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Protecting Human Health from Air Pollution: Shifting from a Single-Pollutant to a Multi-pollutant Approach

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Abstract

To date, the assessment of public health consequences of air pollution has largely focused on a single-pollutant approach aimed at estimating the increased risk of adverse health outcomes associated with the exposure to a single air pollutant, adjusted for the exposure to other air pollutants. However, air masses always contain many pollutants in differing amounts, depending on the types of emission sources and atmospheric conditions. Because humans are simultaneously exposed to a complex mixture of air pollutants, many organizations have encouraged moving towards "a multi-pollutant approach to air quality." While there is general agreement that multi-pollutant approaches are desirable, the challenges of implementing them are vast.

In this commentary, we discuss a multi-pollutant approach for controlling ambient air pollution that describes multi-pollutant concepts for different aspects of air quality management and science: (1) scientific estimation of the health risk of multiple pollutants; (2) setting of regulatory standards for multiple pollutants; and (3) simultaneously implementing compliance with regulatory standards for multiple pollutants.

Air pollution policies worldwide are typically geared toward control of a single pollutant. In the last few decades, most epidemiologic studies of air pollution and health have focused on estimating the adverse effects associated with ambient exposure to a single pollutant, adjusted for exposure to other pollutants and potential confounders. However, the human body is actually exposed to multiple air pollutants at once, in a complex mixture.

The rationale for the historical focus on single-pollutant research compared with multi-pollutant research is clear: single-pollutant research is easier to conduct; the results are more clearly interpretable; and the vast majority of air quality policies to protect human health are based on single-pollutant strategies. In fact, under the Clean Air Act, the U.S. Environmental Protection Agency (EPA) has the responsibility for setting a separate air quality standard for each criteria pollutant. For example, the scientific literature provides evidence on how carbon monoxide (CO) affects various human health endpoints, the EPA sets a numerical standard for CO intended to protect human health with an adequate margin of safety, and other agencies such as a state governments may develop and implement emissions-control strategies to achieve those standards. This approach does not account for the health responses associated with the simultaneous exposure of multiple pollutants.

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The scientific community and the U.S. EPA are moving toward a multi-pollutant approach to quantify the health consequences of air pollution mixtures as a whole, while recognizing that such a paradigm shift will be challenging.[1-5] In 2004, two reports of the U.S. National Research Council recommended the development of a multi-pollutant approach to air quality control. These reports questioned whether the current focus on single-pollutant science, and on separate National Ambient Air Quality Standards for each of the six criteria pollutants, truly addresses the health burden experienced by the population.[3,4] The move toward a "one-atmosphere" approach has been in progress for some time, as evidenced by the EPA's development of the Community Multiscale Air Quality regional air-quality modeling system[6] that simultaneously estimates levels of multiple air pollutants, including ozone and particulate matter (PM).

There are many elements that support a multi-pollutant approach. For example, this approach could: (1) characterize more fully the complexity of the exposure and their health impacts (e.g. humans breathe ozone, PM, and other pollutants simultaneously); (2) identify the most harmful pollution emission sources (e.g., industrial smokestack or automobiles), thus allowing more targeted regulation; and (3) aid effective management of air quality (e.g. reduced hydrocarbon emissions from mobile sources, which would affect levels of PM, ozone and air toxics). However, a multi-pollutant approach to air quality presents many challenges.

In this commentary we discuss the following multi-pollutant concepts: (1) the estimation of how exposure to multiple pollutants simultaneously affects the risk of adverse health response; (2) the design of policies aimed at controlling air quality of multiple pollutants simultaneously; and (3) the design of compliance strategies for multiple pollutants.

A MULTI-POLLUTANT APPROACH TO AIR QUALITY

Multi-pollutant Approach to Estimation of Health Risk

Many studies from a variety of disciplines (including epidemiology, human exposure assessment, and toxicology) have been conducted to characterize the human health response to air pollution. However, most of these studies report the health effect of one pollutant adjusted for the exposure to other pollutants and confounders (e.g., [7,8]). In this paper, we define a "multi-pollutant approach to estimation of health risk" as an investigation that focuses on estimating the total health effect associated with the exposure to multiple pollutants. This total health effect requires acknowledgement that the health burden from simultaneous exposure to multiple pollutants may differ from the sum of individual effects estimated from single pollutant models. As an example, synergistic effects have been reported for the simultaneous exposures of cigarette smoking and asbestos.[9,10]

A variety of approaches can be applied to estimate total health effect from multiple pollutants. A first approach is the use of statistical regression models having as predictors a main effect for each pollutant (adjusted for exposure to the other pollutants) and an interaction term for each pair of pollutants ("the statistical interaction approach"). From the fitted values of the regression model, we can estimate total effect and the associated statistical uncertainty. Similar statistical models can be defined to account for higher-order interactions and therefore to capture the health burden associated with the simultaneous exposure to more than two pollutants. A note of caution: the results of any regression model become highly unstable when incorporating two or more pollutants that are highly correlated (e.g. PM_{10} and nitrogen dioxide [NO_2] both indicators of urban pollution). In this case, the regression model cannot reliably estimate the main effects of these two pollutants nor their interaction. Ideally, knowledge about the biological mechanisms of how air pollution adversely affects health could be incorporated in the development of the statistical model, as several pollutants might lead to the same biologic mechanism of injury.

Statistical regression models with interaction terms for estimating total effect of multiple exposures have started to appear in the literature. In animal studies of environmental exposures, approaches to interaction terms include the use of multiple combinations of exposures. For example, one study used four groups of exposures to estimate the total effect on pulmonary function associated with simultaneous exposure to ozone and nanoparticles.[11]

Current statistical methods are inadequate for addressing the health risks of multiple pollutants and estimating high order interactions. Dimension reduction of some form is needed to reduce the data to a set of key predictors and to remove predictors that do not have explanatory power. Regression shrinkage and penalization methods such as the lasso[12] and its numerous variants attempt to identify a small subset of individual predictors that are highly associated with the response. Penalization methods in general have the advantage that the estimated regression coefficients are directly interpretable and the response variable is used in the estimation procedure, unlike with standard dimension reduction methods such as principal components or factor analysis. Bayesian analogues, such as stochastic search variable selection,[13] have similar estimation and model selection properties. The estimation of interactions between pollutants is of particular scientific interest;[14] however, incorporating interaction effects into any regression model results in an explosion of parameters that need to be estimated. Current methods such as the lasso, SSVS (statistical search variable selection), and related methods handle large numbers of parameters by removing spurious predictors in the model, or by grouping highly correlated predictors.[15,16] A challenge requiring methodologic development is that current methods treat all predictors symmetrically and do not take advantage of the hierarchical nature of the air pollution mixture as a whole. Air pollution can be divided into groups of constituents (e.g. based on sources or chemical properties) that can be further divided into their constituents. Current methods for high-dimensional regression analysis approach the problem in an “unsupervised” manner, grouping correlated predictors without incorporating prior scientific information.

Statistical methods for clustering components of an air pollution mixture based on their biologic mechanism, emission sources, or ability of predict the outcome can be borrowed from other disciplines. New statistical methods have been developed in genomics to handle large amounts of data. Logic regression has been proposed to explore interactions in high-dimensional genomic data.[17] There have also been relevant developments in survival regression analyses with a large number of correlated covariates[18] and methods for supervised clustering of genes (see for example [19,20]).

A second approach for estimating the total health effect of multiple exposures is to use the ambient levels of one pollutant to represent the combined exposure to several pollutants or to an emission source (“the indicator approach”). For instance, selenium $PM_{2.5}$ has been used as an indicator of the overall coal combustion mixture.[21] Other examples include sulfate as a marker of regional pollution[22] and $PM_{2.5}$ filter absorbance as a marker for diesel particles.[23]

A third approach is to define the exposure to one or more emission sources through source identification methods, including factor analysis and source apportionment techniques. For example, one can assign PM chemical constituent data to emission sources by using statistical methods for data reduction, such as principal component analysis, factor analysis, and hierarchical clustering.[24,25] Specifically a Bayesian structural equation model was developed that jointly specifies an exposure model, (using a factor analysis to assign PM chemical constituents to emission sources, e.g. source profiles) and a health-effect model (estimating the association between health outcomes and the source profiles).[26] These statistical methods for data reduction summarize the levels of many pollutants to define emission profiles (e.g., crustal, oil combustion, traffic, vegetative burning) (see for example [27-32]).

Regardless of the approach, there are additional challenges in estimating the health effects of multiple exposures.

Inadequate data—Different air pollutants are measured with varying frequency and with different measurements by season. For example, ozone is typically measured daily and PM is measured every 6 days. Ozone is often measured during the warm season only, whereas PM is measured throughout the year. Therefore a study of these pollutants in combination would have a much smaller dataset available than a study of either pollutant alone. Another example of inadequate data is mercury exposure from industrial sources (primarily through coal and oil combustion). Such exposure is not routinely measured in its airborne form, although efforts are underway to establish comprehensive mercury monitoring networks.[33]

Better methods for collecting and processing exposure data include land-use regression modeling, satellite imagery, air quality modeling, kriging and other spatial interpolation methods, and human exposure modeling.[7,34-38] These methods can generate estimates of pollution levels in locations and time periods where monitoring data are not available; however, as these are estimated values, they introduce their own uncertainties and limitations. Methods such as kriging and inverse-distance weighting are constrained by the data and location of the existing monitoring network. Air-quality modeling produces more accurate estimates for some pollutants than for others. Researchers often face a tradeoff between the certainty of data and the statistical power of a larger dataset.

Data Analysis—Studies of air pollution and health address a growing number of pollutants, particularly in the chemical components of PM. Many pollutants have similar emission sources or formation pathways, or are precursors to other pollutants. Estimation of the total effect of multiple exposures is challenged by these interconnections among individual pollutants. For example, nickel and vanadium PM levels can be highly correlated, as both often result from oil combustion. The effect estimate for an association between a health outcome and nickel could represent the effect of vanadium, or the effect of other products of oil combustion. In such cases, researchers may apply the indicator approach described above using the levels of a single pollutant, such as nickel, to represent the overall source mixture. However, as the pollutants have multiple sources, this technique does not provide a unique identifier for a source. Another complexity of data analysis is that some pollutants are in the formation pathway of others. For instance, volatile organic compounds are precursors to tropospheric ozone, and nitrogen oxides (NO_x) are precursors to ozone as well as secondary particles.

Statistical approaches to a large set of correlated exposure variables include dimension reduction techniques aimed at transforming several correlated exposure variables into a smaller set of almost independent key predictors. Dimension reduction techniques have been used to conduct multi-pollutant studies of air pollution and health. These include the source apportionment methods described (e.g., factor analysis to identify mobile combustion and soil particles[32]). Dimension reduction methods are attractive from a regulatory standpoint because they help to identify specific targets of regulatory intervention. However, these approaches also have limitations. The focus on just a few sources might omit other important (but perhaps more-difficult-to-measure or less-understood) sources. In addition, some source-related approaches require information that may be poor quality or not available at all. For example, comparison of factor analysis results generated by different research teams on the same dataset found similar conclusions but with specific differences such as how to disentangle diesel from gasoline vehicle pollution.[29] It is also difficult to generalize results from source-based analyses to other areas because of the location-specific nature of most source signals. Further, source-based approaches have the general limitation that they substitute one complex mixture (the air) with another complex mixture (the source). The scientific questions involving sources and pollutants can also be somewhat circular. When a given pollutant is associated with adverse health outcomes, the next scientific question may be whether that pollutant is acting as a marker for a particular source; however, if a given source is identified, the next scientific question may be what pollutant or set of pollutants in that source make it harmful.

Exposure assessment—Strategies to improve exposure measurement may work better for some pollutants than for others. While statistical models can account for measurement uncertainty to some degree, the uncertainty may not be fully known or quantified, and will vary by pollutant. Different monitoring networks provide varying quality of estimates based on the number of monitors available, the position of monitors (e.g., distributed more evenly across a county or clustered), the nature of the monitor location (e.g., near major roadway versus background monitor), and potentially different frequency of measurement.

Broad classes of measurement error include: (1) instrument measurement error; (2) detection limits; (3) exposure measurement error relating to the discrepancies between ambient monitor values and personal exposure; and (4) spatial misalignment when the exposure area (e.g., county) and the exposure estimates (e.g., a small number of monitors within a county) are not spatially matched. Instrument measurement error can produce monitor values that are either higher or lower than the true value. For example, one study found sulfate $PM_{2.5}$ levels to be under estimated by 30 to 40%.[39] The quality and consistency of measurement methodologies can differ by pollutant providing, for example, less certain and comparable estimates for organic carbon matter PM than for many other pollutants. Levels of some pollutants may be below current detection limits, and such data are often addressed by substituting a zero or other fixed value, thereby obscuring variation in pollutant concentrations at low levels. The relation between ambient monitor values and personal exposure varies by indoor-outdoor activity patterns, the person, and the pollutant.[40] Personal monitors have been used to estimate air pollution in some studies,[41] and yet the use of personal monitors to estimate exposure can be cost-prohibitive and impractical for large or long-term studies.

The spatial misalignment between the exposed populations and the monitor sites can obscure within-community variability in pollution concentrations and can create a type of measurement error that has been largely ignored. Without proper adjustment, the health-effect risk estimates of the different pollutants can be biased. Recent work has described various approaches for addressing this problem and has introduced statistical approaches for estimating health risks with multivariate adjustment for the spatial variation of the pollutants.[42,43] The degree of spatial misalignment will differ by pollutant, as some pollutants are more homogenous across large areas than others, and will also differ by spatial area. Even if a standard protocol of a given spatial unit (e.g., county-level resolution) is applied, spatial misalignment may vary by area. For example, some counties in the U.S. are considerably larger than others, creating a higher probability of exposure error depending on the monitor coverage. For example, San Bernardino County, California is over 1500 times larger in land area than Kalawao County, Hawaii.[44]

While issues of exposure error are relevant to health studies of a single pollutant, such errors take on a larger role in multi-pollutant studies. Each type of measurement error can affect the exposure estimates for various pollutants differently. A multi-pollutant study often has better exposure estimates for some pollutants than for others, and the true nature of the exposure error for each pollutant may be poorly understood. This can complicate the estimation of the health burden of an air pollution mixture.

The special case of particulate matter—Multi-pollutant research has already been widely conducted with respect to particulate matter. Most studies of PM and health have based exposure on total mass of a particular size distribution (e.g., PM_{10}, $PM_{2.5}$). Studies on PM size distribution (e.g., [45,46]) have been a step towards identifying the part of the PM mixture that is more harmful to human health. As total suspended particles (TSP), PM_{10}, and $PM_{2.5}$ represent somewhat different sources, with crustal materials falling generally in the larger range and combustion particles falling in the smaller range (<2.5 μm). However, even within each size range, particulate matter is inherently a multi-pollutant, with a varying mixture of chemical components. The PM chemical composition varies greatly across the U.S. and by season, and chemical composition may affect toxicity.[46-49]

While research on PM total mass does study a complex mixture, current research has made substantial progress in studying health effects of PM in a multi-pollutant context by examining which PM sources or chemical components are more strongly associated with human health. High-priority questions on PM and human health have shifted from the health effects of total mass to the sources and attributes of PM (e.g., size fraction, chemical components, etc.) primarily responsible for various health outcomes. Multi-pollutant epidemiologic studies of PM chemical components can be conducted on local and national scales now that daily concentration data are available through EPA monitoring of pollutants at a large number of U.S. locations.[47,50-52] This represents an opportunity for multi-city research of PM chemical components that was not previously feasible.

Multi-pollutant Approach to Regulation

Air quality standards are based mostly on a summary of the scientific evidence on the health impact of each pollutant separately, with input from a scientific advisory committee and public comment. For example, the National Ambient Air Quality Standards are established for the six criteria pollutants separately, and PM is considered as a single pollutant based on total mass and size distribution without consideration of its chemical form. While regulators are fully aware that the ambient levels of the criteria pollutants are related (e.g., NO_2 is a precursor to ozone, while both are criteria pollutants) and that air pollution is a complex mixture, each standard is designed to reduce harm to human health for that individual pollutant, regardless of the levels of other pollutants.

The ability of decision-makers to establish multi-pollutant policies is currently limited by the availability of multi-pollutant science on how air pollution mixtures affect health. However, as the scientific community embraces a multi-pollutant framework and provides epidemiologic evidence on air pollution mixtures, multi-pollutant air quality standards will become possible. Some examples are described below to illustrate how a multi-pollutant framework could be applied to air quality regulation.

Setting standards for combinations of air pollution levels—If the total health effects of multiple exposures (and their statistical uncertainty) could be reliably estimated, then air standards could be based on levels of multiple pollutants. For example, if strong evidence were found that the risk of the adverse effects of $PM_{2.5}$ is higher on days with ozone levels higher than a certain level, then, in principle, it would be possible to define a standard for $PM_{2.5}$ that would take into account the levels of ozone.

The U.S. EPA Air Quality Index provides a single score for air quality by converting air pollution levels for five pollutants to an overall quality scale of 0 to 500 (0 representing the best air quality and 500 the worst).[53] The EPA has assigned a general health condition to the index level. For example, an Air Quality Index of 0 to 50 represents “healthy” air quality. Air Quality Index levels of 101 to 150 represent air quality levels that may be “hazardous” for sensitive individuals. An individual air quality index is calculated for every pollutant, and an overall Air Quality Index is based on the highest index for any single pollutant. While this index is not an air quality regulation, it provides an example of how multiple pollutants could be considered together to set a health-based standard.

Setting standards for emission sources—If a specific source is identified as particularly harmful to human health, the development of regulations could target the emissions from that source (e.g., by capping total emissions from a specific industry). This strategy would cover all primary and secondary pollutants from that source. For example, if oil combustion-related particles were identified to be more toxic than crustal-related particles, then a regulation could target the levels of the $PM_{2.5}$ chemical components corresponding to and identified source rather than target the $PM_{2.5}$ total mass. Examples include *Mexico’ s Hoy no Circula* restrictions on driving based on license plate numbers and London’s fee program for driving during peak traffic times in designated high traffic areas.[54]

Setting standards for health risk—Standards could be set more generally to achieve some health benchmark. For example, regulations could require that the excess number of deaths attributable to air pollution exposure not exceed a given percentage of the baseline mortality for a given area. Such a regulatory standard could specify the various air pollutants or sources eligible for adjustment in order to obtain the desired reduction health risk. For instance, one community might achieve lower mortality through reducing particulate matter levels, while another community could lower ozone levels to achieve the same health benefit. This type of multi-pollutant regulation would require an understanding of the health risks of the various different pollutants in key indicators of health. The structure of such a regulation would have to be based on an understanding of the interaction between pollutants. For example, if there is no interaction between two pollutants, decision-makers could reduce either of them to obtain the required reduction in health risk. If there were interaction, this interaction would have to be understood and quantified so decision-makers could incorporate this interaction in estimates of the health benefits achieved by various combinations of the pollutant levels.

Multi-pollutant Approach to Achieving Compliance

We have described how multi-pollutant science could in principle estimate the total health effect associated with simultaneous exposure to several pollutants, and how regulators could develop air quality standards that are based on the levels of multiple pollutants. A third aspect of a multi-pollutant approach to air quality management is the development of strategies for achieving compliance with single-pollutant air quality standards while at the same time accounting for the relationships among the various pollutants. For example, a strategy to lower levels of one pollutant, say PM, may also affect the levels of other pollutants, say ozone. Rather than construct a separate compliance strategy for each air pollutant standard, decision-makers could evaluate various compliance strategies and determine their collective impact.

Recently there have been efforts to develop compliance strategies for multiple pollutants. As an example, the Detroit Multi-pollutant Pilot Project aims to develop a framework to control air quality by a collective assessment of control strategies to address criteria pollutants, hazardous air pollutants, visibility, and ecosystems, and with consideration of other issues such as energy use and climate.[55] The project involves detailed analysis of emissions, air quality modeling, etc., and is specifically focused on multi-pollutant approaches to manage air quality including regulatory compliance. The project evaluates how various potential control strategies, could affect the levels of a variety of air pollutants, rather than developing a separate strategy for each pollutant. While such an approach to compliance would be a significant improvement over considering compliance for each pollutant alone, it still relies on existing single-pollutant standards, which in turn rely on risk estimation for single pollutants.

Multi-pollutant approaches to air-quality management improve upon current approaches by understanding how emissions affect concentrations of numerous pollutants (including chemical and physical transformation). A variety of technologies and tools are available to assess the effects of various control strategies on multiple pollutants simultaneously, including assessment of compliance with regulatory standards. These include air quality modeling, mathematical optimization, and other approaches to develop the most efficient compliance policies. For instance, a state could evaluate several compliance policies with the objectives of meeting specific air quality targets (i.e., regulatory standards for each pollutant), minimizing cost, and providing relatively even distribution of health benefits, or whatever goals the state designates.

CONCLUSIONS

Greater public health protection from air pollution can be achieved by shifting from a single-pollutant approach to a multi-pollutant approach. For this transition to succeed, fundamental changes in the way science approaches air pollution studies and new methodologic developments are needed. Researchers are moving toward this new approach, as evidenced by the case of particulate matter, which was first treated as a single pollutant through studies of total mass, then as a set of different size distributions, then a set of single pollutants through studies of separate chemical components, and most recently to studies of the complex mixture of particles from specific sources. This trajectory is also evidenced by the U.S. EPA’s recent request for proposals on Clean Air Centers, which highlights the importance of multi-pollutant research.[56]

Several organizations and policy-makers have encouraged a move from single-pollutant approaches towards a “one atmosphere” system to control air quality.[3-5,57,58] The EPA’s Scientific Advisory Board Particulate Matter Research Centers Advisory Panel recommended that future attention should be directed towards integrated assessments of multiple air pollutants.[59] These reports provide compelling reasons for a multi-pollutant approach. However, the actual implementation of their recommendations is daunting. This area of research remains incompletely developed, to the point that scientists and regulators may use the term “multi-pollutant approach” in different ways—one referring to the estimation of the health burden from simultaneous exposure to a complex air mixture, and the other to compliance with multiple air pollutant regulations.

Each aspect of a multi-pollutant approach (scientific assessment of health risk, the setting of regulations, and compliance with regulations) has to recognize the involvement of multiple pollutants. Most important, the development of a multi-pollutant approach requires scientific knowledge of how pollutant mixtures affect health. There several hypothesized mechanisms, including mechanisms that are likely shared by multiple pollutants. Future efforts to address health effects of mixtures should rely on our understanding of these biologic mechanisms. For example, scientific knowledge explaining the potential synergism among pollutant exposures (i.e., increased total pollutant solubility/bioavailability, oxidative potential, etc), should inform the characterizations of air pollution mixtures—similar to what is done in genomics, where genes tend to be clustered based on their biologic functions.

As scientists, policy-makers, and other decision-makers move toward a multi-pollutant approach to air quality control, it is critical that the various constituencies understand the differences and overlap in multi-pollutant concepts, and the need for future research in all of these areas.

From an atmospheric-science point of view, the relationships among pollutants are well understood. However, the state of the science on how simultaneous exposure to multiple pollutants affects human health in real-world settings is in its early stages. One of the important components of a multi-pollutant approach to risk estimation is the development of statistical models that can estimate the total health effect associated with the simultaneous exposure to multiple pollutants including their potential interactions. This is a promising area of future development of statistical methods. However, multi-pollutant statistical models face greater risks for misspecification and spurious conclusions than single pollutant models. In order to extend beyond exploratory analysis, information from other disciplines and past epidemiologic investigations is necessary to develop an initial model formulation by (1) determining which pollutants to include, (2) selecting the relevant health outcomes to study, and (3) building an appropriate functional form for the relationships among pollutants. Findings contributing to understanding biological mechanisms, such as from toxicology or human exposure studies, can help reduce dimensionality and inform the structure of statistical models. In turn, epidemiologic studies can test specific hypotheses in real-world settings and human populations that link back to biological findings.

The study of multiple pollutants will require collaboration across various disciplines. This presents its own challenges, such as defining common language. In studies of air pollution and human health, the synergistic effect of more than one environmental agent is often defined as an interaction. However, the word “interaction” has different meanings across scientific disciplines. From a statistical standpoint, “interaction” can refer to the risk associated with changes in the product of two variables (in this case, the concentrations of two pollutant levels). If the statistical interaction between two pollutants is not null, then the total effect of multiple pollutants cannot be estimated by taking the sum of effects based on single-pollutant research. From a biologic standpoint, “interaction” can refer to multiple pathways of various exposures or factors in physiological changes (e.g., gene-environment interaction refers to how environmental exposures affect individuals differently based on their genetics). These definitions are separate from “interaction” in atmospheric chemistry, such as how nitrogen oxides and volatile organic compounds interact together to form tropospheric ozone.

In a multiple-pollutant approach to air quality, connections between epidemiology and toxicology could become increasingly important. Toxicology can study multiple pollutants in a controlled setting, whereas epidemiology can examine effects of ambient air pollution levels in large real-world human populations. Animal-exposure studies have investigated exposure to multiple pollutants, including investigations of the pollutants for confounding and interaction.[14,60,61] However, a multipollutant approach to toxicology is also challenged by the increasing cost and time required to expose a large number of animals to several pollutants simultaneously.

Multi-pollutant concepts could be further expanded to consider other pathways of environmental exposure, such as ingestion, dermal exposure, or mother-to-fetus pathways. Some air pollutants have well established multiple exposure pathways (e.g., lead). Understanding the health effects of the total environment (i.e. air, water, agriculture) can perhaps be seen as a long-term objective. As we move toward a "one atmosphere" approach and as scientific understanding of the health impacts of air pollution grows, decision-makers may eventually be able to regulate air pollution sources and the overall air pollution mixture more effectively, perhaps even to achieve a "one environment" approach.

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