particle size distributions at airports are comparable with those measured during engine tests. Air monitoring carried out in the surroundings of the Los Angeles International Airport found that the upwind site was dominated by particles of approximately 90 nm diameter whereas downwind sites were dominated by finer particles, peaking at approximately 10–15 nm (Westerdahl et al., 2008), which corresponds to the size reported during APEX campaigns for many in-use engines (Kinsey et al., 2010). Similarly, Fanning et al. (2007) and Zhu et al. (2011) reported very high number concentrations of UFPs collected at the blast fence site, with the highest numbers found at a particle size of approximately 14 nm. The same study further observed that the UFP number concentrations measured in a residential community approximately 2-3 km downwind of the airport were intermediate in concentration between the airport runway and the background reference site. This finding was associated with aircraft take-off activities and the authors noted the significant exposure and possible health implications for people living near the airport. Mazaheri et al. (2009) revealed that size distributions exhibit similar modality during all phases of the LTO cycles with particles predominantly in the range of 4–100 nm in diameter. This latter study also reported two distinct modes: a nucleation mode at diameters <30 nm observed in all LTO modes and an accumulation mode between 40 and 100 nm more pronounced during take-offs. While the nucleation mode exhibited the highest number concentration of all modes, the accumulation mode dominated the particle mass size distributions. Lobo et al. (2012) measured the specific PM emissions during normal LTO operations at a distance of 100-300 m downwind of an active taxi-/runway at the Oakland International Airport and associated the data with various aircraft/engine combinations. The size distributions were typically bimodal with a nucleation mode composed of freshly nucleated PM and an accumulation mode mostly made up of soot with some condensed volatile material. These observations closely parallel the mechanisms and size distribution of particles in diesel exhaust (Harrison et al., 2011).

4.14 Chemical Composition of PM

Although the chemical composition of PM may include most of the periodic table of the elements and many thousands of different organic compounds, it is principally composed of few major components, which usually represent several percent of the total mass of particles, and some of those may remain in thermodynamic equilibrium between gaseous and particle phases. The particulate matter emitted directly by aircraft is mostly composed of soot (e.g., Anderson et al., 2005; Timko et al., 2010b), while sulphate and semi-volatile hydrocarbons may further coat the particles after the plume dilution. However, aircraft PM may also contain traces of metals and ions, which are mainly the result of: (i) fuel impurities; (ii) corrosion and wear of mechanical components of engines; (iii) pre-existing PM drawn in the combustor. The following sub-subsections discuss the various components separately.

4.14.1 *Carbonaceous PM*

Carbonaceous PM consists of a complex mixture of elemental carbon (EC) and organic carbon (OC) (jointly referred to as soot) and commonly accounts for a large fraction of ambient fine particle mass in both rural and urban environments. Soot is primarily generated by incomplete combustion processes through the pyrolysis of organic fuels used in combustion processes. Many studies have discussed the various types of such particles; however there are still controversies and open discussion about the terminology to adopt. The terms used to identify the various fractions of carbonaceous aerosols, such as soot, black carbon (BC), elemental carbon (EC), equivalent black carbon and refractory black carbon are mainly associated with the corresponding measurement methods (e.g., Pöschl, 2003; Andreae and Gelencésr, 2006; Bond and Bergstrom, 2006; Kondo et al., 2011; Buseck et al., 2012; Long et al., 2013; Novakov and Rosen, 2013) and more generally refer to the most refractory and light-absorbing component of carbonaceous combustion particles, even if the underlying definitions and measurement methods are different (Petzold et al., 2013). Without going into the merits of this discussion, this section provides an overview of the data concerning the carbonaceous fraction and the terms used (soot, BC and EC) are the same as reported by the original authors. In any case, Lee et al. (2010) indicated that BC is often used interchangeably with soot in the literature relating to aircraft emissions, although in the strictest sense they are different.

The airliners of 1960s and 1970s emitted visible and dark exhaust plumes, especially during take-off. In recent decades, a great effort has been made by most engine manufacturers to reduce such emissions, which consisted mainly of soot and organics, and nowadays most modern airliners do not emit visible plumes. However, soot is still the primary form of non-volatile PM emitted by jet engines (e.g., Timko et al., 2010b), even if its contribution represents only few percent of the global atmospheric BC emission (Hendricks et al., 2004).

From a morphological point of view, soot particles emitted by aircraft engines have nearly spherical shapes with lognormal size distributions peaking at 30–60 nm (Petzold et al., 2003, 2005a; Popovicheva et al., 2004). However, once emitted soot particles quickly build complex agglomerates causing a second mode of larger particles between 100 and 500 nm, which are totally amorphous (Petzold et al., 1998; Popovitcheva et al., 2000; 2004; Demirdjian et al., 2007). Despite the structural characteristics of soot being of primary importance in relation to its atmospheric properties, there is a lack of experimental data on microstructure, composition and hygroscopicity of original soot emitted from aircraft engines. Some studies conducted at cruise height (Kärcher et al., 1996; Gleitsmann and Zellner, 1998) have assumed that all the soot particles in exhausts are hydrophobic. Demirdjian et al. (2007) used a combination of several analytical methods to study the microstructure and the composition of soot agglomerates sampled in an aircraft engine combustor and reported that soot was in two main fractions having quite different physicochemical properties. A major fraction of particles was found to be made up of amorphous carbon with small amounts of oxygen, sulfur and iron and was rather hydrophobic, while a second fraction was characterised by various structures and a large amount of impurities and was highly hydrophilic. Vander Wal et al. (2010) compared the physical structure and the chemical composition of soot produced by different sources, including a modern TF engine, using high resolution transmission electron microscopy and X-ray photoelectron spectroscopy. The results showed that some physical characteristics of jet engine soot, such as the lamella length distributions, are intermediate between soot produced by other sources such as wildfires and diesel, while other characteristics are singular. Jet soot was reported to have the highest sp^3 carbon content, in fact higher than the sp^2 (graphitic) content, the greatest oxygen content in the form of phenolic and carbonyl groups and the widest range of hetero-elements, including S, Na, N, Zn, Ba.

From a chemical point of view, soot is mainly made up of graphitic BC (Petzold et al., 1999; Popovicheva et al., 2004), but some particles can be also coated with organic materials and sulfur species (e.g., Petzold et al., 2003). For example, the hygroscopic properties of jet engine combustion particles have been investigated in several rig-tests and results have confirmed that the water uptake by combustion particles is generally independent of combustor operating conditions, but increases significantly with increasing FSC level, which is attributed to an increasing amount of sulfuric acid adsorbed on the particles (Gysel et al., 2003). The uptake of sulfuric acid and organics seems to be enhanced by the surface irregularities in the soot. The typical fractal agglomerate structure of soot may offer a large specific surface area for adsorption and chemical reactions (Popovitcheva et al., 2000). Recently, Loukhovitskaya et al. (2013) also investigated the uptake of HNO_3 on aviation soot.

The EIs of elemental and organic carbon were investigated during APEX campaigns (Kinsey, 2009; Onasch et al., 2009): results showed that EC ranged from 21 to 98 mg kg Fuel^{-1} and OC between 37 and 83 mg kg Fuel^{-1}. Most studies indicated that BC emissions are a function of engine thrust settings (Anderson et al., 2005; Wey et al., 2007; Kinsey, 2009; Kinsey et al., 2011), but are nearly independent of FSC (e.g., Wilson et al., 2004; Kinsey, 2009). During the EXCAVATE campaign, Anderson et al. (2005) concluded that black carbon emission indices increase significantly from idle to cruise power. These findings are also consistent with the results of the APEX campaigns: Wey et al. (2007) and Kinsey et al. (2011) reported that BC emissions are minimum at low power and increase with thrust settings, reaching values more than 0.3 g kg Fuel $^{-1}$ at power levels higher than 85% F_{00} and dominating the total mass emissions. Agrawal et al. (2008) reported that the carbonaceous PM composition (EC+OC mass) significantly increases with power and shifts from OC-rich at idle to EC-rich with rising thrust regimes. Similar findings were observed by Petzold and Schröder (1998), who indicated that the ratio of BC to total carbon ranged from 11% at idle to >80% at take-off thrust. This result is predictable when considering that the highest emissions of hydrocarbons occurs at low power. Presto et al. (2011) recently investigated both the elemental carbon and the organic aerosol emitted by a CFM56-series engine at varying thrust settings after the exhaust using a smog chamber. Their findings confirmed the U-shaped curves of PM emissions versus thrust commonly reported in the literature, but also added new important knowledge on the relative contributes of EC and OA. At low power (4%–7% F_{00}), most PM is composed of OA, while at 30% thrust very low emissions of both elemental and organic components were observed. At climb power (85%), an abrupt increase of EI(PM) occurred, mainly driven by EC, which accounted for about two thirds of the total PM.

The chemical characterisation of the organic component of the PM indicated that over 70% of the particle-phase organic compounds are made up of SVOC compounds in the *n*-alkane (mainly C_{23} to C_{33}), PAH, and sterane/hopane compound classes (Kinsey et al., 2011). Besides the lighter PAHs, which mainly partition in the gaseous phase, the heavier congeners are principally in the particulate phase and generally also have the highest carcinogenic and mutagenic potencies (Delgado-Saborit et al., 2011). Hu et al. (2009) studied the effect of aircraft movements at a site located 100 m downwind of the regional airport of Santa Monica and reported spikes in concentration of particle-bound PAHs occurring during jet take-offs (440 ng m^{-3}, i.e. 90 times the local background levels), however they did not detect significantly higher average levels of PAHs at airports. It is interesting to note that PAH emissions at airports may also undergo local deposition. In a study carried out at Delhi International Airport, Ray et al. (2008) observed that PAH contamination in the <2 mm surface soil layer reached maximum levels at a site near the landing area. The presence of PM-bound hopanes and steranes is also intriguing because these compounds are present in crude oil and are also largely used as molecular markers of vehicle emissions (e.g., Zielinska et al., 2004; Kam et al., 2012). Additional insights are therefore necessary for the characterisation of these organic compounds, which can derive either from the unburned fuel or from the emission of lubricating oils, which was hypothesised to have an important role in the mass of organic PM (Yu et al., 2010).

The emission of carbonaceous PM was also reported in further studies conducted at airports. For example, Dodson et al. (2009) performed continuous BC measurements at five monitoring sites in close proximity to a small regional airport in Warwick, Rhode Island. By coupling BC data with real-time flight activities (departures and arrivals) and meteorological data, they reported that aircraft departures and arrivals (and other sources coincident in space and time) contribute approximately 24-28% of the total BC concentrations. Further, they also indicated that aircraft take-off makes a greater contribution to BC levels than landing. Hu et al. (2009) studied the effect of aircraft movements in a neighbourhood adjacent to the regional airport of Santa Monica and generally did not observe elevated average levels of BC, although spikes in concentration of this pollutant were observed associated with jet take-offs. At a site located 100 m downwind of the take-off area, jet departures resulted in short time (60 s) peaks with average concentrations of up to 30 $\mu g\ m^{-3}$, i.e. 100 times elevated above the local background.

4.14.2 The smoke number (SN)

Despite soot corresponding to the majority of the non-volatile mass of PM emitted by aircraft, this component is not directly certified by ICAO. However, the ICAO databank requires that an exhaust opacity metric called the smoke number (SN) is measured for TF engines. SN was defined as a "dimensionless term quantifying smoke emission level based upon the staining of a filter by the reference mass of exhaust gas sample and rated on a scale of 0 to 100" (ICAO, 2008). SN was firstly collected on a filter by flowing a defined volume of the exhaust gas (12 to 21 kg of exhaust gas per square meter of filter) by a sample probe positioned directly behind the engine nozzle and inside the exhaust jet. The degree of attenuation of the filter before and after the sampling was thus measured using a reflectometer, and the SN was computed as:

$$SN=100\cdot(1-R_f/R_0)$$

where R_0 and R_f are the absolute reflectance of the filter before and after the sampling, respectively. Unfortunately, SN gives only a qualitative estimate of particle emission and was recognised to be dependent on sampling conditions, soot characteristics and morphology, and therefore was assumed to have little value for estimating atmospheric impacts (Anderson et al., 2005). Moreover, it was reported that particles with a diameter less than 300 nm passed through the filter and therefore only the larger particles are collected resulting in a relative weak accuracy of measurement (Kugele et al., 2005).

Several studies have attempted to correlate SN to BC mass concentration (e.g., Champagne, 1971; Whyte, 1982; Girling et al., 1990; Petzold and Döpelheuer, 1998; Wayson et al., 2009; Peck et al., 2013; Stettler et al., 2013a,b) and today an interim methodology named first-order approximation 3.0 (FOA3) was developed and used to estimate BC mass emissions normalised by fuel burn EI(BC) from SN (Wayson et al., 2009). Although this calculation was reported to be dependent upon the mode-specific SN recorded in the engine databank (e.g., Stettler et al., 2011), recently Stettler et al. (2013b) observed that the correlation between BC and SN depends on the particle size distribution and that the methods suggested to convert SN to BC could lead to heavy underestimations of BC concentrations. An alternative method independent of the SN (FOX) was also recently developed and first studies reported an improved estimation of BC (Stettler et al., 2013a), but it needs to be further tested. To fill this gap, recently an group of experts was called to define new standard procedures for BC measurement at ground level for regulatory purposes (SAE, 2009). In the absence of defined standards, the scientific literature offers a number of studies on the emission of soot, BC and EC.

4.14.3 Inorganic ions

The analysis of the major inorganic ions in aircraft exhaust has a clear dependence on the adopted sampling methodology and can be affected by many artefacts. As for most hydrocarbons, ions may undergo gas-to-particle partitioning and some species may further derive from chemical reactions in the atmosphere or on the filter surface. For example, the concentrations of aerosol nitrate can be affected by the adsorption of nitric acid gas on pre-existing particles, while evaporative losses occur at temperatures >20 °C and the exhaust plumes largely exceed this temperature. In addition, sulphate may form quickly due to the oxidation of $SO_{2,}$ coating soot particles. In view of this, Anderson et al. (2005) firstly reported that the concentration of sulphate aerosol rose considerably as sampling was performed progressively downstream of the engine, suggesting that sulphate particles may originate or undergo rapid growth within aircraft exhaust plumes. These findings were further confirmed by APEX campaigns. Agrawal et al. (2008) noted that the mass of the ions collected at 1 m from the engine exit plane were below the detection limit for most ions, while only sulphate was detectable. On the contrary, APEX samplings at 30 m reported EI(ions) in the range of 30-40 mg kg $Fuel^{-1}$ dominated by sulphate (53%–72% of the total ion EIs) and ammonium (Kinsey et al., 2011). In summary, there is a lack of data on the ionic component of exhaust emissions of aircraft and this merits further investigation.

4.14.10 Elemental composition

There is a severe shortage of data on the elemental composition of PM emitted by aircraft. Kinsey et al. (2011) reported that $PM_{2.5}$ emissions are composed of various trace elements mainly originating from fuels, lubricating oils, engine wear and corrosion, although release from the sampling line and fugitive dust may contribute to the total load. During the APEX campaigns, the elemental composition of PM emitted from aircraft engines was analyzed for a number of different aircraft engines. The total elemental emissions (sum of Mg, Si, P, S, Cl, K, Ca, Ti, Cr, Mn, Fe, Ni, Cu, Zn, Br, Ag, In, Sb, Te, I, Tl) were in the range of 6.3—27.5 mg elements kg $Fuel^{-1}$, corresponding to 2–7% of the total emitted PM and were dominated by sulfur (54%-80% of total element mass) (Kinsey, 2009; Kinsey et al., 2011). As expected, sulfur was well correlated with sulphate and most of the sulfur on the filter exists as sulphate (Agrawal et al., 2008). Moreover, the variability in the metal emissions was observed to be much greater between different engines than between engine thrust settings (Agrawal et al., 2008).

Recently, Mazaheri et al. (2013) investigated the physical and chemical characteristics of individual particles collected in the exhausts of in-use aircraft during landing and takeoff by using transmission microscopy and energy dispersive X-ray spectroscopy. They reported that most of the measured particles have a spherical shape in the nucleation mode (18−20 nm) and only contain C, O, S, Cl, and in some cases K. They also reported fewer particles having a more irregular shape resulting in a larger average aspect ratio and a much greater and diverse range of elements. While the small spherical particles have been linked to the combustion processes of engines, the latter irregular particles have been linked to a diverse range of sources, including tyre wear, fine dusts, vehicular traffic, and possibly engine wear.

4.14.12 Secondary aerosol

Despite the potential role of aircraft emissions in forming SIA and SOA, there is a lack of information on the chain of processes affecting aircraft emissions once emitted in ambient air. A recent study by Miracolo et al. (2011) used a smog chamber to simulate the aging of the particulate matter emitted from a TF engine under typical (summertime) atmospheric conditions. Their findings pointed out the key role of the photo-oxidation processes in forming both SIA and SOA. They reported that after several hours of photo-oxidation, the ratio of secondary-to primary PM mass was on average 35±4.1, 17±2.5, 60±2.2 and 2.7±1.1 for increasing thrusts settings (4%, 7%, 30% and 85% F_{00}, respectively). Miracolo et al. (2011) also observed that SOA dominates the secondary PM at low thrust, while secondary sulphate becomes the main secondary component at higher power.

It is not clear if aircraft emissions can influence the amount of secondary aerosol on a large scale. In this regard, a recent study by Woody and Arunchalam (2013) used the Community Multiscale Air Quality (CMAQ) model to investigate the impacts of aircraft emissions on SOA at the Hartsfield-Jackson Atlanta International Airport. By applying the model at various spatial resolutions, they reported that aircraft emissions reduced SOA by ~6% at 36 and 12-km due to the chemistry of the free radicals with aircraft NO_x, while at smaller resolution the interaction between the aircraft emissions and external biogenic SOA precursors enhanced SOA (~12%).

5. AIRCRAFT NON-EXHAUST EMISSIONS

Although the vast majority of studies have focussed upon the exhaust emissions from engines, there are other aircraft-related emissions that may influence the air quality within an airport. These include emissions from the power units, i.e. APUs and GPUs, primary particles from tyre erosion and brake wear, oil leaks and corrosion of aluminium alloys, all of which have been recognised to impact air quality near airports but at date have received only limited consideration.

5.1 Tyre, Brake and Runway Surface Wear

Tyre and brake wear during landing and runway dust re-suspension have been estimated to be major sources of particulate matter. This is expected as smoke is clearly visible to the naked eye when aircraft wheels contact the ground and spin up to the landing velocity. Despite that, the proportion of the mass lost from aircraft tyres and brakes that becomes suspended as fine PM has not been extensively studied; the few available data indicate that the rubber lost from tyre wear can vary from few grams to ~0.8 kg per landing (Morris, 2006; Bennett et al., 2011 and references therein). Particulate emissions from tyres have been suggested to be dependent upon the maximum take-off weight, but other factors may have a role in the rubber wear, e.g., number of wheels, weather conditions, engine type, airport runway length and taxiway layout and operating procedures (Morris, 2006). The subsequent activation of brakes to bring the aircraft to a stop may further abrade brake lining material from discs and pads and may release fine particles as for road vehicles (e.g., Pant and Harrison, 2013). From a physicochemical point of view, it is plausible that brake wear includes both the emission of material from the abrasion of discs and the volatilisation and condensation of brake pad materials, while soot may arise from the thermal degradation of tyre polymers. This was confirmed by experimental data collected at a major European airport: Amato et al. (2010) reported unusually high levels of both organic carbon and metals possibly sourced from tyre detritus/smoke in runway dust (Ba, Zn, Mo) and from brake dust in ambient PM_{10} (Cu, Sb). In addition to tyre and brake wear, landing field wear and re-suspension can also occur, as usually aircraft land on a runway generally constructed of asphalt, concrete, gravel or grass.

For example, studies at Gatwick airport estimated that tyre and brake wear are dominant sources of PM_{10}, accounting about 22 and 4.5 tonnes y^{-1}, respectively, i.e. about 60% and 12% of all aircraft-related emissions, respectively (British Airports Authority, 2006). However, these emissions are subject to large uncertainties as they are dependent on many factors, including speed at landing, some aircraft characteristics (weight, number of wheels, brake material if carbon or steel) and runway characteristics (length, weather conditions) (Underwood et al., 2004).

Bennett et al. (2011) collected landing and braking dust samples from the undercarriage (oleo legs) and wheel hubs of aircraft and reported that they have bimodal distributions, with peaks at aerodynamic diameters of about 10 and 50 μm. A further SEM-EDS analysis has revealed that particles may contain various materials embedded in a carbonaceous substrate: (i) soot arising from the burning of the tyre rubber, from the asphalt tar or from brake abrasion; (ii) runway dust mainly composed of typical crustal materials (quartz and feldspar particles) which are lifted mechanically from the ground surface; (iii) small droplet (35 μm) of Fe, associated with Co and other transition metals (Mn, Ni, V, Zn) which are commonly found in asphalt concrete and (iv) irregular Fe particles (<10 μm). This study also reported that aluminium, which is typically used as tracer for crustal materials from runway wear, can also derive from Al hydroxide included in some tyre formulations.

5.2 Other Mechanical Components

High-strength aluminium alloys are commonly used as the aircraft fuselage materials in the body and wings, while minor amounts of other elements (Cu, Zn, Mg) may be also present in various airframe components (Wei et al., 1998). Aluminium alloys have a microstructure that can be highly susceptible to intergranular and pitting corrosion, and weathering is recognised as a major cause of structural damage to aircraft structure and coatings (Usmani and Donley, 2002; Russo et al., 2009: Knight et al., 2011), along with long term operations (Ostash et al., 2006), runway de-icing chemicals (Huttunen-Saarivirta et al., 2011) and atmospheric pollution and salts (Cole and Paterson, 2009). The degradation of aircraft mechanical components is also connected with mechanical, and corrosion-mechanical (macrocracks) defects, which lead to a decrease in its load-bearing capacity (Ostash et al., 2006). Corrosion has many forms and affects most structural alloys found in airframes: of particular importance is pitting and intergranular corrosion, which can develop into fatigue cracks, stress corrosion cracks or exfoliation (Liao et al., 2008). In this light, it is plausible that corrosion and mechanical stress of some aircraft components may release metallic particles into the environment. For example, using scanning electron microscopy techniques, Amato et al. (2010) founded the relatively common presence of platy aluminous particles derived from airframe corrosion in the ambient PM_{10} samples collected near the El Prat airport in Barcelona.

5.3 Oil Leaks

In addition to exhaust from jet fuel combustion, oil escaping or burning from lubricated parts may be vented overboard from aircraft engines and therefore may further contribute to the total emissions of aircraft (Onash et al., 2009; Timko et al., 2010b; Yu et al., 2010; 2012). Aircraft lubricating oils are usually composed of a mixture of synthetic C_5-C_{10} fatty acid esters of pentaerythritol and dipentaerythritol with specialised additives (Yu et al., 2010; 2012). Some of these, such as tricresyl phosphate, are recognised as toxic to humans (Craig and Barth, 1999; Van Netten, 1999; Winder and Balouet, 2002: Marsillach et al., 2011) and have been detected in ambient air and aircraft cabins, posing a risk for aviation technicians, loaders, crew and passengers in case of release into the environment (e.g., Solbu et al., 2010; Liyasova et al., 2011; Denola et al., 2011; Schindler et al., 2013). Yu et al. (2010) reported that the degree of degradation of lubrication oil during aircraft engine operations as a result of friction and/or pyrolysis might be negligible, suggesting that most emitted oil is unburned. Because of its low volatility, unburned lubricating oil may exit from engines as vapour or submicrometre droplets and may further condense and add mass to the organic PM in the wake of the aircraft. Results of exhaust characterisation measurements suggest that the contribution of lubrication system releases to the organic PM may be greater than the engine exhaust (Timko et al., 2010b): they estimated that the contribution of oil leaks to the total mass of organics generally lies within the range 10-20% for low thrust and 50% for high thrust settings. A recent study (Yu et al., 2012) has identified and quantified the lubricating oil in the particulate matter emissions from various engines of in-service commercial aircraft at two airports. This study used the characteristic mass marker of lubricating oil (ion fragment intensity between m/z = 85 and 71) to distinguish lubricating oil from jet engine combustion products. Results revealed that lubricating oil is commonly present in organic PM emissions in association with emitted soot particles, unlike the purely oil droplets observed at the lubrication system vent. The contribution from lubricating oil in aircraft plumes was observed to vary from 5% to 100% in mesured aircraft plumes.

Yu et al. (2010) measured the size distributions of submicrometre unburned lubricant oil released from engines with C-TOF-AMS and UHSAS and reported a shift to larger sizes with increasing power. At idle thrust they observed a C-TOF-AMS vacuum aerodynamic diameter (D_{va}) of 260±3 nm, while the UHSAS volume equivalent diameter (D_{ve}) was 281±9 nm. At higher engine power, they observed modes at 272±4 nm and 350±8 nm for C-TOF-AMS and UHSAS, respectively.

6. OTHER AIRPORT-RELATED EMISSIONS

Apart from aircraft exhaust and non-exhaust emissions, other sources can be present within an airport and can contribute to the total pollutant load in the atmosphere. Among others, the emissions of the power units providing power to the aircraft (APUs and GPUs), the GSEs, additional sources on the modern terminals, intermodal transportation systems and road traffic are further considered as impacting upon the air quality and must be taken in account in airport emission measurements.

6.1 Auxiliary and Ground Power Units

The APUs are small on-board gas-turbine engines burning jet fuel coupled with an electrical generator capable of supplying electrical power to aircraft systems when required on the ground or providing pneumatic or hydraulic power to start the main engines. Despite APUs being installed in all modern airliners so as to be energetically independent, their use is becoming less significant over time due to the increasing trend toward mains supplied Ground Power Units (GPU) (Mazaheri et al., 2011). This ground equipment is supplied by the airports and includes diesel powered tugs of various types, ground carts, and also APUs installed on ground carts (e.g., Kinsey et al., 2012b). Some airports also provide electrical power to the aircraft by connecting directly to the ground network and by using fixed ground electrical power (FGEP) units. This system avoids the use of fuelled power units, with a subsequent reduction in local emissions and is thus very useful in airports not complying with air quality standards.

The role of the APUs on the air quality at airports is nowadays widely discussed and an increasing number of studies have estimated their contribution. However, the results are often conflicting. Schäfer et al. (2003) indicated that APU emissions at airport service buildings cannot be neglected in comparison to the main engine emissions. The emission inventory of the airport of Zurich in 2004 (Fleuti and Hofmann, 2005) reported that although the aircraft exhaust accounted for most of CO, hydrocarbons and NO_x (89%, 45%, 82%, respectively of total emissions), a significant percent was from APUs, GPUs, start-up-idle, handling/GSE, airside traffic and stationary sources, with APUs accounting for about half of the total non-aircraft engine emissions. HAL (2011) reported that 19% of the total NO_x emissions of London Heathrow airport are due to the use of APUs. A survey over 325 airports in the USA (Ratliff et al., 2009) estimated the emissions from APUs and

LTO cycles and stated that the greatest percentage that APUs contributed to total aircraft emissions was 10-15% for CO and between 15 and 30% for NO_x and SO_x. However, this study also reported that the airports used by a higher percentage of small and business jets tend to be affected by higher emissions from the APUs. Stettler et al. (2011) estimated that APUs contribute 6% to total $PM_{2.5}$ emissions at major UK airports. The effect of the APUs upon public health was recently estimated by Yim et al. (2013), who calculated the emissions from aircraft LTO activity, aircraft APUs and GSE at the top 20 UK airports, ranked by passenger numbers. Their findings concluded that the ban on the use of APUs would prevent about 11 averted early deaths per year (90% confidence interval 7-16).

Unlike aircraft engines, APU emissions are not certificated by ICAO, and the manufacturers generally consider information on APU emissions rates as proprietary (ICAO, 2011), therefore there are today few data available on APU emissions. Emissions from APU depend on many factors and are subject to change through provision of GPU facilities from the airport. Some airports have implemented policies to encourage the use of the GPU instead of APUs (Mazaheri et al., 2011 and reference therein), however in the absence of GPU availability, the use of APUs is still the only alternative to provide the energy for aircraft operations with engines off and for the ignition of the engines. The first studies of APU emissions started in the 1970s by the US Army (Kinsey et al., 2012b and references therein) and our literature search has found very few data in comparison to those on the jet engine emissions. However, the main studies reporting (or reprocessing) data on the APU emissions are increasing nowadays (Slogar and Holder, 1976; Williams and Lee, 1985; Gerstle et al., 1999; 2002; Wade, 2002; O'Brien and Wade, 2003; Schäfer et al., 2003; Watterson et al., 2004; EASA, 2011; Anderson et al., 2011; Blakey et al., 2011; Kinsey et al., 2012b; Williams et al., 2012).

6.2 Ground Service Equipment Emissions, Vehicular Traffic and Other Sources

As they are strictly linked to the airport operations, the amount of GSE vehicles clearly reflects the airport layout and traffic in terms of both cargo and passengers. Moreover, the operation duration is expected to increase with increasing aircraft size. Other factors include the type of engines installed and the quality of fuels used and the status of the vehicle fleet (age, wear and tear). Therefore, it is not possible to identify the unique characteristics common to all the airports and ICAO databanks not include any information about GSE emissions. Similarly, the amount of road traffic in the form of private cars, taxis, shuttle bus and trucks for transporting people and goods in and out to the airport depends on the airport layout, on the quality of the road links and intermodal transport systems and, finally, is directly related to the number of passengers and goods that the airport handles. As both the airport-induced vehicular traffic and most of the GSEs have gasoline or diesel engines, it is reasonable to consider them as common traffic. The traffic source is recognised to be dominant in many urban environments. Its chemical and physical characteristics are reported elsewhere, in a large number of studies and reviews (e.g., Hueglin et al., 2006; Thorpe and Harrison, 2008; Johansson et al., 2009; Gietl et al., 2010; Kumar et al., 2011; Harrison et al., 2012; Pant and Harrison, 2013; Amato et al., 2013).

Some studies have indicated that GSE may contribute a major fraction of the total AEs. For example, a study carried out at the McCarran airport in Las Vegas reported that approximately 60% of the total airport emissions are related to GSE (Nambisan et al., 2000). Schürmann et al. (2007) calculated that NO concentrations at Zurich airport were dominated by emissions from ground support vehicles, while Unal et al, (2005) estimated that the impacts on ozone and $PM_{2.5}$ of GSE at the Hartsfield–Jackson Atlanta International airport are small compared to the aircraft impacts. In addition, other miscellaneous sources may be also present at airports and may further increase the total pollutant load, including maintenance work, heating facilities, fugitive vapours from refuelling operations, kitchens and restaurants for passengers and operators, etc. Despite being intermittent and depending on the airport layout, these emissions may be dominant in certain circumstances. For example, Amato et al. (2010) reported that the local construction work for a new airport terminal in a major European airport (El Prat, Barcelona) was an important contributor to PM_{10} crustal dust levels along with road dust and aircraft re-suspension, with a clear drop during the weekends.

7. AIRPORT EMISSIONS AND PUBLIC HEALTH

While aircraft emissions at cruising altitudes are an air pollution issue at global scale (Barrett et al., 2010; Koo et al., 2013), the emissions within the planetary boundary layer due to the LTO operations are certainly more local and it is plausible to believe they may have a more direct effect on human health. Nevertheless, the potential subsidence of air masses due to the Ferrell and Hadley circulations, which may displace high altitude emissions toward the ground cannot be disregarded (Barrett et al., 2010).

Air quality degradation in the locality of airports is considered by some to pose a real public health hazard (Barrett et al., 2013) and some recent estimates of the aviation contribution to premature mortality have been reported (e.g., Ratliff et al., 2009; Levy et al., 2012; Ashok et al., 2013, Yim et al., 2013). Although at the current time, no specific target toxic compound has been identified to be used as a marker or indicator for human exposure to jet engine fuels and their combustion products (Tesseraux, 2004), it has been estimated that over 2 million civilian and military personnel per year are occupationally exposed to jet fuels and exhaust gases (Pleil et al., 2000; Ritchie, 2003; Cavallo et al., 2006). Kerosene-based fuels have the potential to cause acute or persistent neurotoxic effects from acute, sub-chronic, or chronic exposure of humans or animals (Ritchie et al., 2001), although evidence is lacking that current levels of exposure are harmful. Occupational exposure can occur by dermal, respiratory or oral ingestion routes of raw fuel, vapour, aerosol or exhausts. It has been postulated that chronic exposure to vapours and exhaust fumes could affect the operators inside the airport (Cavallo et al., 2006) and aircraft crew (Denola et al., 2011; Schindler et al., 2013), while occasional exposure can affect all passengers in transit (Liyasova et al., 2011). In addition, also the population living in the vicinity of airports can be exposed (Jung et al., 2011).

However, the impact of LTO emissions on surface air quality and human health is poorly quantified (Barrett et al., 2010) even though most governments have recently focused attention on management and reduction the environmental impacts of aviation. Some studies have attempted to estimate the direct and indirect effects of aviation to support environmental policy assessments and to evaluate many possible future scenarios. A global-scale study by Barrett et al. (2010) estimated that ∼8000 premature deaths per year can be attributed to aircraft emissions at cruising altitudes, representing ∼80% of the total impact of aviation (including LTO emissions) and ∼1% of air quality-related premature mortalities from all sources.

A series of more local studies have been conducted to assess the impact of AEs on human health. Generally the results have highlighted the potential adverse effects of AEs on public health and also revealed the need for more extensive information about this source. Three estimates were given for US airports in 2005: Ratliff et al. (2009) analysed aircraft LTO emissions at 325 US airports with commercial activity and estimated that 160 (90% confidence interval 64-270) premature deaths occurred due to ambient particulate matter exposure attributable to the aircraft emissions; Levy et al. (2012) estimated about 75 early deaths using activity data from 99 US airports; Ashok et al. (2013) estimated that aviation LTO emissions caused about 195 (90% confidence interval 80-340) early deaths, while the same emissions were forecast to cause ~350 (90% confidence interval 145-610) deaths in 2018. Arunachalam et al., (2011) used the Community Multiscale Air Quality model (CMAQ) to estimate the incremental contribution to $PM_{2.5}$ due to commercial aviation emissions during LTO cycles in two major and one mid-sized US airport and reported that 8-9, 11-15 and 5 (depending on model resolution) premature deaths per year can be estimated for Atlanta, Chicago and Providence airports, respectively. In Europe, Yim et al. (2013) estimated that 110 (90% CI:72-

160) early deaths occur in the UK each year (based on 2005 data) due to airport emissions. The same study also assessed that up to 65% of the health impacts of UK airports could be mitigated by replacing current fuel with low FSC fuel, by electrifying GSE, avoiding use of APUs and use of a single engine during the taxi phase. Lin et al. (2008) estimated that residents living within five miles of Rochester and La Guardia airports are affected by an increased relative risk of hospital admission of 1.47 and 1.38 respectively compared to resident living >5 miles distant. Jung et al. (2011) characterised the levels of BTEX in the vicinity of the Teterboro airport, New York/New Jersey metropolitan area, by exposing passive samplers for 48 h at the end of airport runways, in households close to the airport and out-of-neighbourhood locations. Results indicated that the average concentrations of benzene, toluene, ethylbenzene, m-/p-xylenes and o-xylene in neighbourhood concentrations (0.8, 3.8, 0.4, 1.2 and 0.4 μg m^{-3}, each BTEX respectively) were not significantly different to those measured at the airport runways (0.8, 3.2, 0.3, 1, and 0.3 μg m^{-3}, respectively) and higher than the out-of-neighbourhood locations (0.5, 1.1, 0.2, 0.8, and 0.4 μg m^{-3}, respectively). Cavallo et al. (2006) characterised the exposure to PAHs in airport personnel and evaluated the genotoxic and oxidative effects in comparison with a selected control group. They analysed 23 PAHs collected from various areas over five working days and urinary 1-hydroxypyrene (1-OHP) following five working days as a biomarker of exposure. They reported an induction of sister chromatid exchange due to PAH exposure, although its health significance was not quantified.

8. CONCLUSIONS

The main goal of this review is to give an overview on the current state of knowledge of airport-related emissions and to summarise the key characteristics of pollution and the impacts on local and global air quality. After thoroughly reviewing the latest available scientific literature, it can be concluded that the currently available information on the impact of AEs upon air quality is inadequate and the consequences of future growth in the volume of air traffic are very hard to predict. Most work has focussed upon aircraft engine exhaust during LTO cycles which accounts for a large proportion of the total emitted pollutants. However other sources such as the auxiliary power units, vehicular traffic and ground service equipment are known sources that may seriously affect air quality near to airports. In this way, it is apparent from the literature that while aircraft exhaust may account for most of the pollution at some airports, there are other sources that need to be addressed in more detail in the future, such as:

- tyre, brake, asphalt wear and the re-suspension of particles due to the turbulence created by aircraft movements;
- the emissions from the units providing power to the aircraft when required on the ground (APUs and GPUs);
- the ground support equipment that an airport offers as a service for flights and passengers, including passenger buses, baggage and food carts, container loaders, refilling trucks, cleaning, lavatory servicing and de/anti-icing vehicles, and tugs;
- the effects of the intermodal transportation systems, and road traffic for transporting people and goods in and out to the airport.

Most studies report that airport operations are responsible for significant emissions of a series of non-volatile, gaseous and semi-volatile species. Non-volatile emissions are made up of refractory material such as soot, which is emitted as PM even at high temperatures, but is also comprised of many organics and sulfur compounds, the latter mainly in the form of sulphate. Volatile emissions include compounds that exist as vapour at the engine exit plane and are made up of gaseous and vapour-phase pollutants, such as CO, NO_x, SO_2 and many organics (i.e. aromatics, alkanes, alkenes and a number of other VOCs). The less volatile fraction is of especial interest as it can react in the atmosphere and undergo gas-to-particle conversion by forming new particles or condensing on pre-existing ones.

The volatile emissions have mostly been fairly well characterised, but a comprehensive chemical speciation of the hydrocarbons and complete knowledge of their chemical processing in the atmosphere is still lacking. Detailed information on the non-volatile and semi-volatile compounds is also scarce. In spite of the increasing attention given to AEs, many issues remain unaddressed and represent a serious gap on which scientific research should focus. A list of the key characteristics of AEs that need to be carefully addressed should include:

- a careful quantification of sulfuric acid, HONO and HNO_3 directly emitted by aircraft for a large variety of engines. Currently available data refer only to few engine types and the changes of EI at varying thrusts are not completely clear. This should also include seeking a better knowledge of the characteristics and the evolution of emitted chemi-ions and a better understanding of their role as a source of sulfur and nitrogen species in plumes;
- a more realistic quantification of emission inventories for nitrogen oxides and organic compounds, which includes the variability induced by the common practices of take-off and taxi phases at reduced thrust;
- quantification of the effects of ozone-precursors emitted from aircraft and other AEs on the levels of ground-level ozone at airports, which to date have not been thoroughly investigated. In particular, since well established atmospheric photochemical reactions of many VOCs are known as potential sources of elevated ozone concentrations in the troposphere, improved chemical speciation of organic compounds is much needed. Better apportionment of ozone formation potential from aircraft emissions during LTO cycles and from other AEs should be also estimated;
- standardization of procedures for measurement of engine exhaust at ground level for regulatory purposes, which appear to be lacking mainly for PM and speciated hydrocarbon emissions. Such methodologies should take into account the semi-volatile components, which

have been recognised to make a major contribution to the total mass of emitted PM. Achievement of this objective is vital to be able to obtain data that are comparable across different studies;

- further quantitative knowledge of the chemical and physical modifications affecting many compounds and particulate matter in the atmosphere, including the oxidation of hydrocarbons to less volatile species and the formation of sulphate on the surface of pre-existing particles;
- chemical and physical characterization of PM. Far fewer data exist for PM than for the main gaseous pollutants. The chemical speciation of PM is not fully understood and the role of plumes aging on PM mass and composition is largely unknown. The role of lubrication oils, fuel type and engine technology, age and maintenance upon aircraft PM emissions also needs to be investigated;
- a more detailed assessment of the health effects of the AEs within and in the surroundings of major airports;
- the identification of particular chemical species to be used as a tracers for most of the AE sources;
- the significance of airport operations for emission reduction and management should be investigated in more depth. There is a lack of information on the effects of time-in-modes, aircraft waiting/idling durations, aircraft weight, and use of APU/GPU/FGEP on the actual emission of pollutants. A more detailed knowledge of such operations will lead to a more reliable assessment of the quantities of exhaust pollutants emitted into the air;
- the relative importance of near-airport, regional, and global scale air quality impacts of airport and aircraft emissions need to be further investigated. Most studies focus on local or global effects of the AEs, but there is no comprehensive view of air pollution over a full range of scales.

Quantification of the impact of airport emissions on local air quality is very difficult due to the complexity of airport emissions and the presence of substantial levels of pollution from other sources, with many airports being located near to urban settlements, major highways and roads or industrial installations. This makes the signal of the AEs and, in particular, of aircraft emissions very hard to distinguish. This is a serious gap because development of cost-effective strategies to improve air quality to meet regulatory requirements demands a clear quantification of the contribution of AEs to the total air pollution.

ACKNOWLEDGEMENT

We gratefully acknowledge the European Union for funding the Marie Curie Intra-European Fellowships for career development to M. Masiol through the project entitled 'Chemical and Physical Properties and Source Apportionment of Airport Emissions in the context of European Air Quality Directives' (European Commission proposal n° 328542 Project CHEERS, call: FP7-PEOPLE-2012-IEF).

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TABLE LEGENDS

Table 1: Engine-family mounted in the most popular aircraft. The number of engines for each aircraft in given within brackets. This list represents ~75% of total in-use turbofan engines provided by the ICAO databank at August 2013 and does not report data for regional jets. Average data (mean±standard deviation) for fuel consumption and emissions per LTO cycle are also reported per each engine family.

Table 2: Total annual fuel burned by aviation and emissions of H_2O, CO_2, NO_x, CO, HC, SO_x and soot (when available) provided by recent studies. Forecasts for 2020 and 2025 are also provided. Global emission data for 2008 and forecasts for 2025 were calculated starting from fuel data of Chèze et al. (2011) and emission indices of Lee et al. (2010). Kim et al. (2007) provided fuel burn and NO_x emission during LTO for the 2000-2005 period; LTO emissions of H_2O, CO_2 and SO_2 were calculated starting from fuel data of Kim et al. (2007) and emission indices of Lee et al. (2010). Note that all emissions calculated in this review are in italics.

Table 3: List of recent studies in the literature that measure EIs directly from engine or airplane tests. The table also reports studies on hydrocarbon profiles. Some information about tested aircraft and engine models, selected thrust and sampling methodologies and analytical techniques, type of fuel, date and location of experiments is also given.

Table 4: List of recent studies available in the literature reporting EIs during real aircraft operation. The table also reports supplementary information (if available) about the target of the study, period and location of experiments, tested aircraft or engine models, measured pollutants, analysed LTO phases and sampling methodologies. The list of acronyms is provided in Table 3.

Table 5: List of recent studies available in the literature conducted at airports or in their surroundings. The table also reports supplementary information (if available) about the target of the study, period and location of experiments, tested aircraft or engine models, measured pollutants, analysed LTO phases and sampling methodologies. The list of acronyms is provided in Table 3.

FIGURE LEGENDS

Figure 1: Absolute growth of aviation (1930–2012) recorded by ICAO in terms of RPK, RTK and aircraft kilometres. Data refers to ICAO (2013) and were taken from Airlines for America (2013).

Figure 2: Simplified diagram of a turbofan engine (upper left); products of ideal and actual combustion in an aircraft engine (upper right); and related atmospheric processes, products, environmental effects, human health effects and sinks of emitted compounds (bottom). Adapted from Prather et al. (1999), Wuebbles et al. (2007) and Lee et al. (2009).

Figure 3: Division of the combustion products from an aircraft engine, adapted from Lewis et al. (1999).

Figure 4: Geographical and vertical distributions of aviation: a) column sum of global fuel burn from scheduled civil aviation in 2005, as reported by Simone et al. (2013) using AEIC

model (Stettler et al., 2011); b) annual global vertical distribution of commercial aviation fuel burn for the NASA-Boeing 1992 and 1999 (Baughcum et al., 1996a,b; Sutkus et al., 2001), QUANTIFY 2000 (Owen et al., 2010), AERO2k (Eyers et al., 2004) and AEDT 2006 (Roof et al., 2007) datasets, taken from Olsen et al. (2013).

Figure 5: Standard ICAO LTO cycle. Adapted from ICAO (2011).

Figure 6: Burned fuel and emissions for complete standardised LTO cycle. Data from ICAO databank at April 2013 (EASA, 2013). All engines certified in each period were included in the statistics, without distinction of type, manufacturer, model or technology.

Figure 7: EIs provided by the ICAO databank (EASA, 2013). All in-use engines certified from 1976 to today (April 2013) are included.

Figure 8: Fuel burned and emissions of CO, NO_x and total unburned hydrocarbons during the four LTO phases. Data were calculated from the EIs and fuel consumption provided by the ICAO databank (EASA, 2013). All in-use engines certified from 1976 to today (April 2013) were included and reprocessed as a function of LTO stages and standard times (i.e., 0.7 min for take-off, 2.2 min for climb-out, 4 min for approach and 26 min for idle).

Figure 9: Results of the APEX campaigns. Profile (mass fractions) of individual hydrocarbon species. The single compounds are ordered to show decreasing fractions.

Table 1. Engine-family mounted in the most popular aircraft. The number of engines for each aircraft in given within brackets. This list represents ~75% of total in-use turbofan engines provided by the ICAO databank at August 2013 and does not report data for regional jets. Average data (mean±standard deviation) for fuel consumption and emissions per LTO cycle are also reported per each engine family.

Manufacturer	**Engine family**	**Main aircraft and number of engines**	**Fuel and emissions per LTO cycle** (kg)			
			Fuel	**CO**	**NO_x**	**HC**
General Electric	CF6 series	A300 (2); A310 (2); A330 (2); B747 (4); B767 (2); MD DC-10 (3); MD-11 (3)	811±76	11±5	12±2	2.3±2.2
	GE90 series	B777 (2)	1159±141	14±7	25±5	1.1±0.8
	GEnx series	B747 (4); B787 (2); replacing CF6 series	827±74	7±1	10±3	0.2±0.1
CMF International	CFM56 series	A318 (2); A319 (2); A320 (2); A321 (2); A340 (4); B737 (2): MD DC-8 (4)	419±46	6±2	5±1	0.6±0.4
Pratt & Whitney	JT8D series	B707 (4); B727 (3); B737 (2); MD DC-9 (2); MD80 (2)	477±35	5±2	4±1	1±0.9
	JT9D series	A300 (2); A310 (2); B747 (4); B767 (2); MD DC-10 (3)	842±45	19±10	13±1	7±4.8
	PW 4000 series	A300 (2); A310 (2); B747 (4); B767 (2); B777 (2); MD DC-11 (3)	966±150	8±3	17±6	1±0.8
Rolls-Royce	RB211 series	B747 (4); B757 (2); B767 (2); L1011 (3); Tu-204 (2)	852±128	15±15	15±5	7.1±11.1
	Trent series	A330 (2); A340 (4); A380 (4); B777 (2); B787 (2)	817±370	5±2	19±4	0.2±0.3
BMW Rolls-Royce	BR700 series	B717 (2)	332±32	4±1	4±1	0.1±0.1
International Aero Engines	V2500 series	A319 (2); A320 (2); A321 (2); MD-90 (2)	452±35	3±0.4	6±1	0.04±0.01
Aviadvigatel' Solov'ëv	D30 series	Tu-154 (3)	622±110	21±6	5±1	5.5±2.4

B (Boeing); A (Airbus); MD (McDonnell Douglas); L (Lockheed); Tu (Tupolev).

Table 2. Total annual fuel burned by aviation and emissions of H_2O, CO_2, NO_x, CO, HC, SO_x and soot (when available) provided by recent studies. Forecasts for 2020 and 2025 are also provided. Global emission data for 2008 and forecasts for 2025 were calculated starting from fuel data of Chèze et al. (2011) and emission indices of Lee et al. (2010). Kim et al. (2007) provided fuel burn and NO_x emission during LTO for the 2000-2005 period; LTO emissions of H_2O, CO_2 and SO_2 were calculated starting from fuel data of Kim et al. (2007) and emission indices of Lee et al. (2010). Note that all emissions calculated in this review are in italics.

Global										
Year	**Fleet**[a]	**Fuel**	**H_2O**	**CO_2**	**NO_x**[b]	**CO**	**HC**	**SO_x**[c]	**Soot**	**Reference**
					Tg				Mg	
1999	Scheduled air traffic which includes turboprops, passenger jets, and jet cargo aircraft	128	—	—	1.7	0.685	0.189	—	—	Sutkus et al. (2001)
2000	Scheduled and non-scheduled commercial aviation	214[d]	—	677	2.9	—	—	—	—	Owen et al. (2010)
2000	Civil and military aircraft	169	—	—	2.15	—	—	—	—	Gauss et al. (2006)
	Civil aircraft	152	—	—	1.95	—	—	—	—	Gauss et al. (2006)
	Military (difference)	*44*	—	—	*0.2*	—	—	—	—	Gauss et al. (2006)
	Commercial aviation	181	224	572	2.51	0.541	0.076	0.145	—	Kim et al. (2007)
2001	Commercial aviation	170	210	536	2.35	0.464	0.063	0.136	—	Kim et al. (2007)
2002	Commercial aviation	171	211	539	2.41	0.480	0.064	0.137	—	Kim et al. (2007)
	Civil aviation	156	193	492	2.06	0.507	0.063	—	3.9	Eyers et al. (2004)
	Military aviation	19.5	24.1	61	0.178	0.647	0.066	—	—	Eyers et al. (2004)
	Civil + Military aviation	176	217	553	2.24	1.150	0.129	—	*>3.9*	Eyers et al. (2004)
2003	Commercial aviation	176	218	557	2.49	0.486	0.062	0.141	—	Kim et al. (2007)
2004	Commercial aviation	188	233	594	2.69	0.511	0.063	0.151	—	Kim et al. (2007)
	Commercial aviation [e]	174	215	550	2.456	0.628	0.090[f]	0.102[g]	6.1	Wilkerson et al. (2010)
2005	Commercial aviation	203	251	641	2.9	0.554	0.065	0.163	—	Kim et al. (2007)
2006	Commercial aviation	188	233	595	2.656	0.679	0.098[f]	0.111[h]	6.8	Wilkerson et al. (2010)
2008	From ICAO commercial air carriers—traffic database	229	*282*	*725*	*3.21*	*0.688*	*0.092*	*0.183*	*5.7*	Fuel demand by Chèze et al. (2011)
Forecasted trend										

2020	Scheduled and non-scheduled commercial aviation	336	—	1062	4	—	—	—	—	Owen et al. (2010)
2025	—	317	*390*	*1001*	*4*	*0.951*	*0.127*	*0.253*	*7.9*	Fuel demand forecast by Chèze et al. (2011)
Emission indices										
EI	Mean emission indices	—	1230	3160	14	3	0.4	0.8	0.025	Lee et al. (2010)
LTO cycles										
2000	Commercial aviation	12.9	*15.9*	*40.8*	0.197	—	—	*0.010*	—	Kim et al. (2007)
2001	Commercial aviation	12.3	*15.1*	*38.9*	0.191	—	—	*0.010*	—	Kim et al. (2007)
2002	Commercial aviation	12.2	*15.0*	*38.6*	0.194	—	—	*0.010*	—	Kim et al. (2007)
2003	Commercial aviation	12.4	*15.3*	*39.2*	0.199	—	—	*0.010*	—	Kim et al. (2007)
2004	Commercial aviation	12.9	*15.9*	*40.8*	0.21	—	—	*0.010*	—	Kim et al. (2007)
2005	Commercial aviation	13.9	*17.1*	*43.9*	0.227	—	—	*0.011*	—	Kim et al. (2007)

a) Type of fleet, as specified in different estimates; b) NO_x is expressed as NO_2 in Sutkus et al. (2001), Gauss et al. (2006) and Wilkerson et al. (2010); c) SOx expressed as SO_2; d) normalized to the IEA total aviation fuel sales figure (see Owen et al. (2010)); e) corrected global fuel burn results (see Wilkerson et al. (2010); f) HC expressed as CH_4; g) expressed as S-SO_x, assuming that 96.3% of the SO_x-S was partitioned to SO_2-S and 3.7% to S(VI)-S (particle); h) expressed as S-SO_x, assuming that 98% of the SO_x-S was partitioned to SO_2-S.

Table 3. List of recent studies in the literature that measure EIs directly from engine or airplane tests. The table also reports studies on hydrocarbon profiles. Some information about tested aircraft and engine models, selected thrust and sampling methodologies and analytical techniques, type of fuel, date and location of experiments is also given.

Airframe/Engine	Analyzed compounds	Sampling and experimental (sampling system [analytical methods])	Tested regimes and [fuels]	References
F101 (Military TF with reheat used on the B-1B aircraft); F110 (Military TF with reheat used on the F-16C and F-16D aircraft)	CO_2, CO, NO_x, total hydrocarbons, individual organic species	Samples collected from each engine using a probe positioned just behind the exhaust nozzle	Four power settings from idle to intermediate power	Spicer et al. (1992)
TF-39 (Military TF of Lockheed C-5) and CFM-56 (TF)	CO, NO, NO_x, total hydrocarbons, C_2 to C_{17} organics, PAHs, aldehydes	Sampling: sampling rake behind the engine. Experimental: non-dispersive infrared instruments, chemiluminescence, FID, polymeric adsorbent (XAD) and DNPH cartridges[GC/MS, GC/FID], On-Line Cryogenic Trap/GC, canister[GC/MS], Total Hydrocarbon Analyzer	Idle, 30%, 80%; [JP-4; JP-5; JP-8]	Spicer et al. (1984;1994)
PW 305 (TF in small business jets)	N_2O, CH_4	Sampling: gas samples collected in the core of the engine without any bypass air. Experimental: infrared absorption spectroscopy	5.5%; 23.5%; 33.4%; 71.4%; 95.6%	Wiese et al. (1994)
Various military aircraft: T56-A-7; TF39-GE-1C ; GTCP85-180; GTCP-165-1 ; T700-GE-700; J69-T-25; J85-GE-5A; F110-GE-100; F108-CF-100 ; TF33-P-7/7A; F101-GE-102 ; TF33-P-102; F117-PW-100; AFB F118-GE-100; F404-GE-F102/400; F110-GE-129; F100-PW-100; F100-PW-229; T64-GE-100; TF34-GE-100A (All Military)	CO_2; CO; NO_x; NMHCs; Aldehydes and ketones; VOCs; filterable and condensable particulate	Sampling: various test cells, hush house exhaust rate determined using three methods: carbon balance, tracer gas and F-factor. Experimental: various US-EPA' methods, including continuous emissions monitoring system; canister [GC/MS; GC/FID]; HI-VOL [lab analysis]	Idle; Approach; Intermediate; Military; Afterburner; [JP-8]	Gerstle et al. (1999)
Research aircraft: VFW-Fokker 614 ATTAS. Engine: Rolls-Royce/SNECMA M45H Mk501 (TF)	Aerosol size distribution and chemical composition (total carbon, BC)	Sampling: ground-based measurements (also report in-flight measurements). Experimental: filter substrates[thermal technique], PCASP-100X	Different engine thrust levels: idle run and take-off	Petzold and Schröder (1998); Petzold et al. (1999)
Fighter aircraft: F-22 Raptor (Military); Engine: F119-PW-100 (TF with reheat)	CO_2; CO; NO_x; NMHCs; Filterable and condensable particulate; Aldehydes and ketones; VOCs	Sampling: engine exhaust sampling rake system; augmentor tube slipstream sampling system. Experimental: various US-EPA' methods: continuous emissions monitoring system; canister [GC/MS; GC/FID]; HI-VOL [lab analysis]	Idle (10%); approach (20%); Intermediate (70%); Military (100%); Afterburner (150%); [JP-8]	Gerstle et al. (2002)
NASA Boeing 757; Engine: RB-211-535E4 (TF)	CO_2, H_2O, HONO, HNO_3, SO_2, SO_3, H_2SO_4, nonmethane hydrocarbons, aerosol size, BC	Sampling: 1 m down steam of the turbine exhaust, aerosol-sampling probe was also affixed to the blast fence 25 m downstream of the engine exhaust plane. Experimental: IR spectrometer, DMA, OPC, aethalometer, grab samples, tunable diode laser, AMS	A range of power settings from idle to near take-off thrust; [JP-5, low and high S (810 and 1820 ppm S)]	EXCAVATE: Anderson et al. (2005;2006)

Jet trainer: T-38A Talon; Engine: 85-GE-5A (TJ)	CO_2, aerosol size, BC, nonmethane hydrocarbons, SO_2, CO_2, SO_3, H_2O, HONO, H_2SO_4, HONO, HNO_3	Sampling: 1 m down steam of the turbine exhaust. Experimental: IR spectrometer, DMA and OPC, aethalometer, grab samples, tunable diode laser, AMS	A range of power settings from idle to near take-off thrust; [JP-5 (810 ppm S)]	EXCAVATE: Anderson et al. (2005)
Fighter: F-18 (Military). Engine: F404-GE-400 in twin-engine (TF with reheat)	Particle mass concentration, PAHs, BC	Sampling: Navy jet engine exhaust emissions from tethered aircraft, measurements at a site on the active flightline tarmac, directly from the exhausts of tethered aircraft. Experimental: DustTrak particle mass monitor, PAS, photoacoustic analyzer, Gundel denuder sampler (with PUF/XAD/PUF “sandwich” cartridges), SMPS, MOUDI cascade impactor	Power-setting increases from 65% to 70%, and from 70% to 80%	Rogers et al. (2005)
Engine: dismounted T700-GE-401 (TS), which is fitted in Seahawk, Super Cobra, and Jayhawk helicopters (Military)	Particle mass concentration, PAHs, BC	Sampling: Navy jet engine exhaust emissions from engine maintenance test cells, measurements at Aircraft Intermediate Maintenance Department facility. Experimental: DustTrak particle mass monitor, PAS, photoacoustic analyzer, Gundel denuder sampler (with PUF/XAD/PUF “sandwich” cartridges), SMPS, MOUDI cascade impactor	Power-setting increases from idle to 98%	Rogers et al. (2005)
NASA Boeing 757; Engine: RB211-535-E4 (TF)	Gaseous carbon species	Sampling: 10 m behind the engine exit plane. Experimental: Canister, analyses of whole air samples [GC/FID, GC/ECD, GC/MS]	4–7%; 26%; 47%; 61%; [JP-5 low and high S]	EXCAVATE Anderson et al. (2006)
Bell helicopter; UH-1H (TS)	22 PAHs	Sampling: engine placed in a testing chamber, exhaust samples collected from the stack of the chamber using an isokinetic sampling system. Experimental: GC/MS	Five power settings: idle (50%), fly idle (67%), beed band check (79%), inlet guide vane (95%), and take off (100%); [JP-4]	Chen et al. (2006)
Military jet fighters: F-15 Eagle and the F-16 Falcon aircraft. Engines: PW F-100-PW-100 (TF with reheat)	Automatic measurements: CO_2, CO, NO, NO_2, total hydrocarbons	Sampling: extractive sampling at 23 m behind the exhaust exit plane for tests at idle through military power, and at 38 m for afterburner tests; optical remote sensing measurements 23 m behind the engine exit plane. Experimental: automatic measurements; canisters [GC/MS]; DNPH-coated cartridges [HPLC/UV detector]; OP-FTIR; UV-DOAS	Ground idle (65–70%), low intermediate (80%), high intermediate (85%), military (91–93%) and afterburner (reheat); [JP-8+100]	Cowen et al. (2009)
Aircraft: Boeing DC-8. Engine: CFM-56-2C1 (TF)	CO, CO_2, NO, NO_2, HONO, total VOCs, gas-phase speciated hydrocarbons, particle number concentration, particle size distribution, $PM_{2.5}$[mass, EC/OC, SVOCs, inorganic ions, elemental composition]	Sampling: the exhaust plume was sampled at 1, 10 and 30 m downstream of the engines. Experimental: continuous and time-integrated instruments: IR absorption, TILDAS, PTR-MS, AMS, canister[GC/MS, GC/FID], DNPH cartridges[HPLC], TEOM, CPC, SMPS, DMA, PM-2.5 cyclones [47mm PTFE filter], PM-2.5 cyclones [47mm QFF+PUF], ELPI, aethalometer, PAH analyzer; lab analyses on filters and PUF [GC/MS, TOA@NIOSH, ion chromatography, XRF]	“EPA test matrix” (typical LTO); “NASA test matrix” including 11 power settings); [3 fuels: base fuel, high sulfur (1639 ppm), high aromatic]	APEX-1: Wey et al (2006); Knighton et al. (2007); Wormhoudt et al. (2007); Yelvington et al. (2007); Wong et al. (2008); Onash et al. (2009); Kinsey (2009)

Aircraft: B737-700; B737-300. Engines: CFM56-7B24, CFM56-3B1, CFM56-3B2 (all TF)	CO_2, gas-phase speciated hydrocarbons, particle number concentration, particle size distribution, $PM_{2.5}$[mass, EC/OC, SVOCs, inorganic ions, elemental composition, PAHs]	Sampling: on-wing at the ground run-up enclosure; 1, 30 and 54 m from the exhaust nozzle exit. Experimental: continuous and time-integrated instruments: IR absorption, canister[GC/MS, GC/FID], DNPH cartridges[HPLC], TEOM, CPC, SMPS, EEPS, DMA, PM-2.5 cyclones [47mm PTFE filter, 47mm QFF+PUF], ELPI, aethalometer, PAH analyzer; lab analyses on filters and PUF [GC/MS, TOA@NIOSH, ion chromatography, XRF], AMS	4%, 7%, 30%, 40%, 65%, 85%; [Jet-A]	APEX-2: Agrawal et al. (2008); Kinsey (2009); Timko et al. (2010b;c)
Aircraft: B737-300, Embraer ERJ-145, A300, B775, plus Learjet Model 25. Engines: CFM56-3B1, AE3007A1E, AE3007A1/1, PW4158, RB211-535E4-B (all TF), plus CJ610-8ATJ (TJ)	CO_2, gas-phase speciated hydrocarbons, particle number concentration, particle size distribution, $PM_{2.5}$[mass, EC/OC, SVOCs, inorganic ions, elemental composition]	Sampling: the exhaust plume was sampled at a location 1, and 30 m downstream of the engines (sometimes at 15 and 43 m); Sampling was done at the centre-line using a single probe. Experimental: continuous and time-integrated instruments: IR absorption, TILDAS, quantum cascade-TILDAS, canister[GC/MS, GC/FID], DNPH cartridges[HPLC], TEOM, CPC, SMPS, EEPS, DMA, PM-2.5 cyclones [47mm PTFE filter, 47mm QFF+PUF], ELPI, aethalometer, PAH analyzer; lab analyses on filters and PUF [GC/MS, TOA@NIOSH, ion chromatography, XRF], AMS	4%, 7%, 15%, 30%, 45%, 65%, 85%, 100% [slightly varying for some engines, see Kinsey (2009)]; [Jet-A]	APEX-3: Knighton et al. (2007); Kinsey (2009); Timko et al. (2010b;c)
Military helicopters: Blackhawk, Apache: T700-GE-700 and T700-GE-701C (TS)	CO_2, H_2O, CO, NO, and N_2O (FTIR); particle number, mass and size distributions, smoke number (automatic); elements, ions, EC, OC (on PM filters)	Sampling: extractive sampling at the engine nozzle, plus extractive sampling (4.14 m) and remote-sensing at a predetermined distance downstream of the engine exhaust plane. Experimental: FTIR, TDLAS, UV DOAS, OP-FTIR; CPC, DMA, SMPS, TEOM, smoke machine, sandwiched PM_1 impaction-style sampler [XRF, ion chromatography, TOA@NIOSH]	Idle, 75%, max; [JP-8, FT]	Cheng (2009); Cheng et al. (2009); Cheng and Corporan (2010)
Military transport (cargo) aircraft: Lockheed C-130 Hercules. Engine: T56-A-15 (TP)	CO_2, H_2O, CO, NO, and N_2O (FTIR); particle number, mass and size distributions, smoke number (automatic); elements, ions, EC, OC (on PM filters)	Sampling: at the engine exit plane and at 5 and 15 m downstream of the engine exit. Experimental: remote sensing: FTIR, TDLAS, UV DOAS, OP-FTIR; Extractive measurements: on-line gas analyzer, cross-filter correlation spectroscopy, chemiluminescence, CPC,SMPS, TEOM, smoke machine, PM_1 sampler [XRF, ion chromatography, carbon analyzer]	Low speed ground idle (4%); high speed ground idle (7%); flight idle (20%); cruise (41%); max (100%); [JP-8, FT]	Cheng et al. (2008); Corporan et al. (2008); Cheng (2009); Cheng and Corporan (2010)
Military bomber: B-52. Engine: TF33-P-3/103 (TF)	CO_2, H_2O, CO, NO, and N_2O (FTIR); particle number, mass and size distributions, smoke number (automatic); elements, ions, EC, OC (on PM filters)	Sampling: extractive sampling at the engine nozzle, plus extractive sampling and remote-sensing at a predetermined distance downstream of the engine exhaust plane. Experimental: FTIR, TDLAS, UV DOAS, OP-FTIR; CPC,SMPS, TEOM, smoke machine, PM_1 sampler [XRF, ion chromatography, carbon analyzer]	TF33 (idle, 80%, 90%, 95%); [JP-8, FT]	Cheng (2009); Cheng and Corporan (2010)
Update and consolidation of the existing HAPs profile using data from Spicer et al. (1994), EXCAVATE and APEXs campaigns	Hydrocarbons, EIs and profiles (mass fraction)	Data analysis	Various	Knighton et al. (2009)

Military transport (cargo) aircraft: Lockheed C-130 Hercules. Engine: Allison T56 (TP)	CO_2, CO, NO_x, total hydrocarbons, organic gases including carbonyls	Experimental: non-dispersive IR, cross–filter correlation spectroscopy, chemiluminescence, FID, PTR-MS, canister[GC/MS], DNPH cartridges[HPLC]	Low speed ground idle, High speed ground idle, Flight idle Cruise, Maximum power; [JP-8]	Spicer et al. (2009)
Jet fighter: F-15. Engine: PW F100-PE-100 (TF with reheat)	CO_2, CO, NO_x, total hydrocarbons, organic gases including carbonyls	Experimental: non-dispersive IR, cross–filter correlation spectroscopy, chemiluminescence, FID, PTR-MS, canister[GC/MS], DNPH cartridges[HPLC]	Idle, Low intermediate, High intermediate, Military, Afterburner; [JP8+100]	Spicer et al. (2009)
Summary of the APEX1–3 campaigns: CFM56-2C1, CFM56-7B24, CFM56-3B1, CFM56-3B2, AE3007A1E, AE3007A1/1, P&W 4158, RB211-535E4-B (all TF), and CJ610-8ATJ (TJ)	Physical and chemical characterization of PM; PM mass, particle number concentrations and size, BC, surface-bound PAHs; inorganic ions, EC, OC, SVOCs, elements	As for APEX1–3 campaigns	LTO and others	Kinsey et al. (2010; 2011)
Pratt & Whitney; PW three high-bypass TF, representing two different distinct engine model types	Total particulate mass, chemical composition and size distributions of the emitted oil	Sampling: Particulate matter emitted from the lubrication system overboard breather vent with a self-designed collecting and diluting apparatus. Experimental: C-TOFAMS, TEOM, engine exhaust particle sizer, CPC and ultra high sensitivity aerosol spectrometer	Cycles from idle to 65-70% thrust	Yu et al. (2010)
NASA DC-8; CFM56-2C1 (TF)	CO_2, CO, NO_x, SO_2, CH_4, N_2O, HONO, total and speciated hydrocarbons, hazardous air pollutants; particle measurements included number density, size distribution, mass, aerosol chemical composition, and black carbon composition	Sampling: from inlet probes positioned 1 and 30 m downstream of the aircraft's engines; aged plumes at 145 m away from the engine output in the direction of the predominant wind, 1.3 m above the ground. Experimental: NDIR, CPC, SMPS, EEPS, DMS, MAAP, PAS 2000, AMS, CCN, TILDAS, PTR-MS, conventional gas analyzers, TEOM	7 thrusts: LTO + 4%(idle); 45%(approach); 65%(cruise); [JP-8, FT (Shell), FT (Sasol)]	AAFEX: Anderson et al. (2011), Santoni et al. (2011)
KC-135T Stratotanker (Military); CFM56-2B1 (TF)	CO_2, CO,O_2, NO_x, total hydrocarbon; PM, particle number concentration and size (after exhausts dilution in smog chamber)	Sampling: exhaust sampled using a rake inlet installed 1 m downstream of the engine exit plane; a dilution sampler and portable smog chamber were also used. Experimental: five-gas exhaust gas analyzer; canister[GC/MS], $PM_{2.5}$ cyclone[QFF and PTFE filters, Tenax TA sorbent, GC/MS, OC/EC analyzer], SMPS, AMS	4%, 7%, 30%, 85%; [JP-8]	Presto et al. (2011); Miracolo et al. (2011)

Helicopters; Allison T63-A-700 (TS)	CO_2, CO, NO_x, CH_4, and C_2H_4, unburned hydrocarbons, number and size of particles, BC	Samples were extracted from the engine exit plane via temperature-controlled probes, charcoal tubes, DNPH tubes; NDIR, FTIR, FID, CPC, SMPS, MAAP, GC/MS	3% (low-speed idle), 7% (high-speed idle), 15% (intermediate), 85% (cruise); [JP-8, a synthetic paraffinic kerosene, and four two-component surrogate mixtures]	Cain et al. (2013)

Used acronyms: AMS=aerosol mass spectrometer; BAM=beta-attenuation mass monitor; CPC=condensation particle counter; C-TOF AMS=time-of-flight aerosol mass spectrometer; DMA=differential mobility analyser; EEPS=engine exhaust particle sizer; ELPI=electrical low pressure impactor; FTIR=Fourier transform infrared spectroscopy; GC/ECD=gas chromatography/electron capture detector; GC/FID=gas chromatography/flame ionization detector; GC/MS=gas chromatography/mass spectrometry; HI-VOL=high volume PM sampler; LIDAR=laser interferometry detection and ranging; MAAP=multi-angle absorption photometer ; NDIR=non-dispersive infrared spectroscopy; OPC=optical particle counting and photometry; OP-FTIR=open-path Fourier transform infrared spectroscopy; PAS=photoelectric aerosol sensor; PTFE=Teflon; PTR-MS=proton-transfer reaction mass spectrometry; QFF=quartz fibre filter; SEM/EDX=scanning electron microscopy/energy-dispersive X-ray spectroscopy; SMPS=scanning mobility particle sizer spectrometer; TDLAS=tunable diode laser absorption spectroscopy; TEOM=tapered element oscillating microbalance; TF=turbofan; TILDAS=tunable infrared differential absorption spectroscopy; TJ=turbojet; TOA=thermo-optical OC-EC analyzer (@used method); TP=turpoprop; TS=turboshaft; UV-DOAS=UV differential optical absorption spectroscopy; VOC=volatile organic compounds; XRF=X-ray fluorescence spectroscopy.

4103 **Table 4.** List of recent studies available in the literature reporting EIs during real aircraft operation. The table also reports supplementary information (if
4104 available) about the target of the study, period and location of experiments, tested aircraft or engine models, measured pollutants, analysed LTO phases and
4105 sampling methodologies. The list of acronyms is provided in Table 3.

Target; Period; Airport	**Analyzed compounds**	**Sampling; Analytical**	**Engine thrusts (if know) or LTO phases**	**References**
In service military and civil aircraft at various airports	CO_2, H_2O, CO, NO, N_2O	Measurements performed at distances of 20-40 m to the nozzle exit perpendicular to the exhaust flow via ground-based FTIR analysis	Various thrusts	Heland and Schafer (1997;1998)
Various (90) in service aircraft: from gulfstream executive jets to Boeing 747-400s at London Heathrow Airport (UK)	CO_2, CO, NO, hydrocarbons	The remote sensor positioned at ground level. Experimental: non-dispersive IR spectroscopy, dispersive UV spectrometer	Mix of idle, taxi-out and take-off modes	Popp et al. (1999)
Emission indices of different aircraft engines using non-intrusive measurements at Frankfurt/Main (GER), London-Heathrow (UK), Vienna (AT) airports	CO_2, CO, NO, NO_2, ethene, ethine, formaldehyde	Open paths of 80 up to 150 m length were installed in parallel directly behind the aircraft. Experimental: FTIR with MIDAC spectrometer, FTIR with K300 spectrometer, DOAS	Aircraft operating conditions, idling aircraft	Schäfer et al. (2003)
30 individual planes, ranging from TP to jumbo jets; August 2001; J.F. Kennedy Airport (USA)	CO_2, NO, NO_2	Measurements within 350 m of a taxiway and 550 m of a runway. Experimental: automatic (IR), TILDAS	Taxiway thrust and take-offs	Herndon et al. (2004)
In-use commercial aircraft; period: 2001-2003; Airports: J.F. Kennedy airport in New York City and Logan airport in Boston (USA)	Particulate matter, number concentration and size distributions	Extractive sampling of the advected plumes of aircraft using a novel approach, 200 m of an active taxiway and runway. Experimental: ELPI, CPC	Several different types of plumes were sampled, including approach (landing) and engine start-up in addition to idle, taxi, and take-off	Herndon et al. (2005)
45 intercepted plumes identified as being associated with specific aircraft: regional jets, B737s, MD88s, and B757s; Period: May 2003; Logan airport in Boston (USA)	CO_2; Formaldehyde, acetaldehyde, benzene, and toluene, as well as other hydrocarbon species; NO_y	Ambient air is continuously analyzed through a sample port located near the roof on the front of the truck. Experimental: IR, PTR-MS; TILDAS; total reactive nitrogen instrument	Idle, taxi, approach (or landing), and take-off, as well as engine-start modes	Herndon et al. (2006)
Real time data at Los Angeles International Airport (USA); Period: September 23-29, 2005	UFPs (diameter <100 nm), black carbon, $PM_{2.5}$ mass, and chemical species (PAHs, butadiene, benzene, acrolein, formaldehyde)	At blast fence (140 m from the take-off) and five downwind sites up to 600 m from the take-off runway. Experimental: SMPS (DMA/CPC), aethalometers, E-BAM, automatic PAHs analyzer, canister, cartridge	—	Fanning et al. (2007); Zhu et al. (2011)
Impact of airport emissions at Zurich–Kloten airport (Switzerland); Period: June 2004 to July 2004	NO, NO_2, CO, CO_2, VOCs	Measurements with in-situ and open-path devices; COV samples taken directly within the plume of the engine, about 50–100m behind an aircraft, at a height of 1m. Experimental: FTIR; DOAS; canister [GC/FID]	—	Schürmann et al. (2007)

Emissions from in-use commercial aircraft engines analyzed using continuous extractive sampling and associated with specific engine using tail numbers; Period: September 2004; Location: Hartsfield-Jackson Atlanta International Airport (USA)	CO_2, CO, NO, NO_2, formaldehyde, particle number, BC, particle size, mass-based composition	Two mobile laboratories located downwind of active runways. Experimental: Automatic (IR); TILDAS; CPC; MAAP; SMPS; DMS; AMS	Various	JETS/APEX-2 campaign: Herndon et al. (2008)
Plume characterization from commercial aircraft at Brisbane Airport (AUS)	CO_2, SO_2, NO_x, particle mass, number concentration and size	Plume capture and analysis system mounted in a four-wheel drive vehicle positioned in the airfield 60 to 180 m downwind of aircraft operations. Experimental: CPC, SMPS, NO_x analyzer, aerosol photometer fitted with a $PM_{2.5}$ impactor	Normal airport operations, taxiing phase	Johnson et al. (2008)
In-use commercial airfreight and general aviation at Oakland International Airport (USA); Period: August 20-29, 2005;	Formaldehyde, acetaldehyde, ethene, propene, and benzene	At the end of an active taxiway next to the main runway. Data collected on an ambient sampling manifold consisting of a 3.8 cm diameter tube, ~7 m long drawing ~150 slpm. Experimental: TILDAS; proton transfer reaction mass spectrometer measurements	Idle (taxiway/runway)	JETS/APEX-2 campaign: Herndon et al. (2009)
Real world conditions, 280 individual aircraft at Brisbane Airport (AUS)	Particle number concentration, size and mass ($PM_{2.5}$), CO_2, NO_x	80 m from the aircraft using a novel mobile measurement system. Experimental: CPC, SMPS, NO_x analyzer, aerosol photometer fitted with a $PM_{2.5}$ impactor	Various modes of LTO cycles including idle, taxi, landing, and take-off	Mazaheri et al. (2009)
In-use commercial aircraft at Chicago Midway Airport and O'Hare International Airport (USA); Period: February 2010	CO, NO, NO_x, oil leaks	Mobile laboratory located at downwind locations to monitor air advected from the active taxiways (30−150 m). Experimental: TILDAS; HR-ToF AMS; MAAP, CPC	—	Yu et al. (2012)
Emission of Roanoke Regional Airport in Virginia (USA); Period: July 2011 - February 2012	CO_2, NO_x, particle number, BC	A mobile eddy covariance laboratory with a mast extending nearly 15 m above ground level and placed near active runways. Experimental: automatic devices, CPC, aethalometer	Idle/taxi and take-off	Klapmeyer and Marr (2012)
Real-time measurements of aircraft engine specific emissions at Oakland International Airport (USA); Period: August 26, 2005	CO_2, particle number concentration, size dustributions, PM mass	100-300 m downwind of an active taxi-/runway. Experimental: Automatic IR, Cambustion DMS500, CPC, SMPS, MAAP	Normal LTO operations	Lobo et al. (2012)

Table 5. List of recent studies available in the literature conducted at airports or in their surroundings. The table also reports supplementary information (if available) about the target of the study, period and location of experiments, tested aircraft or engine models, measured pollutants, analysed LTO phases and sampling methodologies. The list of acronyms is provided in Table 3.

Target; Period; Airport	**Analyzed compounds**	**Sampling; Analytical**	**Engine thrusts (if know) or LTO phases**	**References**
Air quality data in the vicinity of Hong Kong International Airport (1997-1998) and Los Angeles International Airport (2000-2001)	CO, NO_x, SO_2, and respirable suspended particles	Data from routine air quality monitoring site and special study	—	Yu et al. (2004)
Airport traffic at Heathrow (UK); Period: Jul. 2001–Dec. 2004	NO_x, NO_2	LHR2 site at 180 m north of the northern runway centreline. Experimental: Common automatic devices	—	Carslaw et al. (2006)
Ambient air and personal at Fiumicino Airport, Rome (Italy); Period: January-February 2005	23 PAHs, urinary 1-hydroxy-pyrene, micronucleus assay, Comet assay, Sister chromatid exchange	Air samples collected from airport apron, airport building and terminal/office area during 5 working days, plus a biomarker of exposure following 5 working day. Experimental: Active ECHO PUF sampler at 35 L/min for the first 20 min and at 120 L/min for the remaining 23 h and 40 min on each day, [GC/MS analysis]	—	Cavallo et al. (2006)
Individual plumes from 29 commonly used engines; Period: October 19-November 15, 2005; Location: London Heathrow (UK)	NOx	180 m from the runway. Experimental: chemiluminescence monitor	—	Carslaw et al. (2008)
Analysis of the extent of Los Angeles International Airport emissions on downwind ambient air in a mixed use neighborhood that includes residences. Period: spring of 2003	UFP, BC, NO_x, particle-phase PAHs	Data collected at various sites in and around the airport: 500 m upwind of the north runway and downwind of the airport (500 m north and east of the centerline of the north runway; 100 m downwind of the taxiway; 100 m downwind of the south runway; 900 m downwind of the south runway) . Experimental: CPC, SMPS, DMA, aethalometer, photoelectric aerosol sensor, NO_x analyzer	—	Westerdahl et al. (2008)
APEX2-3: Oakland International Airport in August 2005, and Cleveland Hopkins International Airport in Oct-Nov 2005.	NO_x and NO_y, including HONO	Panel truck. Experimental: TILDAS; quantum cascade-TILDAS; chemiluminescence analyzer	—	Wood et al. (2008b)
Airport traffic at Warwick, Rhode Island (USA); Period: July 2005-September 2006	BC	Five monitoring sites: 4 close and 1 approx 3.7 km from the airport. Experimental: Continuous with aethalometers	—	Dodson et al. (2009)
General aviation and private jets at Santa Monica Airport (USA); Period: Spring and summer 2008	UFP, PM2.5, BC, particle bound PAHs, CO, NOx, NO, NO2	Downwind of the airport using an electric vehicle mobile platform equipped with fast response instruments. Experimental: CPC,	Idle/taxi and take-off	Hu et al. (2009)

		FMPS, aethalometer, PAS, automatic measurements of gases		
Airport traffic at El Prat, Barcelona (Spain); Period: October 17-November 16, 2007	PM10, PM2.5 and PM1 continuously; PM10 (EC, OC, SO42-, NO3-, Cl-, NH4+, Al, Ca, K, Mg, Fe, S, Na, As, Ba, Bi, Cd, Ce, Co, Cr, Cs, Cu, Ga, Hf, La, Li, Mn, Mo, Nb, Ni, P, Pb, Rb, Sb, Sc, Se, Sn, Sr, Th, Ti, Tl, U, V, W, Y, Zn, Zr)	Mobile laboratory van at about 130 m from the major runway. Experimental: PM_{10}, $PM_{2.5}$ and PM1 with laser-spectrometer dust monitors and PM10 on QFF using HI-VOL sampler	Take-off, sometimes landing	Amato et al. (2010)
Commercial aircraft; Period: 10–20 May 2005; Airports: Manchester and London Heathrow (UK)	Dispersion of exhaust plumes	Rapid-scanning LIDAR system installed at ground 200-330 m on the sides of runways	All modes were observed: taxiing, take-off, rotation, climb-out, approach, and landing. Landing tyre smoke	Bennett et al. (2010); Bennett and Christie (2011)
Commercial airliners at London Heathrow (UK): A320 232; B757 236; B747 436)	PM elemental composition, particle size spectrum	Samples of dust from the undercarriage. Experimental: SEM/EDX; aerosizer/aerodisperser	—	Bennett et al. (2011)
Ambient air and personal at the Teterboro Airport, New York/New Jersey metropolitan area (USA); Period: Summer 2006 and winter 2006–2007;	BTEX	At 15 households located close to the airport (indoor, outdoor, and personal), at the end of airport runways and an out-of-neighborhood location. Experimental: Passive samplers (48 h) [GC/MS]	—	Jung et al. (2011)
High-resolution monitoring and flight activity data to quantify contributions from LTO at T.F. Green Airport in Warwick (USA). Period: 2007-2008	Particle number concentration	Four stationary monitoring sites around the airport. Experimental: CPC	Various LTO phases, especially departures	Hsu et al. (2012)
Aircraft emissions and local air quality impacts from take-off activities at Los Angeles International Airport (USA). Periods: September 2005; Feb-Mar 2006; May 2006	Particle number concentrations and size distributions, and time integrated black carbon, $PM_{2.5}$ mass, and chemical species	Data collected at the blast fence (~140 m from the take-off position) and 5 sites located downwind, up to 600 m from the take-off runway and upwind of a freeway. Experimental: CPC, SMPS, aethalometers, BAM, PAH Tisch Sampler, canister and cartridge samplers[lab analysis]	Taxi-way and take-off operations	Zhu et al. (2011)
Contributions of aircraft arrivals and departures to UFP at Los Angeles International Airport (USA). Period: summer 2008	Particle number concentration	Five sites around the airport. Experimental: Fast Mobility Particle Sizer	LTO phases: aircraft arrivals and departures	Hsu et al. (2013)

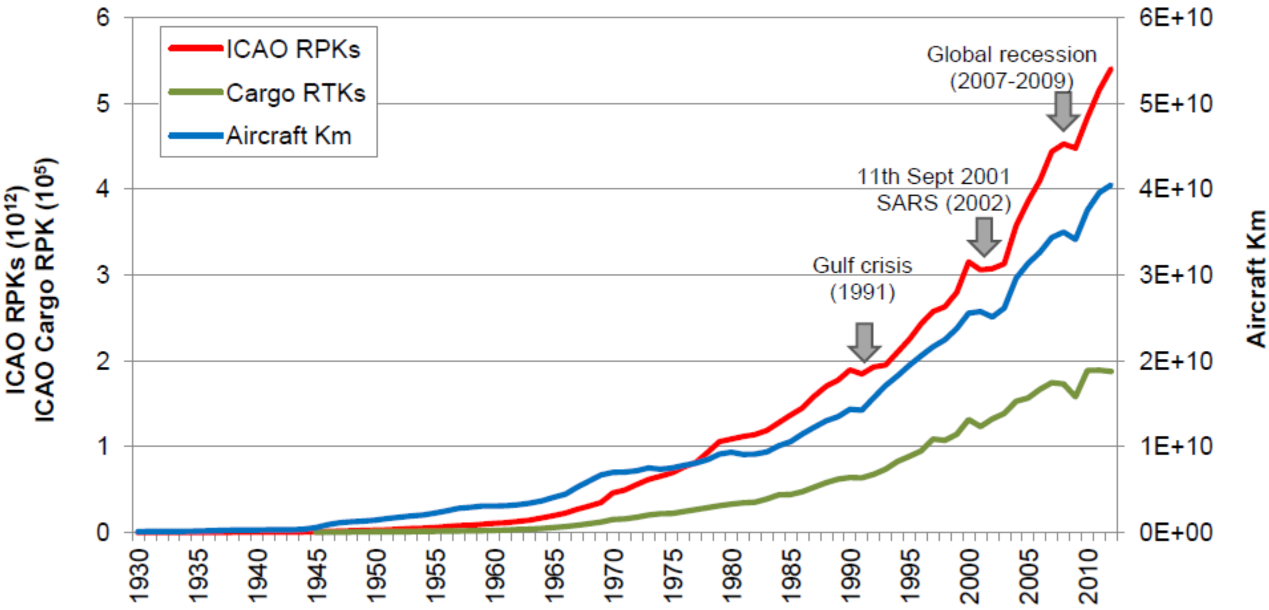

Figure 1. Absolute growth of aviation (1930–2012) recorded by ICAO in terms of RPK, RTK and aircraft kilometres. Data refers to ICAO (2013) and were taken from Airlines for America (2013).

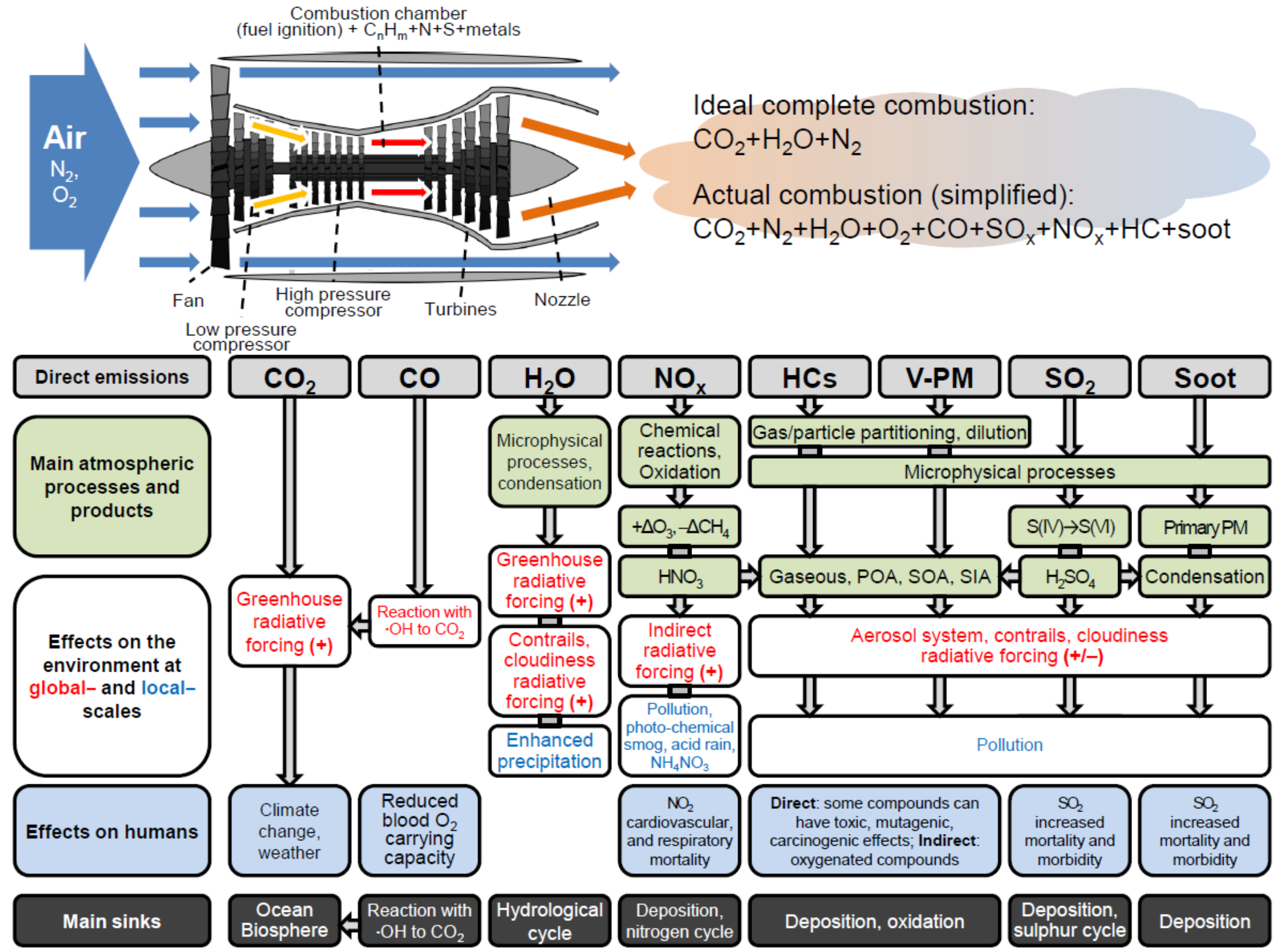

Figure 2. Simplified diagram of a turbofan engine (upper left); products of ideal and actual combustion in an aircraft engine (upper right); and related atmospheric processes, products, environmental effects, human health effects and sinks of emitted compounds (bottom). Adapted from Prather et al. (1999), Wuebbles et al. (2007) and Lee et al. (2009).

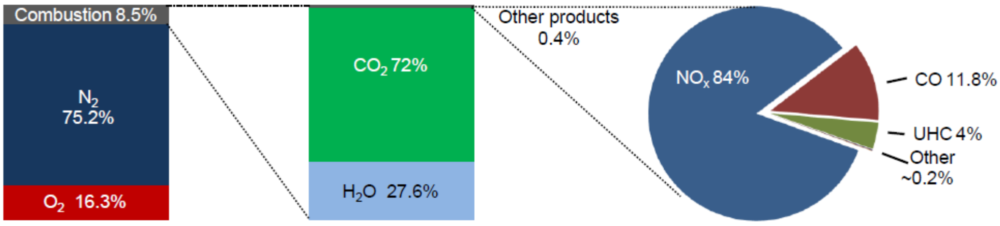

Figure 3. Division of the combustion products from an aircraft engine, adapted from Lewis et al. (1999).

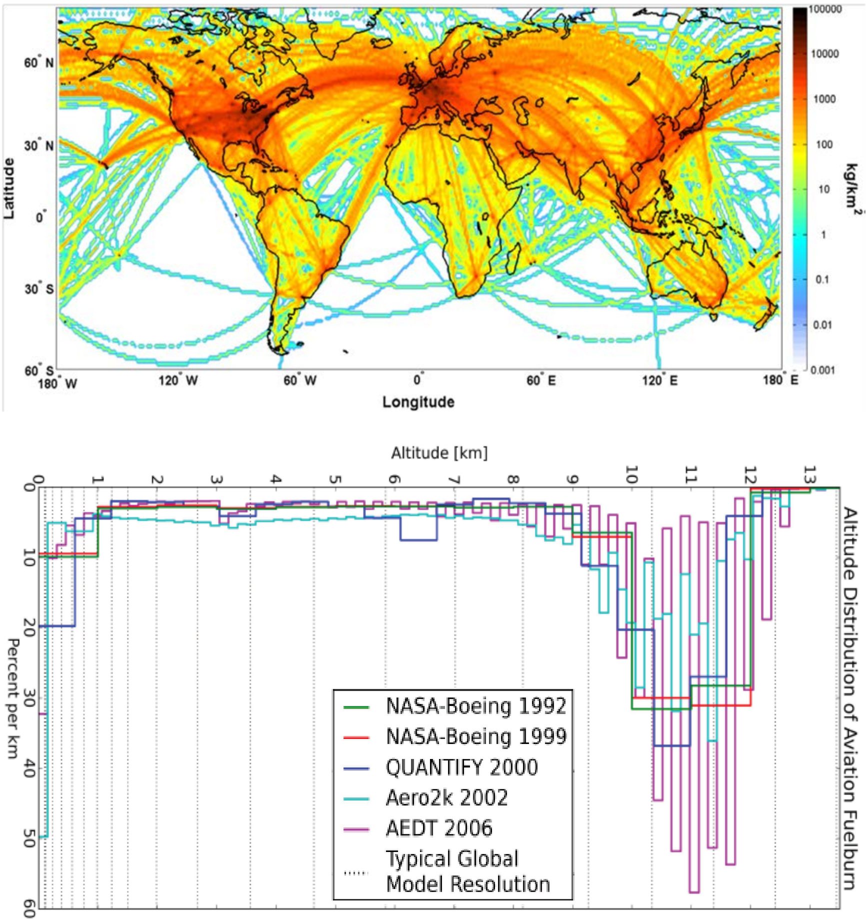

Figure 4a and 4b. Geographical and vertical distributions of aviation: a) column sum of global fuel burn from scheduled civil aviation in 2005, as reported by Simone et al. (2013) using AEIC model (Stettler et al., 2011); b) annual global vertical distribution of commercial aviation fuel burn for the NASA-Boeing 1992 and 1999 (Baughcum et al., 1996a;b; Sutkus et al., 2001), QUANTIFY 2000 (Owen et al., 2010), AERO2k (Eyers et al., 2004) and AEDT 2006 (Roof et al., 2007) datasets, taken from Olsen et al. (2013).

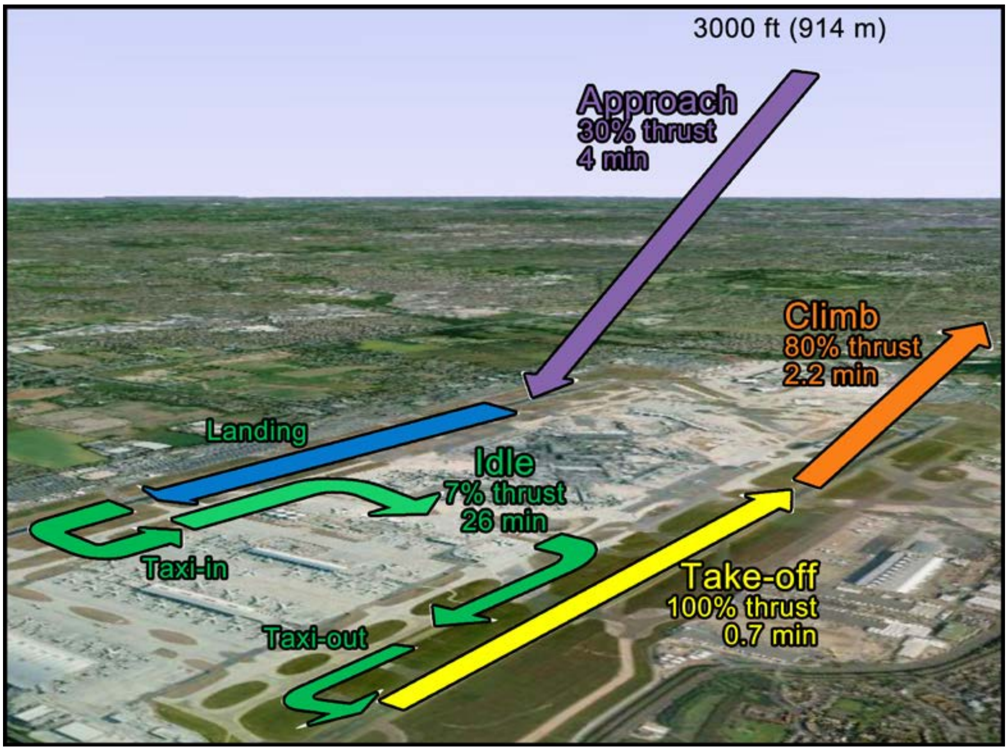

Figure 5. Standard ICAO LTO cycle. Adapted from ICAO (2011).

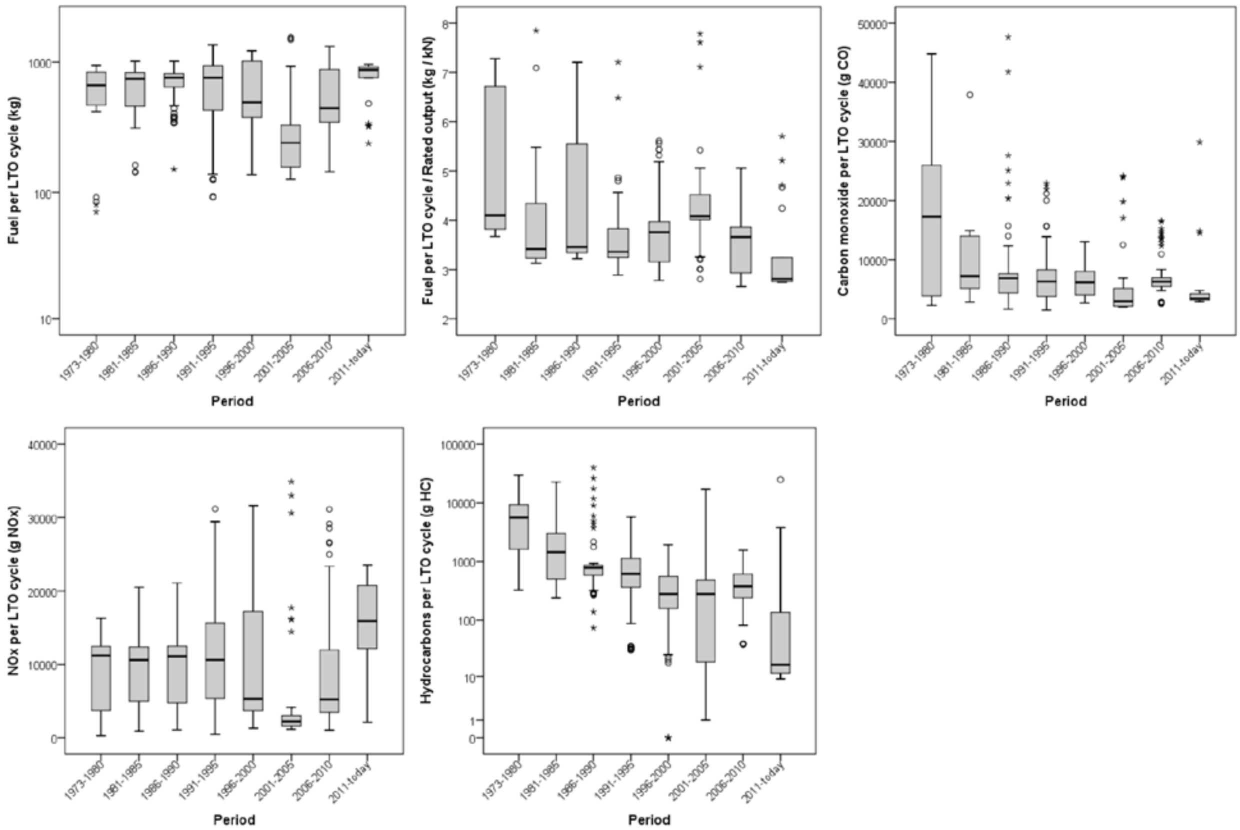

Figure 6. Burned fuel and emissions for complete standardised LTO cycle. Data from ICAO databank at April 2013 (EASA, 2013). All engines certified in each period were included in the statistics, without distinction of type, manufacturer, model or technology.

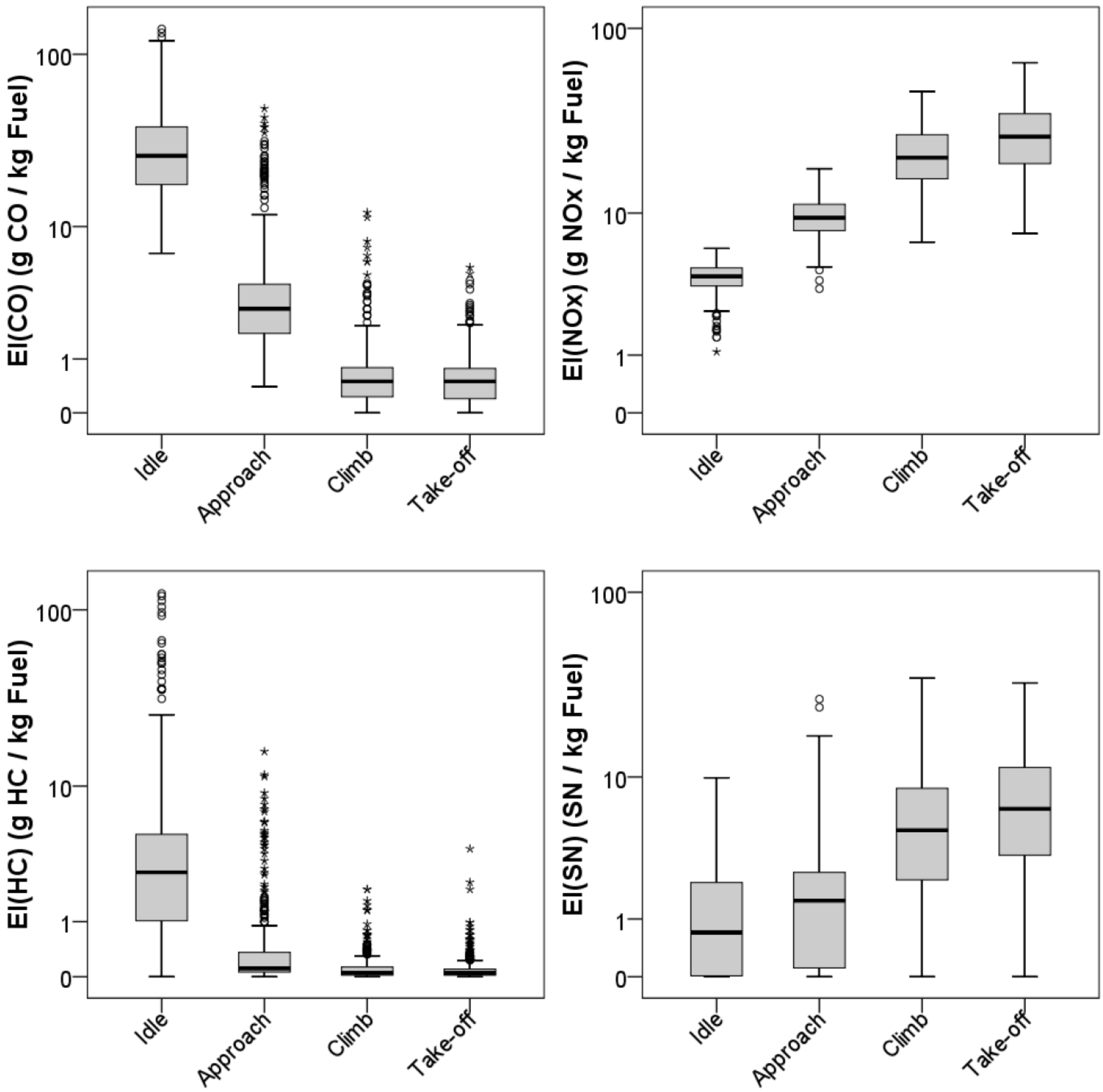

Figure 7. EIs provided by the ICAO databank (EASA, 2013). All in-use engines certified from 1976 to today (April 2013) are included.

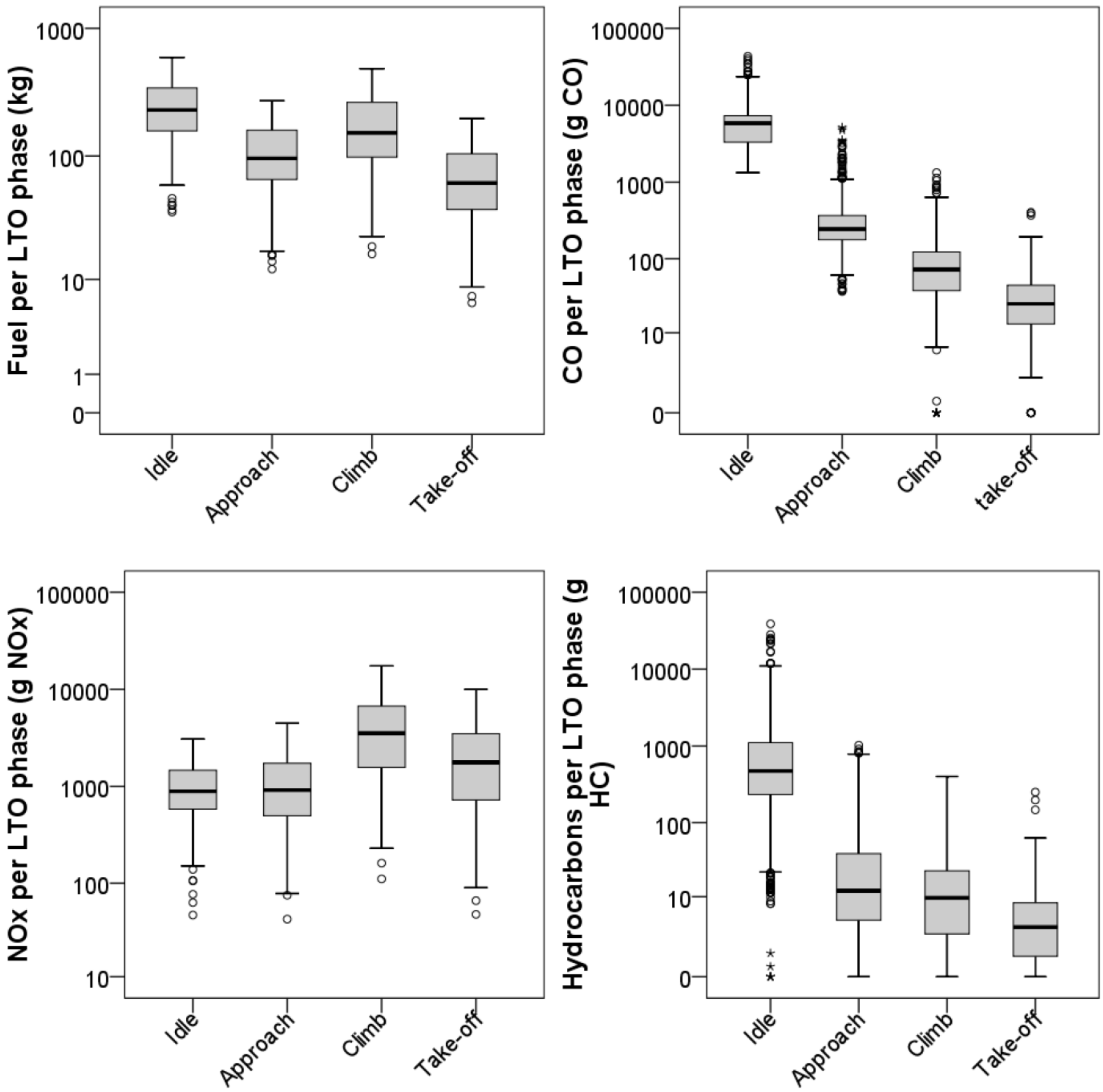

Figure 8. Fuel burned and emissions of CO, NO_x and total unburned hydrocarbons during the four LTO phases. Data were calculated from the EIs and fuel consumption provided by the ICAO databank (EASA, 2013). All in-use engines certified from 1976 to today (April 2013) were included and reprocessed as a function of LTO stages and standard times (i.e., 0.7 min for take-off, 2.2 min for climb-out, 4 min for approach and 26 min for idle).

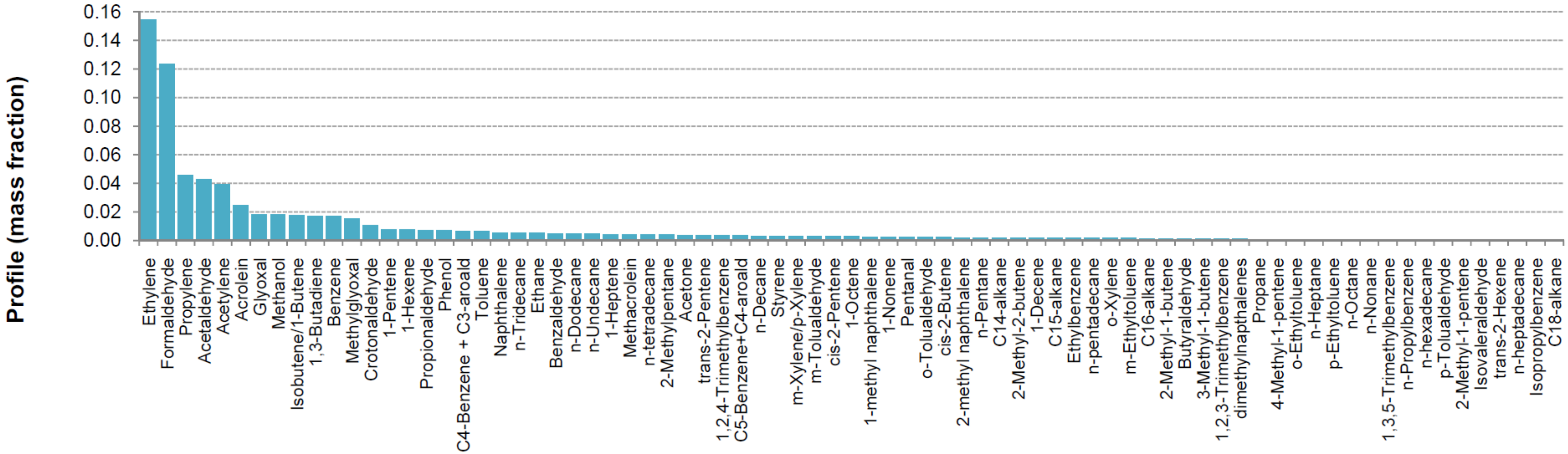

Figure 9. Results of the APEX campaigns. Profile (mass fractions) of individual hydrocarbon species. The single compounds are ordered to show decreasing fractions.

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