Future Research Needs Associated with the Assessment of Potential Human Health Risks from Exposure to Toxic Ambient Air Pollutants

Lennart Möller,1 Dennis Schuetzle,2 and Herman Autrup3

1Center for Nutrition and Toxicology, Karolinska Institute, Huddinge, Sweden; 2Analytical Sciences Department, Research Laboratory, Ford Motor Company, Dearborn, Michigan; 3Department of Environmental and Occupational Medicine, University of Aarhus, Aarhus, Denmark

This paper presents key conclusions and future research needs from a Workshop on the Risk Assessment of Urban Air, Emissions, Exposure, Risk Identification, and Quantification, which was held in Stockholm during June 1992 by 41 participants from 13 countries. Research is recommended in the areas of identification and quantification of toxicants in source emissions and ambient air, atmospheric transport and chemistry, exposure level assessment, the development of improved in vitro bioassays, biomarker development, the development of more accurate epidemiological methodologies, and risk quantification techniques. Studies are described that will be necessary to assess and reduce the level of uncertainties associated with each step of the risk assessment process. International collaborative research efforts between industry and government organizations are recommended as the most effective way to carry out this research. — Environ Health Perspect 102(Suppl 4):193-210 (1994).

Key words: air toxics, ambient air pollutants, emission sources, indoor air pollutants, chemical characterization, source apportionment, emissions control, mobile source emissions, manufacturing emissions, volatile organic compounds (VOCs), semi-volatile compounds (SVOCs), polycyclic organic material (POM), atmospheric transport, atmospheric chemistry, air quality models, personal exposure, personal monitors, exposure models, complex mixtures, short-term bioassays, risk identification, risk quantification, molecular biology, biomarkers, multipathway exposure, comparative potency, unit risk factors, epidemiology, cancer risk.

Introduction

Urban air pollutants are a complex mixture of many organic and inorganic compounds. Most of the research on the potential health effects of air pollutants has been associated with the major pollutants ozone, carbon monoxide, nitrogen oxide (NOx), and air toxics. The term air toxics was coined in the early 1980s by the U.S. Environmental Protection Agency (U.S.EPA) as a generic name for air pollutants that could cause adverse effects on human health. The attention was to focus on health effects as opposed to so-called secondary effects such as visibility degradation, property damage, and crop and plant damage. The primary focus on air toxics has been cancer as a health end point. Other health effects of possible concern are asthma and respiratory toxicity, 

The American Cancer Society has estimated that there were approximately 980,000 cancer cases in the United States during 1989 (2). The 5-year survival rate averaged 51.4% for all cancers and 15.0% for lung cancer during the past two decades. Exposure to environmental pollutants has been estimated to account for about 2% of the total cancer cases (Figure 1). Nearly two-thirds of the total cancer cases may be caused by cigarette smoking and factors related to diet.

Since the last two workshops on air toxics (3,4), a substantial research effort has been directed toward developing reliable data that can be used to form the basis for quantifying the cancer risks associated with exposure to ambient air pollutants. These studies have focused on complex mixtures associated with combustion processes (e.g., particle emissions from mobile sources and wood burning) and specific compounds such as benzene, 1,3-butadiene, acetaldehyde, formaldehyde, methanol, polycyclic aromatic hydrocarbons (PAH), and PAH derivatives (e.g., nitrated PAH).

Today, it is recognized that reliable quantitative risk assessments must incorporate a stepwise systems approach that integrates the qualitative and quantitative character of emissions from mobile and stationary sources, atmospheric transport and chemistry, the assessment of exposure levels, dose-response relationships, and health endpoint. Such a risk characterization strategy.

![Figure 1. Causes of U.S. cancer incidence, (%).](image_url)
Figure 2. Risk characterization strategy (6).

has been formalized by the U.S. National Research Council (5,6) (Figure 2).

Current risk assessment models have indicated that there is a relatively low cancer risk associated with exposure to ambient air pollutants in the United States where stringent emission control regulations have been implemented. The current models estimate an upper limit of between 1700 and 2700 excess cancer cases per year from exposure to ambient air toxic pollutants in the United States (7).

Although great progress has been made, there are large degrees of uncertainty associated with estimates of excess cancer incidence. There are still significant gaps in knowledge concerning the concentration and distribution of toxins in ambient air, the chemical and physical processes that affect their concentration, the distribution and fate of these species in the atmosphere, the quantitative exposure to humans, and the potential human health and environmental impacts of exposure to these chemical species.

A major change in the approach to undertaking research on air pollutants has been an increasing focus on international collaborative efforts (collaboration between industry, government, and university organizations) and on the creation of organizations to help foster these collaborations such as the U.S. Health Effects Institute (8), the Swedish Urban Air Project, the Danish Air Project (9), the U.S. Auto/Oil Air Quality Improvement Research Program (10) and several other coordinating groups.

This report summarizes significant research findings since the last two meetings and provides future research recommendations from the meeting conference and previous risk assessment workshop with respect to assessing the potential human health risk associated with exposure to outdoor ambient air toxics. Although the workshop dealt primarily with air toxics in outdoor ambient air, it was recognized that exposure to indoor air pollutants can be a much more important source of exposure because most people spend 20% or less of their time outdoors (11,12). A special emphasis was placed on international approaches to meeting the recommendations presented in this paper.

The workshop participants emphasized that other health effects may be as important or even more important than cancer. The spectrum of these other potential adverse health effects include asthma, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, and heritable genetic effects. Other less quantitative effects include an increased incidence of colds, allergies, and other respiratory ailments. All of these effects are of potential public health concern because they might affect large numbers of people.

In order to reduce the multitude of pertinent references that could be cited in each section of this report, several of the papers published in this volume were written to serve as critical reviews of current research efforts and results. Key references from other recent workshop proceedings, feature articles, and reviews were used to provide additional background material for this research assessment.

Emission Sources and Characterization

Urban air is affected by many different local emission sources as well as by long-range transport from other urban or industrial areas. The sources considered in this workshop included those from anthropogenic sources (e.g., motor vehicles, domestic heating and cooking, power generation, and manufacturing processes) and natural or biogenic processes (e.g., hydrocarbon emissions from plants). The relative importance of these sources will depend on their nature and magnitude, local geography, and meteorological conditions.

Emission Inventories

Most air pollution studies have focused on the measurement of the pollutants: ozone, NO\textsubscript{x}, sulfur oxide (SO\textsubscript{x}), carbon monoxide (CO), total hydrocarbons (THC), and respirable particles. Although there has been a considerable effort to develop reliable emission inventories of these pollutants or their precursors, significant errors still exist. There are several reasons for such discrepancies.

Because internal combustion engines, power generation, and manufacturing technologies are being modified on a regular basis to reduce emissions, improve productivity and quality, and reduce costs, the qualitative and quantitative nature of emissions from these sources has been changing with time. For example, hydrocarbon (HC), CO, and NO\textsubscript{x} emissions from gasoline-fueled vehicles have been reduced by more than 95% during the past 20 years in the United States (13). Another problem is that, in some cases, laboratory measurements did not adequately predict emissions from sources operating under real-world situations. For example, careful measurements on roadways and in vehicle tunnels show that hydrocarbon emissions are two to three times higher for in-service vehicles than would be expected from laboratory certification procedures (14,15). A primary source of these discrepancies is probably connected with malfunctioning and high-mileage vehicles with inadequate emission control devices. It has been estimated that 20% of these in-use vehicles produce 80% of the total vehicle emissions inventory. This is even more of a problem in some parts of the world where high-mileage, malfunctioning vehicles are much more common. There also is a possible problem with lead-contaminated—lead-free gasoline in regions where both fuels exist simultane-
ously. Such contamination will reduce the functionality of the catalyst, resulting in increased emissions. Other environmental factors, such as low-ambient temperatures and high altitudes, can increase hydrocarbon and CO emissions from vehicles (13).

An increased effort has been undertaken to determine the importance of nontradi-
tional sources of emissions (e.g., cooking, lawn mowers, boats, stationary diesels, etc.) relative to vehicle and manufacturing emissions. For instance, the EPA estimates that a lawn mower operated for 1 hr releases as many hydrocarbons as a car driven 60 miles, and an outboard motor (1 hr operation) releases as much hydrocarbons as a car driven for 2500 miles.

Urban Ambient Air

Three types of urban air sheds generally are recognized. The first is represented by typical western cities such as Stockholm, New York, and Tokyo. Mobile source emissions are a significant source of air pollution in these cities. A second type of urban air is represented by so-called megacities such as Mexico City and Cairo (16). For these cities, industrial sources, residential cooking, refuse burning, and road dust, in combination with exhaust from old and poorly maintained vehicles, contribute to most of the air pollution. Finally, a third type of urban air pollution is represented by city areas such as Beijing and several urban areas in Eastern Europe (17) where pollution primarily is caused by coal combustion and industrial sources. In all three types of urban air sheds, local climatic conditions play an important role. Thus, the complex interactions between the emission sources and the climatic conditions must be considered in any analysis.

Assessment of environmental trends on local to global scales is among the greatest challenges facing the scientific community today. Fixed-site sampling, remote sampling, and modeling form a triad of technologies that may be used for decision making at the local to global level. Trends in regional air quality are important when establishing priorities for health effects research because this research should account for future air quality and exposure data.

Indoor Air Pollution

A major change in the approach to health effects studies has been an increased emphasis on indoor air pollution. Because people spend a major portion of their time indoors, indoor air quality is a major factor in the total integrated exposure assessment. It is known that indoor levels of nitrogen dioxide (NO\textsubscript{2}) and CO are higher than those in outdoor ambient air when unvented gas cooking or coal or kerosene space heating are used (18), while ozone exposures occur primarily in the outdoor environment and are low inside homes.

Several major studies have been undertaken during the past few years to understand the effect of environmental tobacco smoke (ETS) on indoor air quality. A recent EPA report (19) estimates that secondhand smoke causes 3000 lung cancer deaths a year among nonsmokers. The study proposes that passive smoke be classified as a human carcinogen. This classification was based upon studies that showed increased lung cancer in nonsmoking spouses of smokers and respiratory problems in children of smoking parents. In addition, the American Heart Association (1992) concluded that between 35,000 and 40,000 heart disease deaths a year are linked to secondhand smoke.

Other sources of contamination include subsurface transport of volatile contaminants into buildings near hazardous waste sites (20), building and interior finish materials, furnishings, cleaning products, paint, and many other materials that contain volatile organic compounds (21).

Vehicle Occupant Exposures

The amount of time people spend in their vehicles has increased steadily during the past decade. Because of the continuous inflow of ambient air, the level of personal exposure to vehicle emissions during driving is primarily determined by the emissions of other vehicles on the road and is significantly increased in highway tunnels (14), in street canyons, and in traffic with significant numbers of vehicles with inadequate emission controls. In addition, other sources of exposure to vehicle occupants include road dust and other pollutants commonly present in urban ambient air environments (e.g., ozone). This form of exposure needs to be considered as a potentially significant source for some people, such as taxi, bus, and delivery vehicle drivers, who spend most of their working day in their vehicles.

Characterization of Air Pollutants

The ability of analytical environmental scientists to identify and quantify chemical species in emissions and ambient air samples has advanced tremendously during the past decade. It is now known that there are thousands of individual chemical species present in urban ambient air derived from primary emission sources and atmospheric chemical reaction products. The primary focus areas for air-pollutant characterization studies during the past several years has included the speciation of gas-phase hydrocarbon emissions from combustion sources as needed to determine the ozone-forming potential of these emissions, and the identification of key chemical species that may be primarily responsible for adverse human health effects.

The primary purpose of this workshop was to review the potential health risks associated with exposure to specific air toxics. In this regard, it was agreed that the organic species can be best described as existing in the volatile (VOC), semivolatile (SVOC) and polycyclic organic material (POM) phases as listed in Table 1.

Since the early 1980s, chemical fractionation and chemical analysis techniques have been combined with bioassays to simplify the process of identifying the key mutagenic compounds present in air pollution samples (22). The Ames Salmonella mutagenicity assay and a more sensitive version of this assay, the Microsuspension mutagenicity assay (23), have been the most widely used bioassays for this purpose. In some cases, these bioassays have been used as an alternative to chemical characterization as an effective approach to compare samples collected from different parts of the world and to track seasonal changes in the mutagenic character of ambient air samples. For example, the mutagenicity of particle extracts per unit volume of air increases substantially in wintertime because of residential heating, increased emissions from colder engines, and changes in climatic conditions. These measurements suggest that the relative risk increases during this time of the year (24). Samples can thus be selected during these periods for further chemical and biological characterization.

There has been an increasing interest in semivolatile organic species. Recent smog chamber and atmospheric studies suggest that these semivolatile species may be responsible for a substantial fraction of the Salmonella mutagenic activity of urban air particle extracts (25,26). Much of the work presently being carried out does not indicate a concern for human health risks associated with exposure to the semivolatile species; however, further studies are needed to better understand the health impact of exposure to these chemical entities.

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**Table 1. Atmospheric phases of organic air pollutants.**

| Air pollutant phase | Molecular weight range of carbon (C) |
|---------------------|------------------------------------|
| Volatile organic compounds (VOCs) | C\textsubscript{1} - C\textsubscript{11} |
| Semi-volatile organic compounds (SVOCs) | C\textsubscript{12} - C\textsubscript{17} |
| Particulate organic material (POM) | C\textsubscript{15} - C\textsubscript{60}+ |
Source Apportionment

Substantial progress has been made on the development of chemical and biological measurement techniques for the source apportionment of urban–air toxic compounds and mutagenic activity in urban areas (27). For example, the extractable organic matter (EOM), containing POM and mutagenic activity, was apportioned for Boise, Idaho, USA, (28, 29) and Gothenburg, Sweden (30) (Figure 3).

The measurement of radiocarbon $^{14}$C in air pollutant samples has become accepted as an excellent method to distinguish between sources of air toxics derived from fossil fuel combustion and biogenic sources (e.g., wood combustion products and atmospheric reaction products of terpenes). Contemporary carbon sources (e.g., wood, paper) and fossil carbon (e.g., coal, oil) contain different levels of $^{14}$C. Because the combustion products of these fuels contain the same level of $^{14}$C as the original fuel, measurement of the ratio of $^{14}$C to stable $^{13}$C or $^{12}$C in environmental samples can be used as a source apportionment method. Analytical techniques are available now that can make accurate $^{14}$C measurements on a few μg of material (27). The availability of these improved techniques will make it possible to source apportion classes of potentially toxic species (e.g., PAH containing liquid chromatographic fractions) that are present in air pollution samples.

Emission rates for several PAH have been determined by comparison of their concentrations near roadways and for HC, CO, and NOx in vehicle tunnels. Some of these compounds appear to be useful as markers for diesel and gasoline vehicles. For example, benzonaphthathiophene has been used as a tracer for diesel vehicle emissions. However, care must be taken to ensure that variables, such as changes in fuel composition and engine operating conditions, are appropriately considered in estimating emission rates (31, 32). Multivariate statistical methods have proven valuable for the analyses of such variables (33).

Emissions Control

In some parts of the world, the primary approach to mobile and stationary source emissions control in the 1970s was to add control devices such as catalysts, incinerators, scrubbers, and particle collection systems. However, during the past decade, an increased effort has been placed on process modification to reduce emissions. Examples of process modification include the use of reformulated fuels, monomolecu

lar fuels (e.g., pure ethanol or hydrogen), biogenerated fuels (e.g., rapeseed oil), advanced engine and power plant designs, on-line combustion process control using pollutant sensors and computers, materials substitution, and modification of industrial chemical processes. In addition, regulatory approaches to emissions reduction are changing; command and control approaches are being (in some cases) replaced with economic incentives and public/private cooperation (34).

In the late 1980s, U.S. companies and regulatory agencies initiated several cooperative environmental research programs. One of these programs, known as the Auto/Oil Air Quality Improvement Research Program, involved a $40 million effort to develop a reformulated gasoline (10, 35). This extensive program allowed representative testing of a large number of vehicles with many different fuels. Such comprehensive studies are necessary for understanding the emissions from complex multivariant systems.

A number of recent laboratory and vehicle studies have demonstrated that reformulated gasoline and diesel fuels can reduce vehicle emissions (10, 32, 35). Chemometric methods using multivariate statistical and clustering analysis have been used successfully to understand relationships between fuel composition and emissions (32, 35–37). As a result, reformulated gasolines have been introduced in the United States and in Sweden. Environmental fuels include low-sulfur (10 ppm S) diesel fuels as well as reformulated lead-free fuel.

New control methods for diesel vehicles, including engine modifications and new exhaust after treatment methods, have shown the capacity for substantially reducing the emission of particulates, POM, and mutagenic material (36–38). The environmental acceptability of light-duty diesel vehicles needs to be reassessed in view of these reduced emission levels. Such a view also should consider the effect of the potential effect of the diesel engine on reduced regional levels of ozone, carbon monoxide, gas-phase toxic compounds, and greenhouse gas emissions.

Legislation was enacted recently in the United States, Europe, and regions that require the further reduction of vehicle emissions to improve air quality. As vehicle emissions are reduced through the introduction of advanced technology vehicles, and reformulated and alternative fuels, emissions from malfunctioning and high-mileage vehicles will become the predominant sources of mobile source emissions.

Introduction of reformulated fuels and emission control devices will continue to dramatically reduce the contribution from fossil-fuel powered vehicles to urban air pollution. However, this new technology is not available to all parts of the world, and urban air pollution will remain a health problem in megacities and heavily industrialized areas.

Recommendations

Although a significant effort was undertaken during the past decade to collect and measure organic species in ambient and interior air samples, there still exists significant gaps in several areas. The Work Group formulated recommendations in several key areas: a) Develop methods that

![Figure 3. Source apportionment of emissions for Albuquerque, New Mexico, United States (26) and Gothenburg, Sweden.]
can be used to assess more accurately the relative contribution of emissions from various indoor and outdoor sources. b) Update emission inventories from mobile and stationary sources on a regular basis. c) Develop a statistically robust database for VOCs, SVOCs, and POMs for high-mileage and malfunctioning vehicles. d) Determine the relative importance of biogenic to anthropogenic sources of photochemically reactive organic species for a number of urban areas throughout the world. e) Identify and assess the ozone- and particle-forming potential of species in the SVOC phase (e.g., in diesel emissions). f) Establish an international geographic information system to combine environmental data about air, water, and soil to better understand the natural interactions of pollutants between these media and to highlight areas of environmental interest and concern. g) Develop improved urban airshed models to help identify the complex situations and potential trends in the future. Undertake ambient air monitoring studies to validate model assumptions and parameters. h) Expand international collaborative efforts between industry and government organizations to undertake research efforts on the development of low-cost and effective emissions control strategies. i) Initiate a collaborative effort to develop a reformulated diesel fuel in Europe because there is a significant portion of diesel vehicles in these countries. j) Undertake fundamental studies on combustion processes that are capable of developing models that can accurately predict the effects of fuel changes, engine design, and various control strategies on vehicle emissions.

**Atmospheric Transport and Chemistry**

Once introduced into the atmosphere, chemical species in both the gas and particle phases are subjected to transport processes, including wet and dry deposition (39). Atmospheric reactions most likely will occur that influence the ultimate chemical composition to which human populations are exposed (40).

Organic compounds are removed from the atmosphere by wet and dry deposition; photolysis; and reaction with hydroxyl radicals, nitrogen dioxide (NO₂) radicals, and ozone (39,41,42). For the majority of organic chemicals (excluding methane, ethane, and certain halocarbons), the expected atmospheric lifetimes are estimated to range from a few hours to 10 to 20 days (43). Chemical reactions lead to the formation of more polar products that can undergo gas-to-particle conversion (44), such as the formation of particle-phase nitro-PAH from reactions of gas-phase PAH (45).

A knowledge of these reaction products is needed to assess exposure of human populations. These physical and chemical processes depend on meteorology and chemical reactions that can lead to the formation as well as the removal of toxic compounds. Therefore, these atmospheric removal and transformation processes link emissions and exposure.

**Volatile Organic Compounds**

The chemical reactions of each VOC with nitrogen oxides in the atmosphere have different reaction mechanisms and rates. These reactions lead to the formation of ozone and the degradation of VOCs with the concurrent formation of a myriad of reaction products including mutagenic components (45,46,47).

A great deal of work has been undertaken during the past few years to develop simplified methods to calculate the ozone-forming potential of emissions from various sources (43). Such methods have been enhanced greatly by a more complete understanding of the reactive hydrocarbon species that are present in emissions and an improved understanding of ozone and oxidant formation mechanisms (48).

Presently, our knowledge concerning the products formed from the atmospheric reaction of organic compounds is insufficient. Even for such important volatile organic compounds (VOCs) as benzene, toluene, and the xylenes, only about half of the product mass has been accounted for (49,50). Identification of the remaining products is difficult because they are labile and polar. The uncertainties in the atmospheric chemical reactions for the VOCs, in combination with corresponding uncertainties in airshed model predictions, leads to a lack of knowledge of the amount and identity of potentially toxic products (51,52).

**Semivolatile Organic Compounds**

SVOCs are present in ambient air as gases and associated with particulate matter. The distribution of SVOCs between the gas and particle phases controls their removal from the atmosphere by physical (e.g., wet and dry deposition) and chemical and photochemical processes (53).

Studies initiated in the late 1980s demonstrated that the Salmonella mutagenicity of SVOCs in urban ambient air samples can be as high (per unit volume of air collected) as that for the solvent extracts from particles (24,25,54). Concurrent laboratory studies have demonstrated that SVOCs can be converted to gas and particle phase components, the products of which are mutagenic.

Most of these mutagenic products appear to be derived from the atmospheric reaction of gas-phase aromatic and polynuclear aromatic hydrocarbons (PAH) and PAH derivatives (e.g., methoxyppyrene). Recent smog chamber experiments and ambient measurements suggest that atmospheric reaction products of 2- to 4-ring PAH account for a substantial fraction of the mutagenic activity in urban air (45). These reaction products consist of various nitrated products. A major portion of these PAH reaction products remain unidentified, and the potential health risks associated with these species are unknown.

**Polycyclic Organic Material**

POM occurs in the atmosphere primarily as organic compounds adsorbed on the inorganic particle matrix (55). The polycyclic aromatic hydrocarbons (PAH) are present at parts per million levels in the particles. The four-ring PAH (fluoranthene and pyrene) are distributed between the gaseous and particulate phases. Benzo[a]pyrene (BaP, five rings) is only found in the POM phase. BaP represents approximately 4% of the total POM in most combustion-derived particle emissions.

At the 1983 workshop (56), considerable attention centered on the presence of PAH-derivatives in POM such as nitrated-PAH (nitr-PAH). Since that time, an international research effort has been directed toward understanding the abundance, sources, and atmospheric chemistry of these PAH derivatives as well as the possible human health effects associated with exposure to these compounds. An example of such a study was undertaken by the International Agency for Research on Cancer (IARC) (57) that summarizes the evaluation of the carcinogenic potential of 15 different nitro-PAHs.

**Air Quality Models**

The process of dispersion and deposition of nonreactive air pollutants (e.g., CO, methane [CH₄]) is relatively well understood (58). However, this is not the case for reactive species (e.g., toluene). Advanced photochemical air models calculate the evolution of pollutants by accurately describing the physical and chemical
processes responsible for the chemical transformation, transport, and fate of pollutants in the atmosphere. These models use fundamental meteorological parameters such as wind speed, wind direction, relative humidity, and temperature gradients (inversion layers, mixing heights). Different dispersion models have been developed for different geographical scales (e.g., continental, nationwide, regional, urban, and local).

These models are being used increasingly as the basis for determining the effectiveness of proposed pollution control strategies in advance of the adoption of particular emission controls. Thus, they are the most scientifically sound foundation for testing the relative effectiveness of alternative emission controls. They also serve as the basis for policy decisions that must be made between alternative programs designed to improve air quality.

A thorough evaluation of predictions and observations is critical for assessing the performance of photochemical models and providing a basis for confidence in a model's use. Historically, because of a lack of measurements, model data sets have suffered from significant gaps in the knowledge of the prevailing meteorology, emissions, and air quality. The Southern California Air Quality Study (SCAQPS) was conducted in the Los Angeles area during 1987 to help in this regard (59). The data from this study have provided a much more comprehensive set of measurements with which to test urban-scale photochemical models.

**Recommendations**

Research studies during the past decade have demonstrated that atmospheric chemistry plays a critical role in the formation and degradation of toxic substances. However, it is not known which atmospheric reaction products could have a potential positive or negative impact on human health. Further work is needed to (a) obtain updated mobile-source and manufacturing emission factors for gas- and particle-phase hydrocarbons on a regular basis; (b) to determine the key gas- and particle-phase atmospheric reactions that affect the formation and degradation of toxic species in ambient air; (c) to develop improved analytical techniques for identifying the polar-, labile-, and low-volatility atmospheric reaction products; (d) to identify the major mutagenic and carcinogenic products from the atmospheric reactions of HCs and PAH with NO$_2$; and (e) study the atmospheric transformations of vehicle exhaust with respect to chemical products and the potential biological effects of these products; and (f) to reassess the relative importance of gas versus particle phase pollutants in terms of human health effects.

Large-scale air quality studies similar to the SCAQPS study need to be carried out for major urban areas such as Mexico City, New York, and Cairo in order to provide a comprehensive set of measurements with which to test urban-scale photochemical models. Advanced models will need to be developed that link microscale and mesoscale dispersion equations (e.g., combine street canyon and urban dispersion models). Finally, these models will need to incorporate the chemical and physical atmospheric processes that affect the presence of toxic compounds.

**Exposure Levels**

Epidemiological data for humans exposed to high levels of air pollutants (e.g., coke oven workers) support the role of air pollution in human lung cancer (60). A few studies on populations living in urban environments have shown a weak correlation between cancer and air pollution. However, because detailed measurements of exposure levels were not performed and because of the presence of several confounding factors, there is considerable uncertainty about the quantification of the effects because of ambient air pollution as an etiological factor. It is of importance to consider different localizations of cancer because inhaled materials can undergo systemic circulation after absorption into blood. In addition, a large portion of inhaled material is swallowed because of muco-ciliar transport from the lung or absorption in the upper respiratory tract.

Exposure may be estimated through surveys or quantitatively through ambient monitoring, personal monitoring, or biological monitoring. The development of improved methods to accurately assess human exposure to air pollutants has been an area of active research during the past decade. It has become increasingly recognized that an accurate assessment of exposure is difficult to achieve but ultimately necessary if meaningful risk assessments are to be done. Integrated exposure depends upon the magnitude of exposure, the duration of exposure, and the level of human activity.

An alternative approach is to use air quality models, which are based upon detailed emissions inventories, meteorology, atmospheric chemical processes, and other complex parameters. The models can be used to calculate the concentrations, with the inclusion of pollutants chemically formed in the atmosphere, in different microenvironments where human beings can be expected to spend a significant portion of their time in homes and offices; walking, running, or riding bicycles near busy roads and heavy industrial areas; or inside plant environments and other microenvironments. Thus, human exposure can be estimated by many kinds of measurements and by model calculations, including air quality and activity data. A combination of the two approaches seems to be the most efficient.

Since the 1960s, most measurements of urban air pollutants have been obtained using fixed station measurements of total particle mass, sulfur dioxide (SO$_2$), NO$_x$, CO, hydrocarbons, and ozone. Ambient monitoring neglects spatial and indoor and outdoor concentration differences and may lead to significant misclassification of exposure.

Current research focused on the identification of selected chemical species or classes of species that could be measured to represent exposure to complex mixtures of air pollutants. Some examples of indicator substances are given in Table 2. Carbon monoxide and nitrogen oxides have served as good indicator substances for vehicle emissions (58).

Benzo[a]pyrene (B[a]P) was suggested over three decades ago as an indicator substance to help assess exposure to air toxics (61). As a result, a substantial data base for B[a]P has been acquired in source.

**Table 2.** Some representative (indicator) compounds that are present in the VOC, SVOC, and POM phases of ambient air pollutants.

| Air pollutant phase | Representative compounds |
|---------------------|--------------------------|
| Volatile organic compounds (VOCs) | Benzene, toluene, 1,3-butadiene, formaldehyde |
| Semi-volatile organic compounds (SVOCs) | Naphthalene, 1-nitroaniline, pyrene, 2-nitrofluorene |
| Respirable particles | Elemental carbon, lead |
| Polycyclic organic material (POM) | Benzo[a]pyrene, 1-nitropyrene |
| Gas-phase inorganics | CO, NO$_x$, SO$_2$ |

Abbreviations: CO, carbon monoxide; NO$_x$, nitrogen oxide; SO$_2$, sulfur dioxide; Pb, lead.
emission and ambient air samples (62). Although B[a]P is one of the most chemically reactive PAHs, this compound will continue to be an important marker of human exposure to air toxics, particularly for studies of long-term trends. Such use of B[a]P data bases requires, however, an evaluation of the analytical methods used in past studies. Proper care should be taken to minimize degradation of B[a]P during sampling, storage, and analysis. It is recommended that measurement of B[a]P and benzo[α]pyrene ratios be determined to assess if significant loss of B[a]P has occurred (31). Efforts should be undertaken to determine whether a better indicator substance can be identified.

Our increased knowledge base on the qualitative and quantitative distribution of air pollutants is being used to predict the formation of ozone and to identify and validate the use of indicator substances to determine the presence of other components (43).

There are many locations in the world where economic constraints have limited the establishment of extensive sampling networks and analytical environmental laboratories. Therefore, it is very important to carry out studies that can be used to identify easily measured atmospheric constituents or groups of components that are of special interest from the health effects point of view and that can serve as a base set to assess pollution levels and human exposures.

It is essential in selecting or calibrating a specific measurement technique to be conscious of other data to which the measurement will be compared. For example, epidemiologic studies use relationships between exposure measurements and disease incidence. The exposure level to the selected population group is estimated from fixed sampling sites. These data are used in a manner that assumes that the constituents and the concentration of constituents do not change over many years of exposure.

**Total Integrated Personal Exposure**

An accurate assessment of human exposure to toxic air pollutants has been difficult to obtain. Because there are wide variations in exposure levels within an urban area, there has been a trend to increase the number of fixed urban sampling sites, collect samples more frequently, and generate more detailed chemical composition data on the atmospheric pollutants. This trend has been necessary in order to generate a better estimate of the actual exposure of urban populations to localized sources (e.g., homes near roadways and municipal incinerators) (63). In addition, an increased effort has been undertaken to collect samples in other areas where people may spend a significant portion of daily activity.

Indoor air exposure also plays an important role in determining total exposure to B[a]P. Jenkins et al. (64) reported that the average adult Californian spends nearly 62% of the time at home, where exposure to B[a]P and other pollutants may occur at levels well above the typical ambient air exposure the individual may encounter. The B[a]P exposure indoors can range from about five times up to several hundred times higher than the dose received outdoors.

The data that are derived from exposure measurements often have a high level of uncertainty. In general, the mean exposure outdoors, as determined from fixed monitoring stations, gives good agreement with personal samplers, but the variation is greater, which can lead to a poor estimation of the exposure. In any case, the question must be raised as to how accurate the exposure measurement should be made.

The accuracy of actual assessments of exposure to response relationship is dependent upon the reliability of measurements of exposure levels as determined from the ambient air monitoring technique. Each sampling technique that is further removed from the target tissue will yield a less accurate assessment of dose. The least representative samples are derived from fixed sampling sites.

**Personal Monitors**

Currently, personal air sampling monitors provide the most accurate measurements of daily exposure to air toxics. However, it is not practical to use personal monitors to collect 24-hr ambient air samples. A recent Swedish study demonstrated how a personal NOx monitor was used to identify an unknown source of high NOx exposure for children. On normal days, the NOx exposure was low, but some days these children had extremely high NOx exposure. It was found that these children were all exposed to high levels when they visited ice hockey rinks. The ice was prepared with propane-fueled ice-resurfacing machines and the air exchange rate was low, which led to very high NOx levels (65).

**Exposure Models**

Numerous models have been developed and applied to an estimation of human exposure from airborne materials (66). The aggregate risk to human health from exposure to an airborne pollutant results from the characteristics of the agent's action on the people who are exposed to it. The useful expression of the risk depends on joint statistical considerations of agent dispersion and characteristics of the human receptors. The aggregate risk also results from the spread of the primary agent (and its transformation products) from its source(s) to contact with people.

Current exposure models take into account the interaction between each of the main risk analysis elements. Exposure estimates result from the integration of pollutant dispersion patterns and human population patterns. The dispersion patterns, in turn, result from the joint action of emissions and dispersion processes.

It is presumed that the effect of carcinogenic materials is to produce critical cell damage. Thus, carcinogenic health effects models, in general, are dose (e.g., integrated exposure) models, not exposure models. The lack of firm statistical bases often leads to the adoption of nonthreshold, linear models, even in cases where thresholds and nonlinear effects might be expected.

If linear (dose) models without thresholds are to be used for carcinogenic (or other) risk assessments, estimation of exposure at specified levels becomes irrelevant to risk assessment or, at least, its use is nonintuitive. For example, a carcinogen risk analysis may be based on a linear, nonthreshold health effects model. The total collective health risk would thus be proportional to the long-term exposure summed for all affected people for the identified period, and exposure of many people at low concentrations would be equivalent to exposure of a few to high concentrations.

The atmospheric dispersion that reduces concentrations also would lead to exposure of more people; therefore, increments to population risk would not necessarily diminish with increasing dispersion time or distance. Limits to human risk would only exist if the concentration or population patterns were bound, for example, by either chemical decay or scavenging by such phenomena as precipitation and respiration.

It is important in defining any modeling scheme that the analytical elements be consistent in scope, scale, and detail with each other and with the purposes of the analysis. It appears that microenvironments are clearly important in carbon monoxide exposure analysis because automobile-generated CO concentrations are highly correlated with automobile usage patterns.

However, it is not clear if ozone exposures are so correlated.

Considering the large number of compounds in ambient air and the economic and practical impossibility of routine analysis for more than a few of them, it is important to select suitable indicator compounds and to establish the relative concentrations with the indicator as references, in specific analyses of many compounds. This should be done at the emission level as well as in ambient air. Researchers working in the areas of indoor and ambient air have begun only recently to work together. Many pollutants in these two environments are the same, and it is necessary to assess exposure to both environments. In addition, the exposure of humans to air toxics needs to be kept in perspective with respect to exposure from other sources such as food, water, drugs, etc. Thus, it is necessary for scientists working in each of these areas to work more closely together.

**Recommendations**

One of the greatest research challenges of the next decade will be how to accurately assess true exposure to air toxics and assess the composite risk associated with exposure to complex mixtures. Specific research recommendations to help meet this task include the following:  

a) Identify selected compounds or groups of compounds that can be easily measured to better assess integrated human exposure to toxic air pollutants.  
b) Determine relationships between more precise measurement techniques and those that can yield information from remote locations (e.g., satellite measurements).  
c) Increase collaboration between researchers working in the areas of indoor and ambient air pollution.  
d) Obtain better quantification of population activity patterns in order to provide a basis for accurate exposure calculations.  
e) Develop further personal monitoring techniques to provide the information necessary for the validation of deterministic and probabilistic models.

**Risk Identification**

The accurate assessment of potential health risks associated with exposure to air pollutants is a highly complex process that requires the systematic integration of the many basic components that have been described in the previous sections and illustrated in Figure 4.

Risk identification consists of the qualitative evaluation of data from epidemiologic studies, physical and chemical studies, short-term bioassays, animal exposure studies, and molecular biology techniques such as metabolic studies, and structure-activity investigations.

In addition to cancer, there are other noncancer health effects of urban air pollution that may be of more public health importance. Although classical risk assessments generally focus on cancer, the consideration of many noncancer end points such as asthma, respiratory infections, bronchial distress, allergies, and other pulmonary problems that may be associated with urban air pollution will continue to be needed. Application of chemical analytical methods to study the molecular basis for these conditions could shed light on the possible role that certain air pollutants may play in the causation or aggravation of these health problems.

Nearly all chemicals that are ingested by animals undergo biotransformation. Biotransformation is frequently a critical determinant of the toxic and carcinogenic effectiveness of chemicals, because animals metabolize chemicals to more toxic or carcinogenic species (activation) or to less toxic or carcinogenic species (detoxication). Thus, the ultimate carcinogenic species of a chemical is often a metabolite rather than the parent compound. It is now known that this can lead to significant nonlinearities in the cancer dose–response relationship because many metabolic enzymes follow hyperbolic kinetics. At high doses of a chemical, saturation of metabolism can occur. This can serve to limit the amount of carcinogenic metabolite produced, or it can limit the capacity of the animal to detoxicate a carcinogenic species.

Toxicity data are available on only a small number of air pollutants. This necessitates estimation of the health effects for most of the compounds from information acquired in cellular or laboratory animal studies. Another issue is that the risks at low levels of exposure typical of environmental situations must be extrapolated from studies conducted at higher exposure levels.

**Pure Compounds versus Complex Mixtures**

An assessment of the potential health risks associated with exposure to complex mixtures requires more than an understanding and quantification of the effects of individual compounds present in the mixture. Clearly, in a mixture of thousands of compounds, there is a great deal of potential for interactive effects among different components. While the toxicity of a mixture cannot be understood solely by an assessment of the effects of individual compounds, it also is true that it is not possible to assess the toxicity of all possible combinations of these compounds. Some approaches are being developed to understand synergistic actions by comparing the observed lethality of mixtures to the predicted lethality of these same mixtures using an additive model for prediction (67). However, such methodologies require an extensive level of testing. Thus, it will be important to find new approaches to address the toxicity of mixtures.
IARC describes the problem with complex mixtures in the following way:

Estimating the human cancer risks of exposure to complex mixtures presents formidable methodological problems. However, such exposures are thought to account for a large proportion of cancers, in particular because of widespread exposure to such mixtures within populations (68).

Since the early 1970s, several government organizations such as the U.S. National Institute of Standards and Technology (NIST), the U.S. National Cancer Institute, and other organizations have made available small quantities of chemical reference materials for environmental studies. These reference materials have been distributed as pure compounds in solid state or solutions or as mixtures of pure compounds in solution at specified concentrations.

During the 1980s, NIST developed standard reference materials (SRM) that represent complex mixtures of environmental samples. These samples included two ambient air samples (SRM 1648 and SRM 1649), a heavy-duty diesel particulate sample (SRM 1650), and a coal tar sample (SRM 1597) (69).

In 1987, the International Program on Chemical Safety, in collaboration with the EPA and NIST, initiated an international collaborative study on the mutagenicity of complex environmental mixtures in the Ames assay. This study determined the inter and intralaboratory variability associated with the extraction and bioassy of the SRMs 1597, 1649, and 1650. It was found that these SRMs provided useful materials for bioassy studies, in much the same way these reference materials have been valuable for developing methodologies for the measurement of specific chemical species in these mixtures (70).

An International Symposium on Biological and Environmental Reference Materials (BERM) was held in Aachen, Germany, during the same month as this workshop. The BERM also concluded that the use of biological and environmental reference materials are essential for meeting the goals of compatibility and comparability in environmental measurement. Thus, it is expected that complex mixture SRMs will play an increasingly valuable role for the development of chemical and biological assay techniques, for standardizing and comparing procedures used in laboratories, worldwide, and to support fundamental studies on synergistic and antagonistic biological effects.

**Short-Term Bioassays**

Short-term bioassays have been used extensively to compare the total mutagenic activity of samples collected from various sources and ambient air (71,72). The Salmonella mutagenicity assay has been used to demonstrate that most air samples exhibit mutagenic activity. This assay has been used as a fundamental tool to help in identifying the major chemical species responsible for the mutagenic activity of urban air particulate matter. The ease of carrying out this bioassay has focused research activities on the mutagenic activity of urban air emissions, while ignoring many other types of genetic end points. Since the 1982 meeting in Stockholm, more than 100 papers dealing with the mutagenicity of complex mixtures extracted from airborne particulate matter have been published. Several of these papers describe a good correlation between the presence of a particular class of pollutants and mutagenicity (68). This large body of data has made it possible to rank rural, industrial, and urban areas all over the world in terms of mutagenic activity; taking into account modifying factors such as temperature, wind direction, etc. (23).

There is now available a wide array of short-term bioassays that are being used to identify the potential risk associated with exposure to air toxics. Such bioassays include the dioxin-receptor ligand assay (73), the HPRT locus assay (74), and others. The combination of these bioassays with the generation of mutational spectra has extended the dimensionality of such tests (74). DeMarini (75) has used the Salmonella (TA98) assay in combination with colony probe hybridization to detect a common hotspot deletion, followed by polymerase chain-reaction (PCR) and DNA sequencing, to generate mutation spectra. This exciting new technique suggests that unique mutation spectra can be generated by different classes of complex mixtures and that such spectra are a consequence of the dominance of a particular chemical class or classes within the mixture.

Since the early 1980s, several investigators have used bioassay-directed chemical fractionation and bioassay-directed chemical analysis to facilitate the identification of potentially important chemical mutagens in complex environmental samples. Current studies have focused on the identification of oxygenated and nitrated PAH in polar chemical fractions (22,24,76,77). A number of highly mutagenic chemical species have now been identified including 3-nitro-6-azabenzo[a]pyrene-N-oxide (77), nitrodibenzopyranones (45), and nitro-hydroxy-PAH (78).

Mutagenic activity in the gas-phase may not be as important as the presence of mutagenic activity in particulates because of the pharmacokinetics (i.e., uptake, distribution and metabolism) of the active material. Short-term assays, such as the Ames test, are a valuable tool for identifying risk factors; but it is of importance to note that the enormous difference in bacterial mutagenicity for nitro-PAHs (a factor of approximately 100,000) is not seen in vivo. It is therefore of importance to gain understanding on the mechanisms to explain these differences.

**Animal Exposure Studies**

A number of comprehensive animal inhalation studies were carried out in the mid-1980s in the United States, Japan, and Germany, which demonstrated that rats exposed by inhalation to diesel exhaust developed lung tumors, whereas those exposed to filtered diesel exhaust did not. It was the consensus opinion of a meeting held in Tsukuba, Japan, in 1986 that these tumors were caused by carcinogenic organic compounds associated with the particles (79).

The results of the animal cancer tests and epidemiology studies, together with the assumption that the tumors were caused by the organic compounds, were used by the EPA and other agencies (80) to conclude that diesel exhaust is a probable human carcinogen, and the potencies observed in the animal studies were used as a basis for estimating the human cancer risk of diesel exhaust.

The animals were exposed generally to concentrations of diesel particles that were much higher than those found in ambient air. At these very high particle loadings, the animals lungs became burdened with so much particulate matter that some investigators hypothesized that the lung tumors were not caused by the organic material associated with the particles, but rather they were because of the particles themselves, causing tumors by mechanisms related to chronic irritation, cell proliferation, and localized cell killing (81).

Studies were carried out by the Lovelace Inhalation Toxicology Research and Fraunhofer Institutes in the late 1980s to determine if the inhalation of particles without absorbed organic material could cause tumors. In these experiments, animals were exposed to carbon black and titanium dioxide particles that mimicked diesel particles in size distribution, surface...
area, and aerodynamic properties. These studies demonstrated that these particles caused tumors in animals at rates comparable to those observed in the previous diesel-exposure experiments (82). Thus, it can be suggested that the particle loading can help explain the incidence of tumors observed in the mid-1980s from animal cancer tests of diesel exhaust. Previously, similar conclusions have been drawn from instillation experiments with particles of different composition (83,84). Further work is needed to understand the mechanisms of these effects. The surface area of the carbon black particles is much greater than the diesel particles if the surface area of the diesel particles is measured with the organics adsorbed (as they are inhaled). Because the surface area of particles is correlated with the carcinogenicity of particles, then it is possible that in the case of carbon black the tumors are induced primarily by a phenomena associated with the particle surface, whereas the tumor response from inhalation of diesel particles could be a combination of induced mutations by the organics and by the particle surface. It will be difficult to determine if there is a threshold in the dose–response for carcinogenicity associated with exposure to these particles. The significance of these results relative to human risk assessment is uncertain, but the results indicate that efforts to reduce both particle emissions and emissions of genotoxic substances could be of importance as risk-reducing measures.

These studies and others have shown that animal studies have been very useful for identifying hazards from toxic materials (85). The identification of a health effect, such as cancer in animals, provides a warning that the agent tested has the potential for causing a similar effect in humans. However, caution must be used in deriving numerical risk factors from animal data for predicting the incidence of health effects in humans.

Animal bioassays intended to explore human health effects expected to occur after chronic exposures, or at late ages, must include observations of the animals for their life span. In some cases, the typical ending of the observation time (such as at 2 years for the rats) may truncate the development of effects and the significance of late-occurring effects may not be appreciated.

In the past decade, substantial progress has been made in using physiologically based pharmacokinetic models to understand exposure-dose relationships for a number of chemicals in laboratory animals and their extrapolation to humans. There still remain many questions concerning the extrapolation of risk from the animal to the human case. This is especially true for noncancer effects. Understandingly, the mechanisms by which the health effect is produced is a key to these extrapolations. Research is progressively revealing the individual events or steps leading to the expression of the disease.

A major issue is the high degree of uncertainty associated with such extrapolations. The composite level of uncertainty is the result of accumulated uncertainties in many variables including the exposure conditions (exposure route, tissue dose, etc.), extrapolation from high to low dose, repair mechanisms, synergism, antagonism, and others.

**Individual Susceptibility**

Although many individuals come in contact with environmental pollutants, only a limited number of these exposures result in a pathophysiological response. In assessing the risk from exposure to urban air pollution in various parts of the world, it is important to consider if any particular groups may be more susceptible than others. Air quality standards often are related to high-risk groups, such as children, elderly, people with pulmonary diseases or allergies, etc. These groups might require lower limits. Significant biological variability has been demonstrated in the airway response to a number of environmental exposures (86). The difference in disease response may be a function of genetic factors and exposure levels.

For each category of pollutants, the acute and chronic health effects under various exposure conditions should be investigated. For all these effects, it is important to consider what groups might be the most susceptible or the most exposed. In addition to genetic differences, dietary differences, preexisting disease, age, gender, life style or exposure to other pollutants may affect the susceptibility to particular environmental pollutants. Pulmonary conditions (e.g., infections, asthma, chronic bronchitis) may affect susceptibility in some instances.

Several studies have indicated that there may be an inherited susceptibility to certain types of cancer. Genetic differences among individuals may potentially affect their susceptibility to the carcinogenic effects of inhaled chemical toxicants. A few studies have pointed to an association between certain metabolic phenotypes and risk for lung cancer or bladder cancer. These variations include the activities of enzymes involved in the metabolism of environmental genotoxins (e.g., members of the cytochrome P450 family of enzymes and glutathione transferase) in repair of DNA lesions. In addition, dietary factors as well as factors present in air pollution can influence the expression of these enzymes. The level of activity of these enzymes will influence the effective target dose. A genetic polymorphism could serve as marker(s) for increased susceptibility without necessarily being directly involved in the carcinogenic process. A number of other biological processes (e.g., increased cell turnover because of inflammatory responses and changes in immune system function) also may influence the carcinogenic process.

Clinical and epidemiological studies have demonstrated considerable individual variation in the response to acute exposures to ozone as measured by pulmonary function decrements, increases in airway resistance, indicators of an inflammatory response, and other end points like respiratory and nonrespiratory symptoms.

It is important to clarify the interrelationships among the short-term responses that have been observed, their health significance, and their potential relevance to the occurrence of chronic damage after long-term exposure.

**Molecular Biology Techniques**

Since the first report by the Urban Air Committee 10 years ago (3), more mechanistic information has been obtained regarding the molecular basis for cancer induction. In particular, the discovery, characterization and possible role of protooncogenes and tumor suppressor genes has provided a critical underpinning for the mutational basis of cancer induction. The recognition of the important role that mutations in these critical genes may play in tumorigenesis has provided a renewed confidence in the validity and utility of mutational analysis.

The development of the PCR and DNA sequencing techniques now permits the molecular analysis of mutations induced in bacterial as well as eukaryotic systems (75). It is feasible to sequence mutations induced by single components, chemical fractions, and unfractonated urban air samples. Particular mutational mechanisms are being identified that may have general application to eukaryotic organisms, including humans. With regard to analysis of mutations in humans, such work presently is possible only in a limited way. Because of the difficulties of distinguishing
the control or background mutations from those that might be induced by environmental pollution, there remain many technical problems to be solved before such analyses in humans can be considered routine. The major emphasis on human studies should be to examine relevant genes, such as oncogenes and tumor suppressor genes.

Since the identification of highly mutagenic PAH derivatives (e.g., nitro-PAH) in particle extracts, numerous studies have been undertaken to understand the in vivo metabolism and potential genotoxic effects of these species. At this time, the chemistry of metabolite formation, the circulation of these metabolites, and the binding of these metabolites to proteins and DNA have been characterized (87,88). It will be more difficult to assess the ultimate health-effects consequence of these chemical processes.

There are a variety of ways in which molecular techniques can be applied to the health effects studies of urban air (89). Integration of laboratory techniques with epidemiological research strategies is important in order to perform cancer risk assessment of exposure to complex mixtures. An additional goal of the application of molecular techniques to urban air health effects would be the possible prediction of health effects for people at risk from exposure to certain pollutants. A holistic view of urban air pollution would encompass the use of molecular techniques to analyze mutational damage induced by urban air samples in particular environments. Such analyses could determine whether there were excess DNA adducts and mutations in such organisms as compared to those in other, more pristine, environments (89). The use of biomarkers for nongenetic endpoints is in its infancy and requires extensive new research.

**Recommendations**

In the last decade, more information on the carcinogenic process has evolved. New sensitive analytical methods to assess exposure combined with new information about carcinogenic potency have increased the potential for assessment of the health risk associated with exposure to urban air components. There are still a number of areas in which more research is needed: a) Take advantage of opportunities for international collaboration in epidemiological studies, particularly to investigate areas with heavy exposures such as Cairo, Mexico City, Beijing, and Eastern Europe. b) Undertake multinational research studies, covering different ethnic groups, to determine the association between genetic polymorphism in genes that govern the activation and deactivation of toxicants. c) Coordinate an international effort to collect and store selected tissue samples (e.g., blood, surgical, or autopsy tissues) from humans and possibly animals living in polluted environments. d) Undertake a concerted effort to collect and store selected air samples from heavily polluted areas for use in future chemical and biological assays. e) Collect and validate additional complex mixture standard reference materials as needed for environmental tobacco smoke, ambient air particles from highly polluted urban areas, and coke-oven emissions. f) Determine the heritable genetic risk factors that may modify the disease process and, hence, identify individuals with an increased risk of developing adverse health effects following exposure to environmental pollutants. g) Undertake studies to help understand the question of health risks associated with exposure to morphologically different particles and fibers. h) Investigate the sensitivity of individuals in various groups to adverse effects of ozone and nitrogen dioxide, including people with asthma, allergies, and chronic respiratory diseases, and in other groups that are suggested by mechanistic studies. i) Encourage the development and use of new genotoxicity bioassays for in vitro assessment of the biological activity of urban air samples. End points of particular concern would be genetic recombination and other genomic rearrangements that may give rise to changes in gene expression. j) Undertake molecular analysis of mutations induced in Salmonella and in eukaryotic organisms. k) Undertake limited work to better understand the potential genotoxic effects of the semivolatile and the gaseous phase of urban air. l) Use molecular studies to help discern the biological effect of environmental pollutants involved in cancer induction, other than mutations.

**Risk Quantification**

Risk assessments may be divided into qualitative and quantitative approaches (68). IARC has assessed a number of air pollutants in terms of their carcinogenic properties (qualitative risk) to humans. In these assessments, the results of a large number of scientific studies are evaluated concerning the relevance for human cancer. Some individual compounds and complex mixtures formed from combustion products have been classified as carcinogenic (group 1), probably carcinogenic (group 2A) or possibly carcinogenic (group 2B) to humans. Examples are benzene and soot (group 1); PAHs and diesel engine exhaust (group 2A); and nitro-PAHs, PAHs, gasoline and heavy residual oils (group 2B) (Table 3).

It is difficult at this time to use studies of metabolic mechanisms of carcinogenesis in risk assessments. From this point of view, it
Table 4. Risk estimate for the annual incidence of cancer cases associated with air pollution (cases/year/million people).

| Ambient air pollutant | United States | Sweden |
|-----------------------|---------------|--------|
| Particle phase        |               |        |
| POM, PAH (as B[a]P)   | 1.0           | 11.6   |
| POM (rad-equivalent), all cancers | — | 34.9 |
| Gas phase             |               |        |
| 1,3-Butadiene         | 0.9–1.0       | 5.8    |
| Benzene, leukemia     | 0.4–0.6       | 0.6    |
| All cancers           | 0.4–0.6       | 1.2    |
| Formaldehyde, all cancers | 0.1–0.2 | 2.9 |
| Acetaldehyde          | <0.1          | <0.1   |
| Ethylene, all cancers | —             | 3.5    |
| Gasoline              | 0.07–0.3      | —      |

Abbreviations: POM, polycyclic organic material; PAH, polycyclic aromatic hydrocarbons. * Data from U.S. EPA (7). † Data from Törnqvist and Ehrenberg (101); based on present average Swedish exposure levels according to Boström et al. (98).

may be noted, however, that IARC, evaluating each compound from its data, puts ethene in group 3 (not classifiable), although it is known to be metabolized to, and give rise to an in vivo dose of ethylene oxide (present in group 2A) (90). There is a need to develop short-term tests that assess genetic toxicity, cell proliferation, aberrant intercellular communication, receptor mediator effects (such as are recognized for dioxins), and changes in gene transcription.

Table 4 presents risk estimates from several studies expressed in terms of annual incidence of cancer in the United States because of exposure to several air toxics. These are upper bound estimates because they are based on the upper 95% confidence interval of the animal responses extrapolated to humans. In addition, these calculations assume that everyone in the representative countries are exposed continuously to the highest urban air pollution levels for 24 hr/day. As emphasized at the meeting, there are large uncertainties associated with such risk estimates. A discussion of uncertainties is summarized in this report and several of the accompanying papers. The estimated levels of lung cancer would be higher in areas with high levels of air pollution such as Shenyang province in China and several areas in Eastern Europe. There are a number of problems with quantitative calculations of cancer risks. One problem is that these substances cannot be tested on humans. Other problems are that it takes 20 to 30 years to develop a cancer, and after such a long time, there are a great variety of complications to determine the dose of the agent. In addition, there are a number of confounding factors that influence the cancer risk such as lifestyle (including smoking, alcohol, and food habits), age when exposed, duration of exposure, complex exposures when a number of different pollutants could be involved, involvement of drugs and drug abuse, and virus diseases.

The EPA’s 1986 cancer risk guidelines were based on the fact that the mechanisms of carcinogenesis were largely unknown. Research during the past few years to elucidate the molecular biology of cancer has resulted in new findings at an explosive pace. These scientific studies and the resulting data base will continue to change very rapidly. As a result, currently established approaches to risk assessment will have to be very flexible. Such approaches are being adopted by regulatory agencies in the United States (91).

Biomarkers

Increasing attention is being paid to the use of biomarkers for determining the integrated exposure of humans to toxics (68,92,90). Biomarkers include the nonreacted toxic substance, their metabolites, or the reaction products of these toxics with naturally occurring substances in the body. Examples of such biomarkers include DNA or protein adducts, carboxyhemoglobin, and DNA oxidation products. Chromosomal aberrations and in vivo mutations also may serve as biomarkers. Macromolecular adducts are usually a much more sensitive end point than cytogenetic changes (93). Blood can be an ideal medium for the measurement of biomarkers because it is relatively easy to obtain, and measurement of serum-blood protein adducts provides an integrated value for about 120 days of exposure in humans. Identification of biomarkers such as carcinogen-macromolecule adducts, also may be useful for identifying sources of exposures (94) as needed for risk identification (90). In addition, these methods could be used for validation of exposure and exposure-response models.

Significant progress has been made in the measurement of biomarkers during the past several years. Much of this progress has been because of the development of advanced mass spectrometric techniques (95). Quantification of chemically altered DNA in individuals has been a challenge because of problems such as low-adduct levels; efficient repair of the damage, dilution of adduct levels by cell division, and other factors. Stimulated by suggestions from Ehrenberg and his group (84,90,96), many scientists have focused attention on protein adducts with the assumption that levels of carcinogen-protein adducts will reflect levels of carcinogen-DNA adducts. For example, the electrophilic intermediates that react with nucleophilic sites on DNA also will react with nucleophilic sites on other molecules such as serum albumin or hemoglobin (97).

P-postlabeling methods have been developed that can be applied to a wide range of aromatic DNA adducts (98). The high sensitivity (one adduct in 10⁷–10⁹ nucleotides), wide applicability of the assay, and the fact that small amounts of DNA are required make this assay suitable for the study of DNA adducts in human tissue. Such studies are helping to unravel carcinogenic damage to the human genome. However, it is not always a quantitative technique for recovering DNA adducts. More sensitive analytical methods are needed to confirm that the spots detected on the chromatograms are DNA adducts.

DNA-protein crosslinks induced by formaldehyde exposure in rats and monkeys have been identified (99). It was found that the concentration of DNA-protein crosslinks for a given exposure concentration was higher in rats than in monkeys. An empirical model demonstrated that the concentrations of DNA-protein crosslinks in monkeys could be predicted from the data on rat DNA-protein crosslinks by adjusting for species differences in volume and quantity of exposed tissue. This provided increased confidence in the use of these data for extrapolation to the human situation.

Further research is needed to understand the importance of specific DNA or protein adducts in terms of mutations. Also, the degree of binding is an important issue that is of critical importance in dealing with individual substances. In some short-
term assays, a quantitative relationship has been established between levels of specific DNA adducts and mutagenic frequency. Biomarkers would be a very good tool in the field of epidemiology with a defined protocol. Therefore research is needed to clarify further the basic understanding of DNA and protein adducts in relation to dose as well as health risks. This is especially the case when exposure is of a complex nature. The levels of protein adducts (which are not repaired) give more unequivocal measure of dose than the direct measurement of DNA adduct levels, which are subjected to repair at rates that vary between tissues, cells, and DNA regions.

**Multipathway Exposure**

It has become recognized that an accurate assessment of exposure to air pollutants should include both inhalation and non-inhalation pathways of exposure. Exposure through noninhalation pathways results when air pollutants are deposited on soil, crops, and surface waters.

Both primary (direct) and secondary (indirect) pathways may contribute to the total uptake of a pollutant. The paths of exposure are routes by which the person is exposed through direct inhalation, ingestion of dirt and contaminated food products, or dermal absorption. Secondary pathways of exposure are those that result from assimilation of the pollutant into a food source. For example, the dose received for PAH via food is greater than the inhaled dose. Some work has been undertaken to develop a multipathway health-risk assessment model (100) to estimate the potential acute, chronic, and cancer health effects from exposure to air pollutants from stationary sources.

**Relative (Comparative) Potency Methods**

Several major research programs were initiated during the past decade to develop and validate comparative potency methodologies for quantifying risk to selected air toxics. One of these programs, the Integrated Air Cancer Project was initiated in 1985 by the EPA (18) to improve the methodologies and data bases for assessing human exposure to airborne carcinogens.

In Sweden, a rad-equivalence approach was developed to estimate the cancer risk from certain components, particularly the alkenes in ambient air (101).

In the rad-equivalence approach, the risk is assumed to be proportional to the target dose of the carcinogen at a given concentration; the rate of formation of the DNA adducts is proportional to the rate of formation of hemoglobin adducts. This is only valid for certain groups of chemicals because the biologically active metabolites may react differently with hemoglobin and DNA as their nucleophilicity in DNA differ.

In relevant biological systems the genotoxic effectiveness of a compound is compared to the genotoxic effectiveness of gamma-rays or X-rays. In general, the risk estimates have been made on the basis of animal data, but in the absence of such data, an intermediate biological end point like hemoglobin adducts was used (90). The association of risk with a chemical end point increases the sensitivity by several orders of magnitude.

Nevertheless, the rad-equivalence approach has proven to be a useful model in which several of the assumptions have been tested and validated for particular compounds such as ethylene oxide in animal experiments. Moreover, the principles of the rad-equivalence approach should be possible to adopt to any DNA-reactive chemicals.

Table 4 gives the risk estimate for the annual incidence of cancer cases in the United States and Sweden as based upon the unit risk factors and rad-equivalence approaches, respectively. In Table 4, average cancer risks in Sweden have been summarized for a few air pollution components at the person-weighted average concentration determined by Boström et al. (58). These risk estimates were based on the rad-equivalence (for alkenes and, via animal experiments, for benzo[a]pyrene), on epidemiological data, and on results of long-term animal studies (101). Because only a few components were considered, and with regard to the uncertainty of the estimates (by a factor of three), the authors did not try to estimate the total risk.

The risks estimated by Törnqvist and Ehrenberg (101) are some 10 times higher than those obtained by applying the Unit Risk Factor (URF). Some of the causes for the differences between the unit risk factors and the rad-equivalence approach is the hypothetical expectation that the risk is a function of the lifetime accumulated dose rather than of the dose per day, and that the genotoxins will cause cancer in most organs as with ionizing radiation. A reliable risk estimate can't be made without proper integration of data sets for exposed humans and experimental systems at relevant low exposure levels.

**Unit Risk Factors**

The URFs are derived from the analyses presented in the previous section. URFs are estimates of the probability that an individual will develop cancer when exposed to a pollutant at an ambient concentration of $1 \mu g/m^3$ (7). Unit risk assessments have been used as the primary approach of regulatory agencies in the United States to assess and control human exposure to toxic air pollutants.

The most comprehensive use of this approach has been a recent assessment of the potential cancer risk associated with exposure to vehicle emissions in the United States (102). The primary toxic emissions considered in this assessment included benzene, formaldehyde, 1,3-butadiene, acetaldehyde, diesel particles, and gasoline particles. The mass emissions of these toxicants were determined as a function of vehicle technology and fuel composition. These emission factors were used in a model to calculate annual average exposures.

The annual average exposures were then multiplied by the population of interest and the unit risk factor to estimate the cancer incidence in the United States from exposure to vehicle emissions (Table 5) (102).

Table 5 summarizes the estimated cancer incidence in the United States from exposure to vehicle emissions for scenarios in the 1990 to 2010 time periods. For all years, 1,3-butadiene is responsible for the majority of the cancer incidence. The California

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**Table 5. Estimated cancer incidence in the United States from exposure to vehicle emissions (1990 to 2010) (102).**

|          | Cancer cases/year ² |
|----------|---------------------|
| Air toxic|                     |
| 1990     | 1.3-Butadiene       |
| 1995     | 48-385              |
| 2000     | 41-324              |
| 2010     | 47-386              |
| Diesel particles|   |
| 1990     | 109                 |
| 1995     | 66                  |
| 2000     | 27                  |
| 2010     | 38                  |
| Benzene | 41-118              |
| 1990     | 25-72               |
| 1995     | 21-58               |
| 2010     | 19-53               |
| Formaldehyde | 44-133         |
| 2010     | 28-85               |
| 2000     | 21-63               |
| 2010     | 18-67               |
| Acetaldehyde | 53-13.4        |
| 2010     | 3.6-9.1             |
| 2000     | 2.8-7.1             |
| 2010     | 3.0-7.6             |
| Total    | 268.3-333.4         |
|          | 170.6-617.1         |
|          | 124.8-492.1         |
|          | 117-540.6           |

² 95% upper confidence estimates.
Air Resources Board (CARB) estimated that these five toxics can account for more than 99% of the cumulative cancer cases attributable to motor vehicles (103).

It is recognized that there are some limitations inherent in these methods of risk assessment. Caution must be used in deriving numerical risk factors from animal data for predicting the incidence of health effects in humans. The identification of a health effect, such as cancer in animals, provides a warning that the agent tested has the potential for causing a similar effect in humans. The degree of confidence with which the URF can be developed from the animal data is proportional to the degree of confidence one has that the exposure conditions (exposure route, tissue dose, etc.), and the biological response observed in the animal study would be relevant for human exposure conditions. Phenomena occurring in humans and not usually considered in animal studies, such as transplacental and neonatal exposure, should be taken into account.

Understandingly, the mechanisms by which the health effect is produced is a key to these extrapolations. Research is progressively revealing the individual events or steps leading to the expression of disease. However, the complete mechanisms or sequence of steps are not yet known for most of these events at the high doses used in the animal tests. In addition, multiple genetic and epigenetic changes are likely to be involved. As the knowledge of the events is acquired, it should be applied to the interpretation of bioassay results. The value of numerical risk estimates derived from bioassays is increased in proportion to the certainty that the same pathogenetic steps occur in bioassays and humans.

Unit risk estimates result from interactive analyses of health-affecting processes in the human body and observed effects in human populations (epidemiology). The use of unit risk estimates implies knowledge that the dose-risk relationship is linear. Unit risk estimates can only be made from experimental data if there is reasonable certainty that effects in humans could occur by the same mechanisms as those in animals.

Observations of the dose-effect relationship at low-exposure levels could provide data to test the assumption of linearity. Although such relationships have been established over several orders of magnitude in bacterial assays, such experiments have only rarely been conducted in animals.

| Risk ratio | Total cases | Lung cancer | All cancers | Excess cases | Lung cancer | All cancers |
|------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 1.0000     | 567         | 2,766       | 0           | 0           | 1           | 8           |
| 1.0022     | 568         | 3,774       | 1           | 8           | 57          | 377         |
| 1.1000     | 624         | 4,143       | 57          | 377         | 113         | 753         |
| 1.2000     | 680         | 4,519       | 113         | 753         | 284         | 1,883       |
| 1.5000     | 851         | 5,649       | 284         | 1,883       |

Although these methods are not very reliable for estimating absolute risk, they can be used in a relative sense to compare risks among pollutants and scenarios and to assess trends.

**Human Exposure/Rodent Potency Index**

Several approaches to the development of relative risk scales have been proposed recently for comparing possible hazards from several different exposures. Gold et al. (104) has recommended the use of a human exposure/rodent potency index (HERP). It is an index of possible hazard rather than a direct estimate of risk because bioassay results do not provide sufficient information to estimate human risk at low dose. HERP indicates the percentage of the rodent potency (TD$_{50}$, in milligrams per kilogram per day). TD$_{50}$ is the human exposure per kilogram body weight estimated to halve the proportion of tumor-free animals by the end of a standard lifetime. Values of TD$_{50}$ span a 10-million fold range. This may become a useful approach to help regulators and the general public become more aware of the concepts of relative risks.

**Epidemiology**

Good epidemiologic data is a valuable tool in identifying and, in some cases, quantifying a risk. Because epidemiologic studies refer directly to humans, they have two powerful advantages: They entail no interspecies extrapolation, and they do not require extrapolation from the high doses commonly used with experimental animals to the low doses to which people in the general population are likely to be exposed. However, the epidemiologic approach has a number of limitations. The risks for large populations are below the detection limits of present epidemiological methodology (105). Table 6 gives the relationships between risk ratios (RR), cancer incidence, and excess cancer cases (per year for a million people). Risk ratios below about 1.15 are not possible to determine accurately (within 90 to 95% confidence intervals) using current epidemiologic approaches because of several limitations. Such limitations include the difficulty in finding study groups in which two distinct populations can be identified that are similar in nearly all regards but differing with respect to the factor (exposure) to be studied, the limited population of the exposed group, known and unknown confounding factors (e.g. exposure to secondary cigarette smoke), and imprecise estimation of exposures. As discussed earlier, the EPA estimated that there are approximately 2200 excess cancer cases caused by annual exposure to toxic ambient-air pollutants in the United States. These excess cases translate to a risk ratio of 1.0022 (Table 6). Thus, it is not possible to use an epidemiologic approach to determine directly the excess cancer cases that have been estimated to be caused by annual exposure to toxic ambient-air pollutants in the general population.

Hemminki and Pehslagen (105) analyzed data from several reported epidemiology studies and concluded that the relative lung-cancer risk ratio (RR) for people living in urban areas compared to people living in the countryside can be as high as 1.5. Frequently, these risk ratios have been explained by differences in exposure to air pollutants; however, such correlations might have other explanations and cannot represent final conclusive evidence. Therefore, analytic epidemiologic studies (cohort or case-control studies) are required to clarify whether there is an increased risk of developing lung cancers for individuals with an increased exposure to air pollutants (106).

Additional epidemiologic studies are needed on cancer risks between populations living in highly polluted urban areas (e.g., Silesia, Poland) (17) compared to similar groups of people living in adjacent rural areas. Inaccurate exposure data and uncontrolled confounding factors constitute major problems in the interpretation of the epidemiologic evidence on health risks related to ambient air pollution.
Further studies should focus on obtaining more accurate exposure data and better control of confounding factors.

Studies on the exposure of selected occupational groups have shown a causative effect between exposure to toxic air pollutants and lung cancer. Perhaps the most robust of the cohort studies (82) were those of Boffetta et al. (107) and Garshick et al. (108). Boffetta et al. reported a RR for lung cancer among diesel exhaust exposed subjects of 1.6 for railroad workers, 2.6 for heavy equipment operators, and 2.7 for miners who worked in mines where diesel equipment was operated. Garshick et al. conducted a retrospective study of U.S. railroad workers by inferring exposure from job title, assuming that workers with the greatest diesel emissions exposure were the youngest at the time railroads were converted to diesel engines, and judging that smoking prevalence was the same among workers in relatively exposed and unexposed jobs. They calculated a RR for lung cancer of 1.5 for the group that was youngest at the time of diesel conversion and lower RR values for groups older at that time.

A number of risk assessment studies have been initiated for selected populations living in developing countries. One such group is that of Chinese women who have high levels of exposure to air pollutants emitted from unvented coal-fueled stoves. A significant increased risk of lung cancer (RR of 2.5) was observed for this group (106). Current studies on this group are needed including exposure and biomarker measurements and the incidence of other adverse health effects.

Several epidemiological studies have indicated that interactions of complex mixtures do occur (109). In general, it appears that the mechanism varies from purely additive through purely multiplicative. Because of the small size of the sample population groups it has not been possible to obtain a good quantitative model of interactions. However, it appears that when a mixture contains key carcinogens that fall within the same chemical class, then the carcinogenicity could be equivalent to the sum of the effects of the individual classes.

The epidemiological connection between smoking and certain types of lung cancer has been well established (110). Smoking is estimated to account for about 294,000 cancer cases per year in the United States. However, even though about 50 carcinogenic chemicals have been identified in cigarette smoke, it has been difficult to establish a quantitative link between the exposure of these individual compounds and cancer. Workers in foundries are exposed to high levels of air pollutants. A lung-cancer risk estimate of 1.5 to 1.7 has been determined from a number of studies (111). However, because these workers are exposed to many different sources of emissions, it is probably not possible to identify the specific components responsible for this increased risk.

Current human exposure to air pollutants, especially in certain urban areas with high air pollution levels, can give rise to an increased cancer risk in the coming decades. Therefore, if human and environmental samples could be collected and archived, such samples would be of great value for future epidemiologic studies.

Recommendations

Interdisciplinary collaboration involving both epidemiology, experimental, and human clinical toxicology, and including accurate and meaningful exposure assessments is required to understand human health risks from airborne agents. This collaboration should occur on an international basis, and its efforts should focus on the following: a) Develop a comprehensive computer-based risk assessment model that can readily incorporate new scientific findings as they are discovered. b) Expand efforts to understand the best approach for identifying hazards and estimating risk for combined exposures as these are more representative for the actual exposure. c) Consider tumor locations other than the lung in epidemiologic studies. d) Develop short-term tests that assess genetic toxicity, cell proliferation, aberrant intercellular communication, receptor mediator effects (such as are recognized for dioxins), and changes in gene transcription. e) Effect of reducing the existing uncertainties in the risk assessment methods. f) Identify specific biomarkers of environmental exposure that give an accurate assessment of dose. g) Develop rapid, inexpensive, and more sensitive analytical methods for the analysis of biomarkers in blood or urine. h) Develop DNA-adduct analyses techniques to detect and quantify the target dose of specific exposures. i) Elucidate the nature of the association of DNA adducts with exposure and mutations in order for this assay to be used as a specific marker. j) Obtain a better understanding for DNA adduct formation kinetics and repair mechanisms as necessary for the identification of adduct hot spots. k) Clarify the kinetics of DNA repair in terms of permitting the calculation of dose from steady-state DNA adduct levels. l) Focus epidemiological studies on highly polluted areas such as Cairo, Mexico City, Beijing, and heavily industrialized areas in Eastern Europe. m) Determine the degree of binding; individual adducts versus the total amount of adducts in terms of dose and risk, respectively; and the analytical problems with adduct analyses after complex exposures.

Conclusions

Regulatory agencies rely heavily on quantitative assessments of environmental health risks as the scientific basis for decisions about how best to protect public health. Significant scientific advances have been made during the past decade to improve the accuracy of the risk assessment process. Such advances have been made in the identification of potentially toxic compounds in emission sources and ambient air, atmospheric transport and chemistry, and exposure quantification. By providing the methods to make biological measurements of changes in genes, cells, and physiologic processes, the revolution in molecular biology has paved the way to measure environmental exposures more accurately and precisely, to define better associated health effects, and to improve the determination of susceptibility to pollutant exposures.

Although great progress has been made, the workshop participants concluded that there are still significant deficiencies in the data bases used in risk assessments as well as the risk assessment approach itself. Aside from the previously noted problems of inadequate emission inventories, the difficulty of accurately assessing and quantifying exposure, and determining the resulting health endpoint from that exposure, several other areas have been identified where technical improvements are needed.

There are numerous steps associated with the development of quantitative unit risk factors as summarized in the various sections of this paper and illustrated by Figure 4. Because our knowledge base for each of these steps is incomplete, there is a high level of uncertainty associated with developing an absolute quantitative value for a health risk. Additional efforts will be needed to reduce the uncertainties in each step of the risk assessment process as an important part of carrying out the research recommendations presented in this report. In the future, any quantitative expressions of risk that are reported in the scientific and popular literature should include an assessment of uncertainty levels.

The most effective approach to improving the technical basis for risk assessment is...
through expanded international collaborative research and development efforts. In this regard, increased collaborative efforts are needed between industry and government organizations. Such efforts should include the development of low-cost and effective emissions control strategies. Other areas of potential cooperation include technology transfer, development of reference materials for chemical and biological assays, and quality assurance techniques to ensure that laboratories around the world produce comparable results. Epidemiological studies from different parts of the world should be combined if feasible to clearly establish the role of urban air pollution on the health and well-being of people.

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