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Air pollutants and sources associated with health effects

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Abstract This paper provides four complementary perspectives on the understanding of the risk posed to health by particular sources of air pollution. These perspectives are based on contributions to a plenary session "Pollutants and Sources Associated with Health Effects" at the American Association for Aerosol Research meeting. Research that advanced understanding of source impacts is critical to the prospects for more refined air quality management that moves from the pollutant-oriented approaches in place for the "criteria pollutants" to more targeted strategies. Such research will also be needed in support of multipollutant air quality management strategies. Here, after beginning with a discussion of mobile sources (Ayala), we provide brief historical summaries of relevant research and future research directions framed around the core scientific research disciplines: exposure sciences (Brauer), toxicology (Mauderly) and epidemiology (Samet). Overall, we find that the overarching most important need is to "put the regulatory cart behind the research horse", in the sense that the focus of research, funding permitting, should not be limited to supporting existing air quality regulations. We suggest that more informative research can be carried out using increasingly sophisticated tools and drawing on advancing biological knowledge. However, these tools need to be used and managed in an appropriate framework.

Keywords Exposure sciences · Toxicology · Epidemiology · Multipollutant air quality management

Introduction

This paper provides four complementary perspectives on the understanding of the risk posed to health by particular sources of air pollution. These perspectives are based on contributions to a plenary session “Pollutants and Sources Associated with Health Effects” at the 2010 American Association for Aerosol Research meeting. The central question framing the four presentations was: “How does our understanding of the health effects of air pollution (singly or in mixture) help identify pollutants that can be linked to sources, the control of which would provide maximal health benefits?” Understanding source impacts is critical to the prospects for more refined air quality management that moves from the pollutant-oriented approaches in place for the "criteria pollutants" to more

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targeted strategies. For airborne particulate matter (PM), research has shifted over the last decade from a focus on relationships of mass indicators with health outcomes to address those characteristics of particles that determine risk, in part reflecting guidance from the National Research Council's Committee on Research Priorities for Airborne Particulate Matter (National Research Council 2004b). As acknowledged by that committee, research and regulatory efforts now need to move towards identifying the more injurious particles and tracing these back to their sources. Such research will also be needed in support of multi-pollutant air quality management strategies (National Research Council 2004a).

Part 1: mobile source emission reductions for meeting environmental goals

Introduction

This presentation addresses the potential for making reductions on emissions from critical sources. We postulate that since the source-to-health effects paradigm starts with the source, efforts by the health effects research community that seek to uncover health effects associated with exposure to single or multipollutant emissions from a specific source (s) need to include a solid understanding of the source(s) selected for study and an accurate characterization of the factors that determine and influence emissions from that given source(s). Of these factors, source intensity and emissions characteristics are among the most important. These two factors are determinants of the subsequent atmospheric processes at various spatial and temporal scales. These processes, in turn, affect human exposure to air pollutants and ultimately dose and risk for adverse health outcomes. Thus, an air pollution health effects investigation should incorporate accurate (i.e., real world) source characterization. This can be best achieved by working in a multidisciplinary approach.

For a number of reasons beyond environmental concerns alone, mobile sources, particularly the ubiquitous motor vehicle, are evolving very rapidly. To the benefit of the environment, increasingly sophisticated engines, lubricants, fuels, and post-combustion aftertreatment are yielding consistently lower emissions not only when the engines are new, but also, in many cases, for the full useful life of the vehicle. Over the last half century, motor vehicle and engine technologies have undergone tremendous advances that have led to, among other improvements, significant increases in efficiency and remarkable reductions in exhaust emissions. These advances have enabled the vehicle and engine manufacturers to meet increasingly more stringent and technology-forcing standards in many parts of the world. Because cars and trucks and all other mobile sources can contribute significantly to regional air and climate pollution and affect more acutely those living in close proximity to roadways (Somers et al. 2010; Winer and Paulson 2010), starting off with the minimum amount of pollution at the tailpipe for new and in-use vehicles is a cornerstone for environmental efforts for meeting air quality and climate protection goals.

There is also increasing interest in motor vehicle technology that is more energy efficient and that reduces greenhouse gas pollution. President Obama summed up, in his Presidential Memorandum, a vision for cleaner, more efficient trucks, and next-generation cars, including advanced electric vehicles (The White House and Office of the Press Secretary 2010). Given the broad focus on local, regional, and global environmental protection, the transition towards low-greenhouse gas (GHG), advanced clean cars that rely on low-carbon fuels as alternatives to conventional fossil fuel-based internal combustion is well underway as evidenced by the rising popularity of hybrid and electric vehicles.

This discussion highlights some key technological developments in light- and heavy-duty mobile source applications that are yielding lower emissions and increased efficiency and that are expected to be commonplace in the future. The relevance for the health effects researcher is twofold. First, it is not always possible to infer future emissions based on our experience with older technology because newer, cleaner technologies and fuels result in different emissions. In fact, in many cases, new, lower-emitting technologies will yield tailpipe pollutants that can be chemically, physically, and toxicologically very different from those of older technologies. Second, car and engine technologies will likely continue to evolve, leading to a need for ongoing research to continually study emissions and assess the consequences for the interested health effects investigator of changing real-world motor vehicle pollution.

Therefore we suggest that when studying mobile source impacts, the health effects researcher consider a multidisciplinary approach that includes the specialized field of vehicle emission characterization. As stated, motor vehicle technology is rapidly evolving and becoming increasingly complex. Not only is there new technology like hybrid and electric vehicles, but there is also further ongoing development of conventional spark- and compression-ignited engine technologies whose emissions are influenced by the interplay of many factors including hardware, such as engine and powertrain design, fuel, lubricant, aftertreatment, durability, software, the operator, vehicle/engine activity, and the conditions under which the engine is operated. All these factors lead to a level of complexity that is best handled by multiple disciplines in a research approach that also has the best chance of avoiding potential pitfalls. For example, health researchers have sometimes erred in generating realistic or most meaningful atmospheres for toxicological studies by running the test vehicle/engine at high-speed idle, but without an engine load (de Bruijne et al. 2008; Guarieiro et al. 2010)! Load, more than engine speed, generates emissions.

What we know and have learned about mobile sources of air and climate pollution

We know much about which sources contribute to air pollution generally and to greenhouse gasses specifically. We have learned that motor vehicles can be prominent sources of emissions and exposures. True, they are vital to the fabric of modern society; we depend on them for personal mobility and for the movement of goods, and this dependence is growing as vehicle fleets enlarge particularly in low- and middle-income countries. In their recent book, Sperling and Gordon talk about the world fleet moving rapidly towards two billion cars from the existing fleet of over one billion on the road (Sperling and Gordon 2009). We have learned that the desire for the automobile appears to be almost universal. The introduction of the Tata Nano, Tata Motors innovative and inexpensive ($2,500) “people’s car” for the Indian market exemplifies the room for growth still expected by the car industry (Tata Motors 2011). Unfortunately, we have also learned that motor vehicles can be energy-intensive and represent a major source of emissions that adversely impact air quality, health, and the local, regional, and global environments. More vehicles mean more demand for fossil fuels, and more pollution. In California, we know that the transportation sector is the single largest contributor to GHG emissions accounting for nearly 40% of the total GHG burden in the state (California Air Resources Board 2010). Similarly, mobile sources—for example, cars, trucks, ships, locomotives, and diesel equipment—also load our air with more carbon monoxide (CO), PM, oxides of nitrogen (NO_X), and hydrocarbon (HC) emissions than any other sector. These facts have taught us the increasing need for the environmental reconciliation between our growing reliance on fossil fuels and reductions in air and climate-active pollutants. But transforming a fleet like California’s towards lower emissions and higher efficiency will take time. In the near-term, air quality and climate protection efforts will also necessitate further advances of the conventional internal combustion engine (ICE) and clean and low-carbon fuels. Fortunately, progress is being made in the fight for clean air by those responsible for it and by those who sell us the products that can pollute it.

Over the last two decades, California has recorded important improvements in summertime smog episodes in the South Coast Air Basin and, over the last decade, less PM pollution across the state. At the same time, there have been consistent increases in human and vehicle populations and the number of vehicle miles traveled. But we have learned that much more needs to be done in California and in the rest of the nation. Madsen et al. (2010) refer to four decades of progress cleaning up the automobile in the unfinished battle to improve our air (Madsen et al. 2010). The United States Environmental Protection Agency (US EPA) reports that more than 120 million people are still living in areas in non-attainment of one or more of the National Ambient Air Quality Standards (NAAQS) (Michaels et al. 2010).

What we know and have learned about motor vehicle emissions, especially exhaust particles

Motor vehicle air pollution control started in California half a century ago and "lessons learned" in the state have been applied throughout the world. Significant success in reducing new car emissions has been achieved (Bedsworth and Taylor 2007). Particle emissions have been of special interest. Older diesel technology has been followed by “clean diesel” through improved engine design and the application of external measures such as the diesel particle filter (DPF) which reduces particle emissions by an order-of-magnitude and eliminates diesel soot. Using compressed natural gas has also been a feasible approach to lowering PM emissions. Conventional gasoline technology based on port-fuel injection (PFI) is evolving towards boosted, direct injection (GDI) for achieving lower CO_2 emissions. But traditional, lean-burn GDI can put upward pressure on particle emissions unless further advances such as stoichiometric combustion GDI equipped with center-guided injection are pursued. Also, unlike PFI gasoline particle emissions, GDI particle mass emissions can be comparable to old diesel technology emissions and, hence, be dominated by black carbon (BC) or soot. In the future, we have learned that what is needed to end urban pollution from motor vehicles are policies that will promote all new passenger vehicles to be as clean as the current best, super ultra-low emission vehicles (SULEV) in use today.

It is acknowledged that although per vehicle emissions are only one determining factor for total exposure or, in general, environmental burden, we have learned that reducing them is still the most practical approach to counter balance the potentially offsetting effect of other factors such as a growing car fleet, increasing vehicle miles traveled, and proximity to roads. The legacy diesel truck and equipment fleet also require reductions either through aftertreatment control or by accelerating turnover towards lower emitting, newer engines. Today, SULEVs represent nearly one third of all of the cars on California’s roads. Li et al. (2006) showed that current gasoline SULEV vehicles are emitting a total particle mass below 1 mg/mi level while the applicable standard stands at 10 mg/mi (Li et al. 2006). Thus, great additional air quality benefits from gasoline clean cars have resulted from overcompliance with current limits. Interest by the research community in PM emissions has also led to extensive efforts in recent years that have been focused on understanding the nature of the particles emitted. Ultrafine particle emissions (i.e., particles in the 100 nm size range and smaller) from gasoline motor vehicles have been of particular interest. Kittelson et al. (2004) established that under high speed and acceleration, a gasoline engine produces a large number of ultrafine particles that, in some cases, can approach the concentrations seen from a diesel engine (Kittelson et al. 2004). The large number of very small particles does not contribute substantially to the total mass of PM emitted. The US EPA has recently completed the most extensive study of gasoline car emissions to date and confirmed what has been known for some time; as vehicles age, their PM emissions increase (US Environmental Protection Agency 2008). Seagrave et al. (2002) showed higher relative potencies of acute toxicity and cytotoxicity (LDH) for gasoline-powered vehicles emitting smoke compared to normal emitting gasoline or even normal emitting diesel vehicles (Seagrave et al. 2002).

Towards 2050: the vision for advanced clean cars and engines

Motor vehicle technology is advancing rapidly. The extensive hybridization of the motor vehicle fleet in progress now is part of the transformation towards electrification and zero tailpipe emissions. In the near term, car improvements will include further advances in conventional ICE technology in order for new vehicles to meet smog and particle standards that are expected to be 50–70% more stringent than present limits. In addition, these same vehicles will be expected to reach efficiencies upwards of 40 mpg with the use of biofuels and more hybridization. When the year 2050 approaches, current indicators suggest that lower GHG emissions and efficiency targets will be achieved in a car fleet dominated by alternatives such as fuel cell and battery electric vehicles (US DOE 2009; Cackette 2010). But to achieve goals for reducing GHG to the extent needed to arrest global warming beyond 2°C above pre-industrial temperatures, a multipronged approach to transportation and climate change is needed. In such an approach, multifaceted policies are expected not only directed at cleaner, more efficient vehicles, but also at cleaner, low-carbon fuels, and urban planning that leads to less dependence on the car and more livable communities. These policies are in place and ready for implementation in California and many other states. The lack of action at the federal level only raises the visibility and need for these concerted efforts at the subnational level for motor vehicles and other sources of air and climate pollution.

Cleaning up the “trusty workhorse”

The diesel engine has been and remains of particular interest to the environmental community. The US EPA’s Health Assessment Document for Diesel Engine Exhaust reviewed the possible health hazards associated with exposure to diesel engine exhaust (US Environmental Protection Agency 2002). The attributes of diesel technology—better fuel economy than gasoline, lower GHG emissions, superior torque performance, and durability—also can result in substantially higher emissions of NO_X and PM than other ICE options. With the enactment of the first applicable emission standards in the 1987 in California and the year after in the USA, engine makers sought initially to clean up emissions through internal measures by improving engine design. To meet the current and most stringent limits, engine makers have also added external measures—aftertreatment for PM and NO_X control. Abatement efforts have led to 40 years of progress in diesel PM emissions (US Environmental Protection Agency 2002). By deriving BC emissions from coefficient of haze measurements in California, Kirchstetter et al. (2008) discovered an 18-fold reduction in diesel engine soot emissions factors and a threefold reduction in diesel soot present in ambient air, despite an approximately sixfold increase in diesel fuel usage (Kirchstetter et al. 2008). Presently, high-pressure common-rail fuel injection, cooled exhaust gas recirculation, and variable geometry turbo charging, among other design improvements, will be deployed by engine makers to complement the two *game-changing* advances in new diesel engine emission control: the DPF and selective catalytic reduction (SCR).

Diesel particle filtration has been around since the 1980s and since 2007, the current generation DPF began showing up as original equipment in new heavy-duty diesel engines in the USA. Many studies of the DPF can found in the published engineering and scientific literature (Lanni et al. 2003; Mayer et al. 2004; Herner et al. 2009). They describe the merits and benefits of soot particle filtration for on- and off-road applications to light- and heavy-duty vehicles. Coupled with a conventional two-way oxidation catalyst, integrated aftertreatment systems can yield simultaneous, order-of-magnitude reductions of HC, CO, and PM soot emissions. A seminal study in 1996 sponsored by the Health Effects Institute raised questions about advances in diesel control that reduce PM mass emissions but increase the number of particles emitted (Bagley et al. 1996). What followed was one of the most intense, multiyear, multimillion international races to characterize those emissions and understand their implications for health. The race is not over, but we have indeed learned a great deal about what operating conditions and fuels, lubricant, and hardware characteristics can lead to mass reduction and ultrafine particle formation. Today, the inverse association between PM mass and total particle number concentration in diesel exhaust equipped with various different types of aftertreatment control has been well established (Biswas et al. 2008). We also know that ultrafine particles can be found in the PM emissions from all ICE engines; small particles are no longer a *diesel-only* issue. In fact, other sources of combustion-generation particles and secondary aerosol formation in ambient air can be the dominant contributions to the total burden. Biswas and Wu wrote about the universe of ultrafine particle sources and the fact that anthropogenic sources of particles are numerous and include stationary, mobile, industrial, occupational, and atmospheric conversion (Biswas and Wu 2005). The overviews by Kittelson (1998) and Burtscher (2005) explain particle formation and the nuances of mass and particle number control. Fuel and lubricant sulfur level, exhaust temperature, and catalytic surface areas are all determining factors for particle formation. We also know that “not all particles are created equal.” The increase in particle number emissions in a DPF-equipped engine is due primarily to volatile ultrafine particles formed by nucleation under some operating conditions. But the composition of these emissions, often at or near background levels, is dominated by volatile, relatively nontoxic sulfur-based ions like sulfate. Hu et al. (2010) showed that in spite of an increase in the total number of particles in the emissions from a diesel engine, the toxicity of those emissions as assessed in various acellular assays is reduced (Hu et al. 2010). Earlier, McDonald et al. (2004) had clearly established that diesel exhaust produced statistically significant biological effects in the mice used for assessment of lung toxicity due to exposure by inhalation. The use of low-sulfur fuel and a catalyzed DPF either completely or nearly eliminated the effects (McDonald et al. 2004).

A slightly newer and less well-known approach is the application of SCR to the diesel engine for mobile source application—on- and off-road. SCR has a long history in stationary source applications. Engine manufactures are deploying SCR to meet stringent NO_X limits. Reduction of nitrogen compounds in diesel exhaust is achieved with the injection of urea. Such approach can yield impressive 3–5% improvements in fuel consumption for heavy-duty diesel applications. For meeting the US 2010 PM and NO_X standards, diesel engine makers will deploy oxidation, filtration, and reduction control in their original equipment. The result is upwards of 90% reduction in PM emissions and better than 75% reduction in NO_X emissions (Herner et al. 2009).

In the future, homogenous charge compression ignition, sometimes also refer to low-temperature combustion, appears to be the direction for diesel engine design. And because emissions are of interest not only when the vehicle/engine is new, increasing attention to in-use emissions will lead to the introduction into the market of various methods and instruments for on-board monitoring for in-use compliance. As a result, we will be taking the emissions laboratory to the vehicle rather than taking the vehicle to the emissions laboratory.

Final remarks

With the expanding recognition of the associations between adverse health outcomes and exposure to mobile source emissions, the health effects community has a strong interest in characterizing risks of those emissions. But characterizations of source–receptor relationships used to inform source-specific health assessments are only as good as the representation of the factors that influence emissions from a given source. Fortunately, mobile-source research is keeping pace with the evolution of emission-reduction technology for light- and heavy-duty applications. Recent and ongoing studies are advancing our understanding of the nature of vehicle emissions and their precursors, and the ways that advances in clean fuels, lubricants, engines, and aftertreatment are changing those emissions and their health-relevant characteristics. This will enable health scientists to have the most useful source-specific inputs for their research.

Part 2: understanding exposure to sources (of outdoor air pollution)

Introduction

Understanding the relationship between the emissions from specific pollutant sources and the resulting population exposures is critical for effective air quality management. Specifically, the relative importance of different sources can be approached by describing a “pyramid of concern” where those sources that are the main contributors to health-relevant exposures are identified and targeted for management. Such an approach differs from typical emissions-based controls, targeted towards specific pollutants or PM components.

To date, air quality management has led to demonstrated successes in many of the developed countries of the world. Pollutant concentrations have generally declined with evidence of resulting improvements in health metrics. Similar trends are also becoming evident in urban areas of many developing countries. As ambient concentrations decline, the distinction between “polluted” and background becomes more difficult to discern and it therefore becomes increasingly difficult to identify specific local emission sources (vs. regional and global contributions that have contributions from multiple sources) that are the main contributors to population exposure. This challenge is compounded by a need for sustained exposure reduction in light of evidence for health impacts at near-background concentrations, emerging understanding of a growing number of health impacts that appear to be associated with air pollution and the potential for increases in the size of the population vulnerable to air pollution impacts. Below we elaborate on these issues and suggest exposure-based approaches to mitigate air pollution health impacts.

Historical perspective on air quality management

Implementation of air quality management in response to high profile episodes (e.g., those in Donora and London) led to dramatic reductions in air pollution, especially targeted towards those emissions originating from coal combustion. These management approaches were inherently source-based. For example, low sulfur coal was used in place of higher sulfur fuel, centralized heating with emissions controls replaced individual coal furnaces in residences and tall stacks were built to aid in pollutant dispersion. Such management approaches not only led to improved air quality, but also to demonstrable population health benefits. For example, although implemented several decades after similar efforts in other developed countries, Dublin’s ban on the sale of coal (for home heating) in 1990 was associated with a decrease in winter levels of black smoke and a corresponding decrease in mortality (Clancy et al. 2002). This example shows the comparably large (approximately 116 fewer respiratory deaths and 243 fewer cardiovascular deaths per year were seen in Dublin after the ban) health benefits that were gained as a result of such source-based air quality management. While air quality management in this era was typically focused on source control, it is interesting to note that a simple form of exposure reduction was also broadly implemented in the form of zoning restrictions to separate emissions sources from the population.

In the 1970s and 1980s following the 1970 passage of the Clean Air Act in the USA and its pollutant-specific standards, the emergence of tropospheric ozone (O_3) and acidic substances as major pollutants of concern, and the rising importance of mobile sources, management approaches were re-oriented towards pollutant-based airshed-level emissions reductions. These management programs emphasized overall emissions reductions and regional air quality with relatively little attention paid to land use, zoning, or exposures resulting from emissions of local sources. Point source emission controls such as scrubbers selectively reduced sulfur oxide emissions, while catalytic converters on vehicles effectively reduced ambient concentrations of CO and later, NO_x and HCs. More recent efforts have focused on fuel quality (for example reductions in sulfur content), engine technology, and on inspection and maintenance programs to identify high-emitting vehicles. As with the early air quality management efforts, these collective programs led to reductions in concentrations of most major air pollutants as well as significant health benefits. For example, Pope et al. reported on the increase in life expectancy associated with air quality improvements in the 1980–2000 period. Considering 51 metropolitan areas across the USA, a 10 ug/m^3 reduction in $PM_{2.5}$ concentration was associated with a 0.61 year increase in life expectancy; this improvement in PM was estimated to account for as much as 15% of the mean increase in life expectancy across the country (Pope et al. 2009).

Current challenges

Today, air quality management is faced with a spectrum of issues that varies globally. While it has been estimated that approximately 80% of the global population lives in areas where the WHO $PM_{2.5}$ Air Quality Guideline is exceeded (van Donkelaar et al. 2010), the highest concentrations occur in many rapidly developing countries. In these locations, much work remains to be done and activities generally follow approaches that have been successfully implemented in developed countries. In developed countries, the dramatic improvements in air quality have yet to eliminate all adverse health impacts and evidence suggests that further improvements will continue to provide benefits (Ballester et al. 2008). Further, advances in understanding of air pollution health impacts, and especially the emergence of evidence linking air pollution exposures to systemic inflammation suggests a much wider range of health effects and a larger potentially susceptible population than previously considered. This understanding also argues for continued improvements in air quality, especially in locations with growing numbers of potentially susceptible individuals, for example regions with aging populations and those affected by surging rates of noncommunicable disease. However, as a result of the general air quality improvements that have been implemented over the past 40 years, it is has become more difficult to isolate the air quality impacts of specific sources on exposures and, in many locations, increasingly challenging to identify approaches to further improve air quality.

A further challenge arises from air quality management that is largely focused on pollutant-based regulations that inevitably lead to pollutant-based air quality management.

Given that individual sources typically emit multiple pollutants which are subject to atmospheric transformation, disentangling the impact of specific sources on individual pollutants or PM components is a complex task. Understanding of pollutant-based source to exposure relationships is further complicated since individuals are exposed to mixtures originating with emissions from multiple sources.

In the context of declining ambient pollutant concentrations, given these complexities in source–pollutant relationships and the continuing uncertainty regarding the health impact of specific particle components, novel approaches have the potential to lead to increased effectiveness of air quality management. Efforts focused on understanding of the source to exposure to impact pathway for sources as opposed to components or individual pollutants offer one possible approach. Further, it is now clear that most exposure, even to "outdoor" air pollutants, occurs indoors, suggesting additional opportunities for exposure reduction related to control of the indoor environment.

Identifying source impacts

A number of approaches to assess the air quality and health impacts of sources have been developed. Analytical methods such as source apportionment, factor analyses, and the measurement of source-relevant indicator compounds have been used in a relatively large number of epidemiologic studies (Thurston et al. 2005; Bell et al. 2009, 2010; Cakmak et al. 2009; Mordukhovich et al. 2009; Ostro et al. 2009). Studies using these approaches have identified the relative importance of some source categories and especially the importance of combustion-source PM, but results have not been consistent and such analyses can only evaluate specific sources in relation to others that are actually present in the study setting. While less common in epidemiological research, emissions-based models have also been used in a number of health impact assessments to evaluate the impacts related to specific source categories (Corbett et al. 2007; Tonne et al. 2008; Barrett et al. 2010; Boldo et al. 2010). A limited number of studies have focused on areas where specific sources dominate and in some cases included comparisons based on natural experiments or specific interventions. Among the most notable examples is the seminal work of Pope and colleagues in the Utah Valley, where a strike at a steel mill was associated with improved air quality and reduced cardiopulmonary mortality and respiratory hospital admissions (Pope 1989, 1996). Finally, one can isolate the impacts of specific sources through controlled exposure studies that are conducted either in real-world settings (McCreanor et al. 2007) or in the laboratory (Barregard et al. 2006; Mills et al. 2007; Peretz et al. 2008). Collectively, these studies have identified a large number of combustion sources as associated with adverse health impacts and in some cases also demonstrated health benefits resulting from elimination or decreases in source activity.

Exposure reduction to mitigate the health impacts of air pollution

While air quality management emphasizes improvement in ambient concentrations, a focus on modifiers of exposure such as indoor infiltration, individual mobility, and source proximity may in fact be more effective in reducing exposure. Emerging approaches such as intake fraction (Bennett et al. 2002), studies of spatial variation (Karr et al. 2009) and source proximity (Yu et al. 2006), and methods to attribute exposure between indoor and outdoor components (Ebelt et al. 2005) offer insights into the impacts of sources on exposures and suggest novel approaches to reduce exposures in the context of current ambient pollutant concentrations.

The above approaches have also identified a number of outdoor source contributions to exposure which are likely to be important for future management efforts including (1) sources related to global change such as dust storms (Bell et al. 2008), vegetation fires (Morgan et al. 2010), and changes in the ambient "background" as a result of general global increases in emissions (Vingarzan 2004) and (2) very local sources such as the impacts of traffic corridors (Health Effects Institute 2010), marine vessels (Perez et al. 2009), nonroad vehicles, and distributed combustion (Gilmore et al. 2006).

Exposure reduction as a form of managing the impact of air quality on health suggests the benefits of approaches to modify contact with sources through changes in source proximity (Giles et al. 2010). Modification of time–activity in relation to pollutant spatial or temporal variability may also be a way to modify exposure (Nethery et al. 2008; Setton et al. 2010). Further, models indicate that for PM variability, infiltration can have major effects on exposure (Hystad et al. 2009) so that it is possible to consider construction and building operation as a form of exposure reduction (Sultan 2007). As well, a number of studies have indicated the effectiveness of room air cleaners in leading to reduced indoor concentrations of ambient-source particles and in some cases, health improvements (Barn et al. 2008; Brauner et al. 2008; Allen et al. 2011). These studies suggest, rather provocatively, that exposure reduction consequent to alterations in indoor air infiltration ought to be considered alongside community-level air quality management. Exposure reduction also has the potential to directly address inequalities in exposure that may lead to inequalities in health impacts.

Part 3: what have we learned from experimental exposures?

Introduction

Our approach to this question focuses on combustion sources of anthropogenic air pollution, although the key issues pertain to apportioning health hazards and risks among all air contaminants. We distinguish the question "what have we learned" from the questions, "what have we done", or "what do we know", the answers to which would involve reviewing an enormous body of information. After noting the long history of experimental research on the health effects of combustion products (more precisely, the products of incomplete combustion), we summarize key lessons learned, what we need to know in order to properly understand health effects of combustion-derived pollutants, potential approaches to gaining that knowledge, and key facilitators of progress.

We have been at this a long time!

It is instructional to note that there is perhaps a longer history of experimental exposures to combustion emissions, and earlier studies of greater sophistication than is commonly appreciated. Published results of experimental exposures to intact, highly complex combustion emissions date at least back to the paper by Bond (1910) who documented an increased coronary vascular blood flow during inhalation exposure of dogs to tobacco smoke (Bond 1910). By the mid-1950s, it had been established that the composition of gasoline and diesel engine emissions varied by speed and load, as did the carcinogenicity of solvent extracts of collected filter mass, and that responses differed among strains of mice (Kotin et al. 1954, 1955). Complex experimental designs were being used to study causal interactions among single and complex inhaled pollutants by the early 1960s. For example, Salem and Cullumbine (1961) exposed mice, rats, guinea pigs, and rabbits to H_2SO_4 aerosol in two particle sizes, SO_2, acetaldehyde, and acrolein alone or during or after exposure to smoke from a kerosene lamp (Salem and Cullumbine 1961). The mid-1960s produced the first published results of animals exposed directly to urban (Los Angeles) air pollution (Swann and Balchum 1966). Also by the mid-1960s, the National Air Pollution Control Administration (forerunner of EPA) laboratory in Cincinnati had initiated the longest-duration (5 years) repeated exposure to inhaled engine exhaust to date (Hinners et al. 1966; Vaughan et al. 1969). In this landmark project, dogs were exposed chronically to not only raw or irradiated (aged) gasoline engine exhaust, but also to nitrogen dioxide (NO_2) and SO_2 alone, or exhaust plus SO_2. This study also was the first to demonstrate the continued development of lung lesions over a multiyear period after exposure ceased (Hyde et al. 1978). By the late 1960s, the same laboratory had studied interactions between pre-existing emphysema (induced by high-level exposure to NO_2) and inhaled SO_2 and H_2SO_4, alone and in combination (Lewis et al. 1969).

The point of noting the above studies is not to suggest that everything needing to be learned has been learned, but rather to demonstrate that the fundamental experimental designs required to learn much of what we yet need to know are long-established. It is true in science, as well other endeavors, that a failure to learn from history predisposes toward repetition. It is not news that one can readily study complex mixtures and multipollutant interactions in the laboratory, that the nature and hazards of products of incomplete combustion vary with combustion conditions, that there are non-additive interactions among pollutants, that real-world pollution can cause detectable effects in laboratory models, that responses vary among strains within species, that pre-existing disease can modify responses, or that effects of chronic exposure can be progressive and continue after exposure ceases. Yet, studies of responses of single models to single pollutants or emissions from unrealistically operated sources under single exposure scenarios are often reported without acknowledgment that results might differ under different circumstances.

Much progress has been made in the detail with which we can measure biological responses, but our fascination with new biological tools and discovery of biological mechanisms sometimes diverts our attention from answering questions more central to the management of air pollution-related health risks. We need to judiciously employ both contemporary and longstanding biological assays within experimental designs that go beyond a single experimental point to explore dose–response, different types of responses, causal components of complex exposures, non-additive interactions among pollutants, effects of pre-existing susceptibilities, biologically relevant response times, etc.

What have we learned?

Our experience to date has taught us several fundamental lessons that are too often ignored. Perhaps chief among them is the uncomfortable fact that our investment in experimental exposure studies to date has not prepared us well to answer many of the questions raised by the current trend (or stated goal) of managing the health effects of air quality by increasingly "multipollutant" strategies. This dilemma, the key questions, current information gaps, and potential strategies for reducing the gaps were recently summarized by a multidisciplinary group of authors specifically commissioned to that task (Mauderly et al. 2010). In its ultimate form, "multipollutant air quality management" might be defined as managing all controllable air contaminants (and source emissions) in an integrated manner that seeks the greatest reduction of the total health burden of air pollution—considering trade-offs among alternate air quality management strategies regarding the types and magnitudes of residual health impacts and economic costs. It is not envisioned that air quality management will evolve to meet this ultimate definition in the foreseeable future; however, it is certain that air quality management in most developed nations will take steps progressively in that direction. Key information gaps pertaining to this need are summarized below.

We have learned that the evolution of source emissions often outpaces the relevance of information gained at any point in time. A prime example is on-road diesel emissions, which are very different today from even 10 years ago, but which are still frequently studied using engines, fuels, or samples typical of decades-old technologies (Hesterberg et al. 2005).

We have learned that the biological effects of individual pollutant species can seldom (if ever) be integrated into an accurate prediction of the effects of those species in combination, much less as present in realistically complex pollutant mixtures. Yet, the majority of experimental exposures to pollutants involve single pollutant species or classes (e.g., O_3 or PM).

We have learned that the effects of two or more pollutants in combination are sometimes non-additive, but we have scant knowledge of how often this occurs or why, and have little ability to predict synergies or antagonisms (Mauderly and Samet 2009).

We have learned that it is extremely difficult, if not impossible, to draw a line of "adversity" with regard to the biological effects of air pollution. A progression of effects from transient, subclinical, inconsequential biological responses to death can readily be described, but it remains elusive to achieve consensus on the level of response that is worthy of expenditure of substantial resources to prevent (Samet et al. 2000a). Experimental studies demonstrate an increasing range of biological responses as we explore increasingly detailed response pathways, but there has not been a parallel progression in our ability to place the responses in a hierarchy of importance.

Finally, as suggested above, we have learned that there will always be another clever biological tool or new hypothesis concerning a biological mechanism of response, and the intrinsic and extrinsic pressures on researchers to use the most recent tool or pursue the most recent hypothesis often exceeds the pressure to focus on the most important air quality management information needs. This is certainly not to say that advances in biology should not be incorporated into studies of environmental air pollution. Rather, it is to contend that informing the development of air quality management strategies to most effectively reduce pollution-related health burdens is not always accomplished by giving equal or higher priority to exploration of fundamental biology than to understanding and addressing the most important information needs of air quality management decision makers.

Part 4: what have we learned from epidemiological studies?

Introduction

Epidemiological research on the health effects of air pollution has now been in progress for more than a half century (Fig. 1). While the well-documented air pollution disasters of the mid-twentieth century are widely cited as

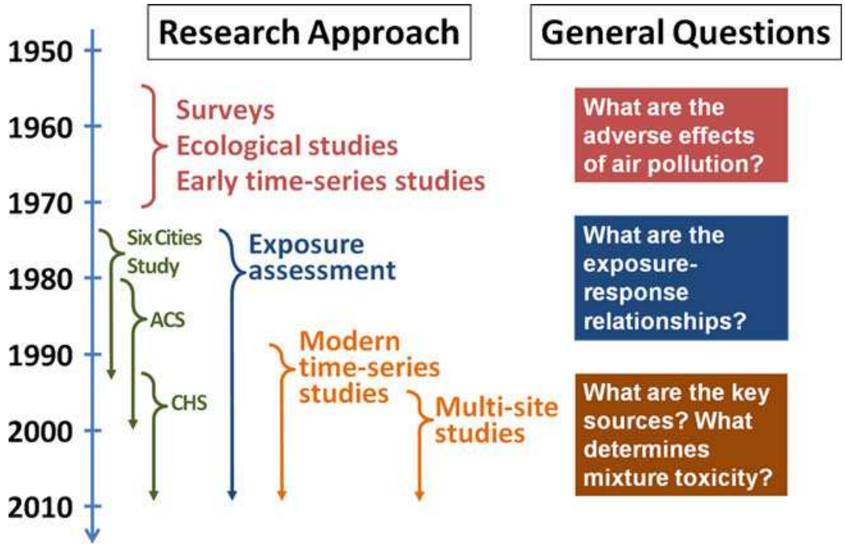

Fig. 1 Overview of epidemiological approaches in air pollution research, 1950–2010. *ACS* American Cancer Society study, *CHS* Children's Health Study

motivating epidemiological research, some of the earliest formal epidemiological studies addressed the hypothesis that air pollution was the cause of the rising epidemic of lung cancer in men. In their well-known case-control study of lung cancer in London, Doll and Hill entertained two hypotheses, giving equal credence to each at the outset: that the rise in lung cancer across the first half of the twentieth century reflected air pollution in cities or the increasing smoking of cigarettes that had antedated the lung cancer epidemic (Doll and Hill 1950, 1952). Other studies in the early 1950s also addressed the air pollution hypothesis, although cigarette smoking was soon identified as the main causal factor for lung cancer.

Subsequently, epidemiological studies on air pollution and respiratory health were initiated, primarily in the UK and using methods, including respiratory questionnaires and spirometry that had been first developed for use in studies of workers (Samet and Jaakkola 1999). Studies were also carried out that used population-level indicators of health, making comparisons between more- and less-polluted areas or tracking health indicators over time as air quality changed. Source-directed studies were also undertaken.

In the USA, the first studies were carried out in the 1950s and early 1960s, some using methods adopted from the UK research [see for example (Deane et al. 1965; Ferris et al. 1971; Hexter and Goldsmith 1971)]. In the USA, the passage of the 1970 Clean Air Act and the implementation of standards, the NAAQS, for single, major pollutants (referred to as "criteria pollutants"), provided a framework for the design, analysis, and interpretation of epidemiological studies. Researchers gave emphasis to studies that would provide information about particular criteria pollutants, e.g., PM or O_3, through design or analysis. The Harvard Six Cities Study, for example, was intended to provide evidence on PM and sulfur oxides, particularly around changes in coal utilization that were anticipated in the early 1970s as the study was initiated (Ferris et al. 1979). The Harvard 24-Cities Study was designed to provide exposure contrasts for acid aerosols and O_3 (Speizer 1989; Dockery et al. 1996) while the Children's Health Study carried out by the University of Southern California was directed at four pollutants: O_3, PM, acids, and NO_2 (Peters et al. 1999). Studies were also directed at particular point sources or classes of point sources, such as smelters and coal-burning power plants [see for example, (Schenker et al. 1986)].

The approach to epidemiological research on air pollution expanded about 20 years ago, as time–series studies became more feasible and informative because of enhanced computing capacity and the development and application of statistical methods (Bell et al. 2004). Initially, the time–series studies largely had daily mortality within single cities as the outcome measure, but the approach was soon generalized to indicators of morbidity. The wave of analyses of data from single-city studies was soon followed by multi-city studies that provided greater precision of estimates and the possibility of exploring variation in the effects of air pollution across cities and regions. These studies typically involved data on multiple pollutants, such that multivariate models could be used to estimate effects of individual pollutants or to explore interactions among pollutants (Katsouyanni et al. 1996; Samet et al. 2000b). Nonetheless, emphasis was given to estimating "independent" effects of particular pollutants, using multivariate models.

The evidence developed over the decades is voluminous and largely targeted at particular pollutants (Fig. 2). This paper covers this epidemiological literature, addressing what has been learned across more than a half-century of research.

What have we learned?

The epidemiological approaches outlined above have advanced understanding of air pollution, largely of single pollutants. The epidemiological evidence focuses on particular pollutants with effects isolated by design or analysis. The evidence has supported powerful conclusions about causation of adverse effects by ambient pollutants at contemporary levels. For example, the most recent review by the EPA of the evidence on airborne PM led to a number of conclusions with regard to causal associations of PM with morbidity and premature mortality (Table 1; US Environmental Protection Agency 2009). These findings and a complementary risk and exposure assessment have been used to support a proposed reduction of the NAAQS for PM (US Environmental Protection Agency 2010a, b). In the example of PM, however, epidemiological research has been far less informative for identifying those particular sources contributing the PM that causes injury and increases risk. The topic of key sources and toxicity-determining characteristics of particles was central in the research agenda proposed by the National Research Council's Committee on Research Priorities for Airborne Particulate Matter (National Research Council 1998, 2004b).

From the evidence available, there is some indication that metal content, particularly transition metals, may be relevant to risk of inhaled PM. This finding comes from several studies that have carried out elemental analysis on particle samples. For example, Lippmann et al. (2006) used a mouse model of cardiovascular disease to explore elemental composition of fine PM and cardiovascular effects. They found associations with nickel content with heart rate change and variability. Parallel analyses of the

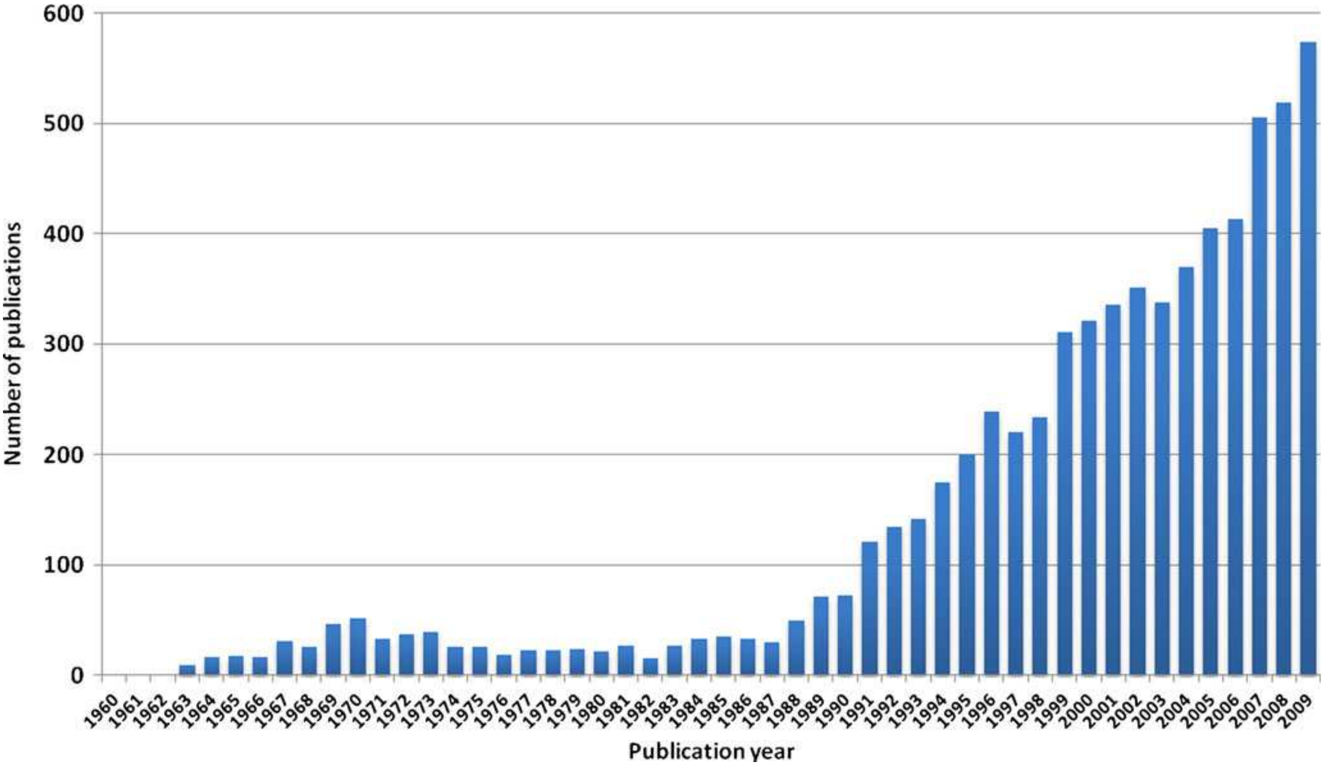

Fig. 2 Annual number of publications in air pollution epidemiology, 1960–2009. Search conducted using PubMed with terms "air pollution" and "epidemiology", and with English as delimiter

National Morbidity, Mortality, and Air Pollution Study (NMMAPS) data showed associations of daily mortality with nickel and vanadium. A subsequent analysis of the NMMAPS data found an alternative explanation for this finding (Dominici et al. 2007). Laden et al. (2000) carried out analyses in the Six Cities Study data testing whether particular source signatures developed from elemental analysis of particle samples are associated with premature mortality. They found that signatures associated with mobile sources and with coal combustion were associated with mortality while a signature associated with fine crustal material was not. The potential complexities and difficulties of addressing PM characteristics were further characterized by Bell et al. (2007) using data from the Environmental Protection Agency's Speciation Trends Network. They found that most of the variation in $PM_{2.5}$ mass across the sites could be explained by a limited number of components. Explorations of associations of $PM_{2.5}$ components

Table 1 Summary of causal determinations for exposure to particulate matter

Size fraction	Outcome	Causality determination
$PM_{2.5}$ (short-term exposure)	Cardiovascular effects	Causal
	Respiratory effects	Likely to be causal
	Mortality	Causal
$PM_{2.5}$ (long-term exposure)	Cardiovascular effects	Causal
	Respiratory effects	Likely to be causal
	Mortality	Causal
	Reproductive and developmental	Suggestive
	Cancer, mutagenicity, and genotoxicity	Suggestive
$PM_{10\text{-}2.5}$	Cardiovascular effects	Suggestive
	Respiratory effects	Suggestive
	Mortality	Suggestive
Ultrafine particles	Cardiovascular effects	Suggestive
	Respiratory effects	Suggestive

Adapted from the Integrated Science Assessment for Particulate Matter (final report; US Environmental Protection Agency 2009) with daily hospitalization counts further illustrate the challenges of research on PM characteristics and source surrogates.

Further relevant experience was gained in the Air Pollution and Health: A Combined European and North American Approach study (Katsouyanni et al. 2009). This collaborative project involved pooled analyses of daily time–series data on mortality and hospitalization from Europe and North America. The data were analyzed with a common protocol and potential source effects were assessed using surrogates. There was little evidence for modification of the effect of PM when effect modification was explored using crude indicators of the sources of the mixture.

A broad body of work has linked one source, vehicle emissions, to a range of adverse health effects. Broadly, this public health problem has been framed as stemming from exposure to "traffic," a conceptualization that reflects the exposure indicators that have been used in the epidemiological studies: residential proximity to major roadways, traffic density, and pollutant indicators of traffic, particularly NO_2. For example, in the Children's Health Study, an indicator of traffic exposure was associated with rate of lung function decline (Gauderman et al. 2007), and in a case–crossover study in Germany, exposure to traffic in the last several hours was associated with risk for acute myocardial infarction (Peters et al. 2004). Additionally, toxicological studies have been carried out that involve roadside exposure of rodents (Araujo et al. 2008).

The evidence on traffic and health was recently reviewed by the Health Effects Institute (2010). This systematic review covered a wide range of health effects. The evidence was found to be sufficient to conclude that traffic exposure, defined as a zone extending out to 300–500 m from a major road, is causally associated with asthma exacerbation. Suggestive evidence was found for several other adverse health outcomes. The implications of these findings are far-reaching, extending to the design of cities and the siting of residences and schools (Giles et al. 2011).

What do we need to know?

The answer to this question is context specific. In the USA, for example, the NAAQS for some pollutants, e.g., PM and O_3, are approaching the so-called policy-relevant background, that is the background concentration that cannot be lowered by air quality management initiatives within the country. As noted previously, perhaps the most surprising finding of recent epidemiological research has been the repeated demonstration of risk for adverse health effects at ever lower pollutant concentrations. The findings have been most striking for cardiovascular outcomes. Further epidemiological research, particularly time–series studies, may not bring much greater understanding of the form of the exposure–response relationship for these adverse effects at lower concentrations. Power is limited at low concentrations for distinguishing between policy-relevant alternative forms, including whether a threshold concentration can be identified and whether the assumption of linearity can be justified. Greater certainty about these critical aspects of the exposure–response relationship will be gained by better mechanistic understanding so that the plausibility of identified exposure–response relationships and the models used to characterize them can be supported.

There is increasing recognition that research directed towards single pollutants does not address the most pressing public health concerns about air pollution at the moment: what are the risks of air pollution mixtures and do traffic-related pollutants pose a threat to public health? The concern about mixtures is not new, but the need for informative approaches to investigate mixtures has increased, given the continued threat posed to public health by air pollution. Beyond characterizing the risks of the total mixture, strategies will be needed to link back to the sources that contribute the risk-determining components of the mixture, if such components can be identified. For airborne PM, this same need has been highlighted repeatedly; airborne PM represents a complex mixture with many sources and evidence on the most critical sources has been sought to guide air quality management strategies.

The international context also needs consideration. High levels of air pollution persist in much of the world, particularly in the low- and middle-income countries where industrialization is increasing, often without adequate attention to controls, vehicle numbers are growing rapidly, and biomass burning contaminates indoor environments and contributes to outdoor pollution as well. Additionally, the number of megacities, metropolitan areas with more than 10 million inhabitants, is increasing. In some middle- and low-income countries, such cities have worsening pollution profiles from increasing industrialization and rising vehicle fleets. Additionally, transboundary movement of air pollution may become increasingly prominent, particularly as pollution levels continue to fall in more developed countries and emissions rise in less developed countries.

Can we do better research?

Since the first epidemiological studies on air pollution and health, there has been progressive methodological refinement, bringing greater sensitivity and precision to the results of epidemiological research on air pollution. The major advances include the use of increasingly refined approaches for exposure assessment, sharpening of methods for characterizing outcomes, new study designs and analytical methods, and the capability of using large administrative and air pollution databases. Studies that reflect these advances have led to far more certain understanding of the risks of individual pollutants, particularly PM and O_3. However, in spite of these advances, epidemiological studies have not yet provided evidence linking particular sources, other than the very general findings on traffic, to risk for adverse health effects.

The underlying challenge can be readily identified; there are many sources that may be relevant, generally highly specific signatures of exposures to sources are lacking and the associations with health outcomes are non-specific and not traceable to a particular pollutant. There are two general "solutions" to this problem; gaining statistical power through having larger databases and continuing to refine exposure assessments for epidemiological research. With regard to databases, for the scale needed, we are limited to administrative databases such as those of healthcare systems, e.g., Kaiser or Medicare. These types of databases have the general strengths of reasonable cost, access, and broad geographic coverage; the weaknesses include the inherent weaknesses of the data, which have not been collected for research purposes, and the need to estimate exposures using available data and models. With regard to exposure assessment, more valid indicators of exposures to specific sources might come from more detailed pollution characterization in geographic areas of interest; the resulting data might be sufficient to support the development of more refined source-based models, analyses directed at identifying source signatures, or source apportionment methods.

The answer to the question "Can we do better research?" is a guarded "yes". However, if we are to do so, both leadership and funding will be needed. The model afforded by the strategy and related funding for PM represents one approach. It involved focused funding, a research strategy, and coordination among research funders and researchers. That approach might again prove useful if put into action with sufficient attention to a systematic research framework and followed to completion.

Overall conclusions

What do we need to know?

The consensus views of a diverse group of researchers concerning this issue were recently published and are paralleled in these four contributions (Mauderly et al. 2010). Considering the critical information gaps slowing multipollutant air quality management, this group considered improved knowledge of exposure and of the linkages of sources to exposures to be the most immediate overarching need. Without adequate characterization of exposures, toxicological studies may be focused on the wrong target and epidemiological research may be misdirected. There needs to be ongoing linkage of sources to exposures to keep research grounded in actual atmospheres. More specifically, we need to address the following questions: (1) what are the characteristics of source-relevant air pollutant mixtures: air contaminants, their concentrations, and their temporal–spatial distributions?; (2) what are the acute and time-integrated exposures of the population to these mixtures?; (3) do, and if so how do, exposures of presumed susceptible subpopulations differ qualitatively and quantitatively from population average exposures?; (4) what are the integrated exposures within biologically important time frames? Experimental exposures can help address the latter two issues; the first two require field studies. The last issue compares temporal exposure profiles with the time frames of different biological responses—which will be determined by both epidemiological and experimental studies.

We also need to have a much better understanding of pollutant–risk relationships. We have long oversimplified research paradigms to focus on single pollutants, even though we recognize that exposures to these pollutants occur in the context of mixtures. Although there are examples of studies aimed at identifying causal pollutants among pollution mixtures, there has been far too little emphasis on this issue, perhaps because of the difficulty of such research. Additionally, single-pollutant standard setting has engendered a research focus on single pollutants but the sponsors of air quality health research are now shifting emphasis toward a more realistic research perspective. Considering that pollutants have overlapping mechanisms of injury and effects, we need a better ability to rank the relative hazards and risks among causal species and combinations of concern. We also need better methods for understanding the interplay of air pollution with other causes of these same effects.

In approaching the risks of sources, we need to know what combinations of pollutants may pose heightened risk. This issue is part of the “what causes what” dilemma but deserves special emphasis. Although synergies (the effects of two or more pollutants being greater or different than the sum of their individual effects) are of obvious relevance to risk management, we also need to understand if such synergisms are at play in the "real world" setting. Both synergism and antagonism can impact choices among alternate air quality management strategies.

In considering multipollutant and source-oriented air quality management strategies, we need to learn to what extent it is useful to “lump” (group) multiple air pollutants, combinations, or source emissions together as single-exposure categories. We will never be able to understand the effects of each of the thousands of air contaminant species and their near infinite combinations and certainly cannot regulate them individually. To make substantive progress, we need to develop lumping strategies for both research and regulatory purposes. For example, a long-standing strategy is to group by physical–chemical class (e.g., PM and polycyclic aromatic hydrocarbons). Pollutants might be grouped by the nature of their biological reactivity or effects in short-term testing batteries (e.g., oxidative potential, covalent binding to DNA, or other biomolecules). Although emissions from different source types comprise obvious groups (e.g., diesel exhaust, coal emissions, and wood smoke), the diversity and continuous evolution of the compositions of many source emissions markedly limit the utility of that strategy. Having developed different categories, testing the relative strength of linkages between categories and biological responses or health outcomes will provide useful input into choices among air quality management strategies.

We also need to know more about the mechanisms of biological responses to air pollutants. This need is not about discovery for discovery's sake, but derives from the needs to: (1) create lumping strategies, (2) understand and predict susceptibility, and (3) develop and validate useful biomarkers of exposure and effect.

Implications for air pollution health research management strategies

It is axiomatic that the entities providing funding for research determine the nature of the research that is conducted and thus, at least indirectly, the overall outcome and usefulness of the research. It is logical that air pollution health research should be driven by the information needs of air quality managers who are the end users of the results; although that linkage is sometimes weakened by intervening layers of decision making that may be influenced by other forces. Sponsors of research should give particular attention to two issues that especially limit our current ability to inform multipollutant air quality management. The overarching most important need is to "put the regulatory cart behind the research horse", in the sense that the focus of research should not be limited, funding permitting, to supporting existing air quality regulations. Research funded primarily in reaction to debates concerning current single-pollutant regulations does not tend to produce information clarifying the causal roles of those single pollutants as components of mixtures, the relative importance of those single pollutants vs. other air pollutants or the relative importance of those single pollutants and non-pollutant causes of the health burden of concern. Put simply, research focused on single pollutants mitigates against placing the results in a realistic context. More research needs to be aimed in a forward-looking direction that may inform air quality management strategies beyond those existing today.

Another issue long needing greater attention is to more systematically address the multidimensional matrix of information gaps. Finding that a single biological model gives a certain response to a certain pollutant (or class) at a certain exposure concentration or duration is a useful bit of "information". However, much more useful "knowledge" is gained by knowing how different biological models respond to the same exposure, how response varies by dose and exposure pattern, and whether the pollutant yields the same response as a component of a more realistic mixture. Generally, however, we do not carry out research in such a systematic fashion and the result is too often a scattering of data points within the three-dimensional pollutant-model-exposure matrix that are difficult to integrate into a coherent understanding.

Conclusion: can we do better?

The answer is "of course—if there is a will to do so". It is not so much a need to do different things, as it is the need to do things differently. For air pollution research, as in many other types of biomedical research, there are increasingly sophisticated research tools and advancing understanding of biological processes. To better inform future air quality management, however, we need to attend to the deployment of those tools and improve knowledge within a framework suitable to the task. What we have learned to date indicates that: (1) air quality health research has not prepared us well to inform truly multipollutant air quality management and (2) sponsors of research will bear much responsibility for our progress from this point. There is no shortage of clever researchers and few shortages of research tools. Those resources will evolve regardless—it is the management of the incentives to use those resources in a manner that meets future information and knowledge needs that requires attention.

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