

Environmental Air Toxics: Role in Asthma Occurrence?

Gary L. Larsen,¹ Craig Beskid,² and Lata Shirnamé-Moré²

¹Department of Pediatrics, Division of Pediatric Pulmonary Medicine, National Jewish Medical and Research Center, University of Colorado School of Medicine, Denver, Colorado, USA; ²The Mickey Leland National Urban Air Toxics Research Center, Houston, Texas, USA

The National Urban Air Toxics Research Center (NUATRC) hosted its first scientific workshop in 1994 that focused on possible relationships between air toxics and asthma. From that meeting came recommendations for future research including a need for more complete individual personal exposure assessments so that determinations of personal exposures to pollutants could be made. In the spring of 2001, NUATRC held a second such workshop to review progress made in this area during the intervening 7 years. Peer-reviewed articles from the workshop are published in this issue of *Environmental Health Perspectives Supplements*. As in 1994, academic, government, and industry scientists participated. Dave Guinnup of the Environmental Protection Agency discussed the nature of air toxics, their definition, and the basis for federal regulation. George Leikauf from the University of Cincinnati reviewed the 1994 workshop and subsequent research in this field. Current research funded by NUATRC that is addressing individual personal exposure was presented by Clifford Weisel (Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey), Patrick Kinney (Columbia University) and Candis Claiborn (Washington State University). David Corry from Baylor College of Medicine highlighted new insights into asthma pathogenesis while Stephen Redd from the Centers for Disease Control presented an overview of asthma epidemiology as well as the societal costs of the disease. Mary White (Agency for Toxic Substances and Disease Registry) discussed recent epidemiologic investigations by public health agencies into community concerns about asthma and hazardous air pollutants. David Peden (University of North Carolina) reviewed scientific studies into the links between asthma and air toxics as well as criteria air pollutants. In a session on occupational asthma, Lee Petsonk (National Institute for Occupational Safety and Health) discussed risk factors for work-related asthma, whereas Ralph Delfino (University of California, Irvine) addressed limitations of extrapolating from occupational asthma to asthma in the general population. These presentations were followed by panel discussions focusing on future research programs, both for NUATRC and similar research institutions. Recommendations for future research included improved assessments of personal exposure to air toxics as well as research focused on specific hazardous air pollutants. The latter recommendation was based on medical literature that suggests certain pollutants from the list of 188 air toxics are most likely to adversely affect respiratory health. **Key words:** air toxics, asthma, hazardous air pollutants. *Environ Health Perspect* 110(suppl 4):501–504 (2002). <http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/501-504larsen/abstract.html>

The Mickey Leland National Urban Air Toxics Research Center (NUATRC) in Houston, Texas, USA, was established by the Clean Air Act Amendments of 1990 (1). The mission of the organization is to support research in the environmental health science disciplines on possible health risks posed by ambient levels of air toxics in urban atmospheres. The NUATRC has a Board of Directors appointed by the President of the United States, the Speaker of the House of Representatives, and the Senate Majority Leader. This organization is funded cooperatively by the federal government through the U.S. Environmental Protection Agency (U.S. EPA) and by private corporations and foundations. Working through a Scientific Advisory Panel selected by a Board of Directors, NUATRC has developed and supported peer-reviewed research to assess the residual risk to public health from air toxics.

The NUATRC first hosted a medical/scientific workshop in 1994 that focused on possible relationships between air toxics and

asthma. From that meeting came recommendations for future research directions, including the need for more complete individual personal exposure assessments so that determinations of personal exposures to various pollutants could be made (2). In the spring of 2001, NUATRC held the “Symposium on Environmental Air Toxics: Role in Asthma Occurrence?” held 30–31 May 2001 in Houston, Texas, USA. Peer-reviewed papers from this symposium are published in this issue of *Environmental Health Perspectives Supplements*. A major goal of the symposium was to review progress made in the area of air toxics and asthma research during the intervening 7 years. To accomplish this, speakers reviewed current hypotheses regarding the immunopathogenesis of asthma. Information on air toxics concentrations and individual personal exposures from studies supported by the Leland Center and other organizations was highlighted. The science of air toxics and occupational asthma was addressed in detail. From this information conclusions regarding the relationship between air toxics

and asthma in the general population were to be drawn. As part of this process, gaps in knowledge were identified, which then led to recommendations for new research programs. As in 1994, academic, government, and industry scientists participated in the presentations and discussions. A major outcome of the meeting was the identification of areas in which future research should be focused.

Presentations

The tone of the symposium was set in the Keynote Address by Phillip Lewis, Vice President for Safety, Health and Environment at the Rohm and Haas Company (Philadelphia, Pennsylvania). Dr. Lewis is a member of the Board of Directors of the Leland Center, and in this position has been involved in developing research priorities for this organization. His remarks (3) stressed the importance to public as well as private concerns of addressing the relationship between air toxics and asthma and emphasized this should be done in an environment of cooperation among the many interests represented at the symposium. He also noted there may or may not be a cause and effect relationship between personal exposure to air toxics and asthma symptoms. However, Dr. Lewis pointed out that it is in everyone's interest to address this issue with scientifically sound approaches.

Dave Guinnup from the Office of Air Quality Planning and Standards at the Environmental Protection Agency (U.S. EPA, Research Triangle Park, North Carolina) then discussed the nature of air toxics, their definition, and the basis for regulation (4). As part of his presentation, he also reviewed the U.S. EPA national regulatory-based program where the goal is to characterize, prioritize, and equitably address the serious impacts of hazardous air pollutants on public health and the environment. There are four major components of the U.S. EPA program and they include *a*) source-specific and source sector-specific regulations, *b*) partnerships and initiatives that focus on

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Address correspondence to G.L. Larsen, Dept. of Pediatrics, National Jewish Medical and Research Center, 1400 Jackson St., Denver, CO 80206 USA. Telephone: (303) 398-1201. Fax: (303) 270-2189. E-mail: larseng@njc.org

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multimedia impacts and cumulative risks, *c*) ongoing research and assessment activities, and *d*) education and outreach activities. Integration of the four components of the total program is especially important as the program evolves from a focus on technology-based regulatory development into one in which the focus is directed toward reducing or eliminating health and ecologic risks from exposure to air toxics.

George Leikauf from the University of Cincinnati (Cincinnati, Ohio) reviewed the 1994 workshop (2,5) and subsequent research in this field. Before the 1994 meeting Dr. Leikauf was commissioned by NUA-TRC to research the role of air toxics in asthma incidence by conducting a review of existing literature. His presentation of the results of that review (5) was a focal point of the first meeting, and provided much of the framework for the recommendations that came from the initial meeting. In updating research relevant to this area in the intervening years, Dr. Leikauf noted that very large gaps in our knowledge still exist (6). He also noted that in considering air toxics and asthma, we must distinguish between the ability of an air toxic to exacerbate already established disease and the potential ability of at least some air toxics to cause asthma directly. Furthermore, once the disease is established, it is also possible that exposure to air toxics may lead to disease progression such that the frequency and severity of the process along with the associated morbidity are increased. During his presentation, Dr. Leikauf reminded the participants that many of the major components of environmental tobacco smoke (ETS) are urban air toxics. He noted the several studies suggesting a link between exposure to ETS and onset of asthma as well as exacerbations of asthma (7,8). Dr. Leikauf pointed to an important future research direction in noting the increasing use of microarrays to study gene-environment interactions. The ability of investigators to assess the effects of individual air toxics on gene activity should provide important insights into how hazardous air pollutants contribute at basic levels to several pathological processes within the respiratory tract including asthma.

Research funded by NUATRC to address individual personal exposure was presented by Clifford Weisel (Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey), Patrick Kinney (Columbia University, New York, New York), and Candis Claiborn, (Washington State University, Pullman, Washington). Dr. Weisel's program, Relationship of Indoor, Outdoor and Personal Air (RIOPA), is designed to assess the influence of ambient air

toxics sources on both indoor and personal exposures (9). In this program, air samples have been collected from individuals and homes in close proximity to ambient air sources in three urban centers: Elizabeth, New Jersey; Houston, Texas; and Los Angeles, California. Preliminary results indicate that the correlation between outdoor air concentrations and either the indoor or personal air concentrations vary greatly with each air toxic. Even for compounds with overall indoor/outdoor ratios near unity (indicative of an outdoor source dominating the exposures for those compounds), individual homes or personal exposure samples at times had ratios in excess of one, indicating that sources other than ambient emissions were important contributors to the air toxic exposures for these individuals. Dr. Kinney's study, "Air Toxic Exposure Among Inner City High School Students in NYC and Los Angeles" or the "TEACH Study," involves assessing personal exposure to air toxics in high school students in two urban areas (10). In addition to personal exposures, both urban and nonurban fixed-site air toxic and criteria pollutant measurements are being collected. Preliminary results have shown that significantly higher volatile organic compound (VOC) concentrations can be found at the urban fixed-site location compared to a nonurban fixed-site location for several VOCs. In addition it appears that local sources can significantly influence VOC concentrations. Personal VOC data indicate a range of indoor and outdoor influences. Dr. Claiborn's study, "Testing the Metals Hypothesis in Spokane, Washington," is the most recently funded of this trio of studies (11). The objective is to test the hypothesis that particulate metals are associated with observed cardiovascular and respiratory health effects. In previous work that helps provide a base of data for this study, Dr. Claiborn and colleagues showed a statistically significant association between particulate measures taken at a central monitoring site and hospital admissions for asthma. The association between particulate metal species (Sb, As, Cr, Co, Mn, Hg, Se, Cd, Ni) and health outcomes (emergency department visits for asthma, hospital admission for respiratory or cardiovascular events, total respiratory mortality) is now being addressed.

David Corry from the Baylor College of Medicine (Houston, Texas) reviewed new insights into the pathogenesis of asthma (12). Since the workshop in 1994 when this topic was also reviewed (13), there have been several advances in knowledge. He highlighted recent findings demonstrating the importance of the interleukin (IL)-13/IL-4 receptor alpha (IL-4R α)-dependent signaling pathway in determining airway hyperresponsiveness, mucus overproduction, IgE secretion, and

other features of disease. In terms of insights into the genetic basis of the disease, he pointed out that perhaps the most interesting locus is 5q31, which contains several type 2 cytokine genes including the genes for IL-4 and IL-13. He also addressed recent studies suggesting that environmental factors such as tobacco smoke and diesel exhaust particles may exert adjuvant properties that increase the activity of T-helper cell type 2 (T_H2) cells that underlie the disease. Regarding other environmental factors, one of the most important may be the biochemical characteristics of the allergen including its protease activities. These biochemical features help dictate T-cell activation and recruitment to the lung.

Stephen Redd from the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia) discussed the burden, costs, and possible causes of asthma in the United States (14). Dr. Redd noted that asthma has emerged as a major public health problem in this country over the last 20 years and that the number of asthma cases has more than doubled since 1980. Over the same time period, the rate of asthma deaths has also increased (approximately 5,500 asthmatics die from their disease each year). Racial differences exist in terms of the impact of asthma. The rates of death, hospitalization, and emergency department visits are 2 to 3 times higher among African Americans than among Caucasian Americans. Over the last decade, the direct and indirect costs of this disease have more than doubled. To explain the increase in asthma prevalence, both lifestyle and environmental hypotheses have been put forth. It appears that obesity predisposes to the development of asthma, as do environmental exposures to house dust mite allergen and ETS. Conversely, both day care attendance and having a larger number of siblings have been found in some studies to protect against developing asthma. The latter observation has led investigators to suggest that increased exposure to microbial agents may protect against asthma (hygiene hypothesis). Difficulties in identifying and measuring rates of incident cases of asthma continue to hinder understanding of the causes of disease onset.

Mary White of the Agency for Toxic Substances and Disease Registry (ATSDR, Atlanta, Georgia) discussed recent epidemiological investigations by public health agencies into community concerns about asthma and hazardous air pollutants (15). Some of the difficulties in investigations within a community were highlighted. They include a lack of data on asthma prevalence or incidence at the local level, limited information on the identification and concentration of air contaminants in residential areas, and major gaps in the scientific evidence

regarding the association between different air toxics and asthma. Still, the experiences gained through these investigations illustrate not only the challenges but also the opportunities associated with studying these relationships within individual communities.

David Peden from the University of North Carolina (Chapel Hill, North Carolina) reviewed several scientific studies that addressed links between asthma and both air toxics and criteria air pollutants (16). The latter includes ozone, particulate matter, nitrogen dioxide, and sulfur dioxide as well as carbon monoxide and lead. Dr. Peden again emphasized that asthma is characterized by a T_H2 eosinophilic inflammation within airways. The disease is also characterized by increased responses to a number of non-specific irritants including ozone, particulates, and endotoxin. Dr. Peden believes that T_H2 cytokines such as IL-4 and GM-CSF may modify the response to pollutants, but also noted that pollutants can change the response to allergen. For example, pollutants can modify both immediate and late-phase responses to allergen. The mechanisms via which this occurs are not well understood. Dr. Peden speculated that important primary and secondary targets of pollutants are epithelial cells as well as monocytes within airways.

Occupational asthma was a focus of discussion during the workshop held in 1994 (17) and was again highlighted in this symposium. In the first session devoted to occupational asthma, Lee Petsonk from the National Institute for Occupational Safety and Health (NIOSH, Cincinnati, Ohio) discussed work-related asthma and implications for the public at large (18). Dr. Petsonk noted that much can be learned about asthma in the general population through investigation of asthma onset in the workplace, since exposures are often qualitatively similar, although often more intense in the occupational environment. In reviewing this scientific literature, there were several conclusions drawn. First, there is a dose-related increase in sensitization and symptoms for exposures to both chemical and protein sensitizers, and a high proportion of highly exposed working groups can be affected. Second, sensitizing exposure to the skin may affect respiratory outcomes. Third, atopy increases the risk of sensitization and illness after workplace exposure to high molecular weight antigens but not to chemical sensitizers. Fourth, experimental and some clinical evidence suggests that irritant exposures may act as adjuvants among individuals exposed to sensitizing substances, increasing the proportion that become sensitized. Evidence also indicates that atopy may be a result of irritant exposures in some individuals. Fifth, occupational asthma resolves completely in a

significant minority of subjects when exposures have been adequately controlled in a timely fashion.

Ralph Delfino from the University of California, Irvine also discussed occupational asthma but addressed the limitations of extrapolating from occupational asthma to asthma in the general population (19). Relevant confounding issues include the complexity of pollutant mixtures as well as the heterogeneity of asthma. The relevance of adult occupational asthma to pediatric asthma was also questioned. In addition Dr. Delfino pointed out other important issues concerning classes of air toxics and asthma within both occupational and nonwork-related settings. For example the types of compounds identified in associations between occupational asthma and VOCs are often not the same as those identified in community studies showing respiratory effects of VOC mixtures on adult and pediatric asthma. In terms of future studies Dr. Delfino highlighted the need for epidemiologic research on the relationship of asthma onset and exacerbation to air pollution with emphasis on disentangling the effects of air toxics from certain criteria air pollutants (ozone, particulate matter, nitrogen dioxide, sulfur dioxide). In addition he suggested that future studies should focus on air toxics identified as asthmo-genic in occupational studies (e.g., certain metal compounds). He also believed that research should be initiated on air toxics expected to have adverse respiratory effects based on known biological mechanisms.

Panel Discussions

These formal presentations were followed by two panel discussions focused on current and future research programs at a national level that could be pursued by NUATRC and similar research institutions. The first discussion focused on federal programs and included panel members from the U.S. EPA (Hillel Koren), National Institutes of Environmental Health Sciences in the Research Triangle Park, North Carolina (J. Patrick Mastin and George Malindzak), NIOSH (Lee Petsonk), and CDC (Stephen Redd). The second panel again included Dr. Koren of the U.S. EPA but also included members from industry and academic institutions. Myron Harrison represented ExxonMobil Corporation (Irving, Texas) and Will Ollison represented the American Petroleum Institute (Washington, DC). Nathan Rabinovitch from the National Jewish Medical and Research Center (Denver, Colorado) also took part in the discussion, as did Dr. Stuart Abramson of Texas Children's Hospital and Baylor College of Medicine. In terms of future research directions, the consensus was that additional assessments of personal exposures to air toxics

is needed to more accurately determine associated risks. There was also general agreement that research should focus on a subset of urban hazardous air pollutants that have been associated with asthma induction and/or exacerbation. One way of achieving this focus is for researchers to concentrate on compounds that appear on both Dr. Leikauf's list of 30 hazardous air pollutants most likely to impact asthma and respiratory health (5) and the U.S. EPA 1999 list of 33 hazardous air pollutants posing the greatest threat to public health in the largest number of urban areas. From these two lists, seven classes of compounds emerge: acetaldehyde, acrolein, formaldehyde, hydrazine, and cadmium, chromium, and nickel compounds. In addition to concentrating on these compounds, several individual presentations and the panel discussions also highlighted the importance of understanding the respiratory effects of ETS and diesel exhaust. Both are mixtures of various combustion-related particles and air toxics that may interact to enhance asthma incidence and/or severity. The point was made that future work must include the most vulnerable populations. Included in the most vulnerable groups are children, among whom the incidence of asthma has shown the greatest increases during recent decades (20).

In addition several speakers stressed the need for expanded surveillance efforts. Much can be learned from surveillance activities about effective intervention and assessment. Other speakers emphasized the need for a better understanding of the mechanisms of asthma formation and exacerbation, which are still not clear. More knowledge of these mechanisms may facilitate the task of explaining the complex relationship between asthma and environmental exposures. Other important future research needs included the interplay between allergy and asthma; issues of susceptibility and sensitivity; the effects of genetic factors on asthma; and reasons for the severity of asthma which is now worse than in the past. Last, it was also recommended that researchers must strive to increase the time and concentration resolution of exposure measurements. Improvements in modeling of personal exposures will lead to improved knowledge of personal exposures.

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